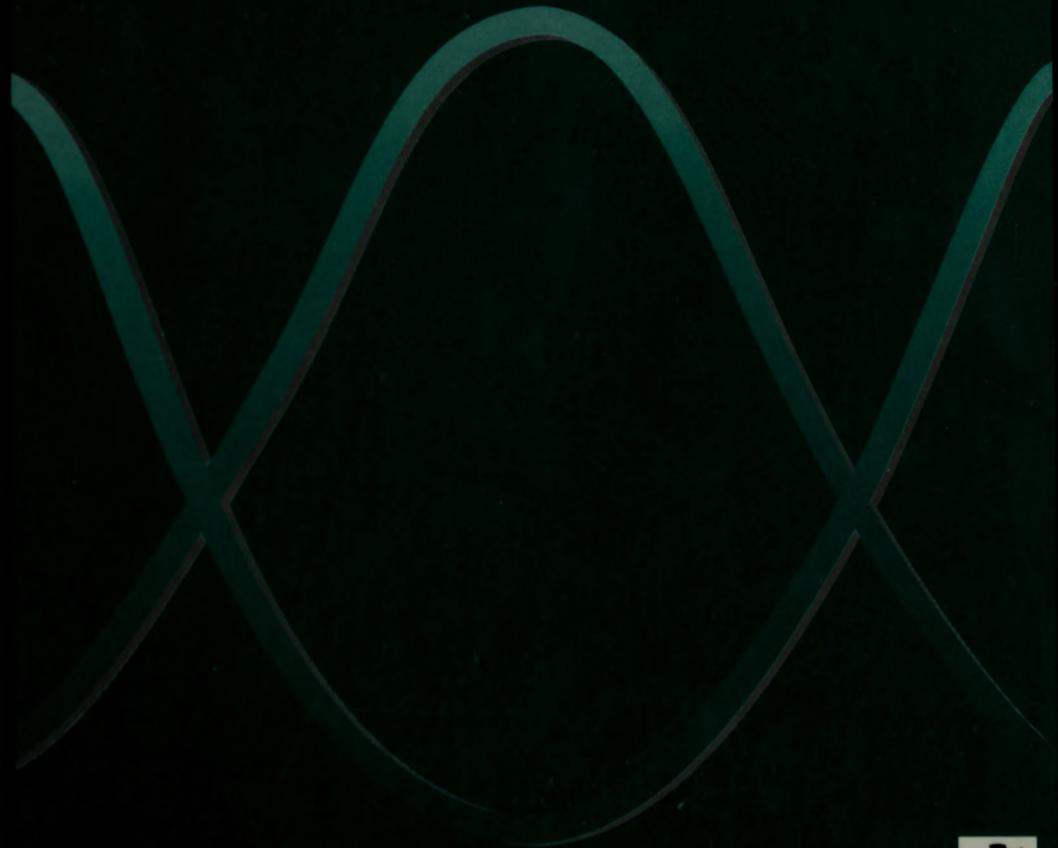


INTRODUCTION TO
**QUANTITATIVE
GENETICS**

Falconer & Mackay



FOURTH EDITION



Introduction to Quantitative Genetics

Fourth Edition

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Contents

PREFACE TO THE THIRD EDITION	ix
PREFACE TO THE FOURTH EDITION	x
ACKNOWLEDGEMENTS	xi
INTRODUCTION	xiii
1 GENETIC CONSTITUTION OF A POPULATION	1
Frequencies of genes and genotypes	1
<i>Mendelian variation in natural populations Causes of change</i>	1
Hardy–Weinberg equilibrium	5
<i>The Hardy–Weinberg law Applications of the Hardy–Weinberg law</i>	
<i>Mating frequencies and another proof of the Hardy–Weinberg law</i>	
<i>Multiple alleles Sex-linked genes More than one locus</i>	
Non-random mating	19
<i>Assortative mating</i>	
Problems	20
2 CHANGES OF GENE FREQUENCY	23
Migration	23
Mutation	24
<i>Non-recurrent mutation Recurrent mutation</i>	
Selection	25
<i>Change of gene frequency under selection Effectiveness of selection</i>	
<i>Number of generations required Average fitness and load</i>	
Equilibria	34
<i>Balance between mutation and selection Changes of equilibrium</i>	
<i>Selection favouring heterozygotes</i>	
Polymorphism	42
Problems	45
3 SMALL POPULATIONS: I. CHANGES OF GENE FREQUENCY UNDER SIMPLIFIED CONDITIONS	48
The idealized population	49
Sampling	51
<i>Variance of gene frequency Fixation Genotype frequencies</i>	
Inbreeding	57
<i>Inbreeding in the idealized population Variance of gene frequency</i>	
<i>Genotype frequencies</i>	
Problems	63

4 SMALL POPULATIONS: II. LESS SIMPLIFIED CONDITIONS	65
Effective population size	65
<i>Exclusion of closely related matings Different numbers of males and females Unequal numbers in successive generations Non-random distribution of family size Minimal inbreeding Overlapping generations</i>	
Mutation, migration, and selection	72
<i>Non-recurrent neutral mutation Recurrent mutation and migration Selection</i>	
Random drift in natural populations	76
Polymorphism	78
<i>Neutral theory</i>	
Problems	81
5 SMALL POPULATIONS: III. PEDIGREED POPULATIONS AND CLOSE INBREEDING	82
Pedigreed populations	82
<i>The inbreeding coefficient of an individual Coancestry or kinship</i>	
Regular systems of inbreeding	88
<i>Close inbreeding Fixation Repeated backcrosses Crosses and subsequent generations Mixed inbreeding and crossing Change of base: structured population Mutation Selection favouring heterozygotes</i>	
Problems	98
6 CONTINUOUS VARIATION	100
Metric characters	102
Properties of metric characters	104
Problems	106
7 VALUES AND MEANS	108
Population mean	109
Average effect	112
Breeding value	114
Dominance deviation	116
Interaction deviation	119
Problems	120
8 VARIANCE	122
Components of variance	122
<i>Components as proportions of the total Estimation of the degree of genetic determination, V_G/V_P</i>	
Genetic components of variance	125
<i>Additive and dominance variance Total genetic variance Interaction variance Variance due to disequilibrium</i>	
Correlation and interaction between genotype and environment	131
<i>Correlation Interaction</i>	

Environmental variance	134
<i>Multiple measurements: repeatability</i>	
Summary of variance partitioning	143
Problems	143
9 RESEMBLANCE BETWEEN RELATIVES	145
Genetic covariance	146
<i>Offspring and one parent Offspring and mid-parent Half sibs Full sibs</i>	
<i>Twins General Epistatic interaction</i>	
Environmental covariance	155
Phenotypic resemblance	157
Problems	158
10 HERITABILITY	160
Estimation of heritability	163
<i>Offspring-parent regression Sib analysis Intra-sire regression of offspring on dam Combined estimates</i>	
Twins and human data	171
Assortative mating	174
Precision of estimates and design of experiments	177
<i>Offspring-parent regression Sib analyses Selection of parents</i>	
Problems	181
11 SELECTION: I. THE RESPONSE AND ITS PREDICTION	184
Response to selection	185
<i>Prediction of response Selection differential and intensity of selection</i>	
<i>Improvement of response</i>	
Measurement of response	194
<i>Variability of generation means Weighting the selection differential</i>	
<i>Realized heritability Maternal effects</i>	
Change of gene frequency under artificial selection	199
Effects of selection on variance	201
Problems	204
12 SELECTION: II. THE RESULTS OF EXPERIMENTS	208
Short-term results	208
<i>Repeatability of response Sampling variance Asymmetry of response</i>	
Long-term results	215
<i>Selection limits Mutation Causes of selection limits</i>	
<i>Number of loci (effective factors) and standardized effects</i>	
Problem	226
13 SELECTION: III. INFORMATION FROM RELATIVES	228
Criteria for selection	229
<i>Simple methods Prediction of response Combined selection</i>	
<i>Relative merits of the methods</i>	

Index selection	240
<i>Construction of an index Accuracy Response to selection</i>	
<i>Actual achievements</i>	
Problems	245
14 INBREEDING AND CROSSBREEDING: I. CHANGES OF MEAN VALUE	247
Inbreeding depression	247
<i>The effect of selection</i>	
Heterosis	253
<i>Single crosses</i>	
Problems	261
15 INBREEDING AND CROSSBREEDING: II. CHANGES OF VARIANCE	263
Inbreeding	264
<i>Redistribution of genetic variance Environmental variance Uniformity of inbred strains</i>	
Mutation	269
<i>Subline divergence</i>	
Crossing	272
<i>Variance between crosses Combining ability</i>	
Problems	279
16 INBREEDING AND CROSSBREEDING: III. APPLICATIONS	281
<i>Selection for combining ability Three-way and four-way crosses; backcrosses Reciprocal recurrent selection Overdominance Naturally self-fertilizing plants</i>	
Problems	288
17 SCALE	290
<i>Distribution and variance Interactions Conclusions</i>	
Problems	297
18 THRESHOLD CHARACTERS	299
<i>Liability and threshold Two classes, one threshold Adequacy of the liability model Scale relationships Three classes, two thresholds Selection for threshold characters</i>	
Problems	310
19 CORRELATED CHARACTERS	312
Genetic and environmental correlations	312
<i>Estimation of the genetic correlation</i>	
Correlated response to selection	317
<i>Indirect selection</i>	
Genotype–environment interaction	321

Index selection	325
<i>Construction of the index Response Effect of selection on genetic correlations</i>	
Problems	332
20 METRIC CHARACTERS UNDER NATURAL SELECTION	335
Natural selection	335
<i>Fitness and its components</i>	
Relationships between metric characters and fitness	337
<i>'Fitness profiles'</i>	
Responses to natural selection	339
<i>Fitness Correlated responses Strength of selection</i>	
Equilibrium populations	342
<i>Fitness Major components Characters with intermediate optima Characters with minimum fitness of intermediates Neutral characters</i>	
Origin of variation by mutation	348
<i>Mutational variance</i>	
Maintenance of genetic variation	351
<i>Balance between neutral mutation and random drift Mutation-selection balance</i>	
Problems	354
21 QUANTITATIVE TRAIT LOCI	356
Major genes	356
<i>Methods of detection</i>	
Methods for mapping QTLs	359
<i>Marker loci QTL genotypes Single marker analysis Interval mapping analysis</i>	
Genetical and statistical considerations	366
<i>Experimental design Multiple tests Maximum likelihood estimation Multiple QTLs</i>	
Experimental results	370
<i>Number of loci Gene effects Consistency</i>	
From QTL to gene	375
Problem	377
APPENDIX TABLES	379
GLOSSARY OF SYMBOLS	381
<i>Equivalence of symbols used by Mather and Jinks</i>	383
SOLUTIONS OF PROBLEMS	385
REFERENCES	437
INDEX	459

Preface to the third edition

This book was written with the intention of providing an introductory textbook, with the emphasis on general principles rather than on practical applications. I tried to make the book useful to as wide a range of readers as possible, particularly biologists who, like myself, have no more than ordinary mathematical ability. The mathematics does not go beyond simple algebra; neither calculus nor matrix methods are used. Some knowledge of statistics, however, is assumed, particularly of the analysis of variance and of correlation and regression.

The second edition kept the same structure but was somewhat enlarged by the inclusion of developments in the intervening twenty years, and by more attention being given to plants. In consequence the book came to contain a good deal more material than is needed by those for whom the subject is part of a course on general genetics. The section headings, however, should facilitate the selection of what is relevant. My main regret then, as it is now, was the impossibility of mentioning more than a very few of the experimental studies that have illuminated the subject since the book first appeared.

The revisions made in this new edition are less extensive. The desire not to increase the length of the book has meant that many of the recent developments are noted by little more than references to the sources. The demonstration that mutation is not negligible for quantitative genetics has, however, necessitated more substantial revision of Chapter 12 and to a lesser extent Chapters 15 and 20.

The Problems, which were hitherto published separately, are now put together with the text, following the chapters to which they refer. They are of varying difficulty and I hope that all students will find some that they can solve immediately and some also that will tax their ingenuity to the full. Some of the problems are based on the data and solutions of earlier ones. Students are therefore advised to keep their workings for later use; this will save the repetition of calculations. I have based the problems on real data wherever I could, to make them more interesting and realistic. In consequence, however, the arithmetic seldom works out simply, and a pocket calculator will be needed for most of them. A few of the problems have been revised for this edition. The solutions are at the end of the book, arranged in a different order from the problems so as to avoid the risk of inadvertently seeing the solution of the next problem. The solutions are not simply answers but give fairly full explanations of how the problems are solved.

Acknowledgements It is not exaggeration to say that this book could not originally have been written without the help of Professor Alan Robertson. My understanding of the subject grew from my frequent discussions with him. I owe the same debt of

gratitude to Professor W. G. Hill for his guidance on the preparation of the second, and now this, edition. Without his advice many of the revisions could not have been attempted. Dr R. C. Roberts read the manuscripts of the first and second editions and his suggestions led to many improvements being made. Dr Paul M. Sharp checked the solutions of all the problems and made many valuable suggestions. I have had help also from many other colleagues who have advised me on particular matters. To all of these, and to my wife who helped me in many ways, I am deeply grateful. The mistakes and misunderstandings that remain are entirely my own. I should be grateful to be told of these.

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D. S. Falconer
February 1988

Preface to the fourth edition

Quantitative genetics is now merging with molecular genetics and this very active area of the subject needs more consideration than it was given in the previous edition. Accordingly, a new chapter has been added, on quantitative trait loci (QTLs) – the location and characterization of the genes causing quantitative variation. Chapter 20, on natural selection, has been largely rewritten, with fuller treatment of mutation and the maintenance of genetic variation; we hope these additions will make the book more useful to students of evolutionary quantitative genetics. In the earlier chapters, the treatment of polymorphism and of neutral mutation has been expanded, and some sections in the chapters on inbreeding have been shortened.

We gratefully acknowledge advice from Dr James D. Fry, Professor W. G. Hill, Dr Peter D. Keightley, Dr Mark Kirkpatrick and Dr Michael Turelli. We are indebted also to Dr Richard Lyman for producing Figures 21.3 and 21.4, and to Dr Hartwig H. Geiger for pointing out an error in equation [15.8], which has now been corrected. Finally, the first author is most grateful to Professor Hill for the hospitality provided in his laboratory.

D. S. Falconer
T. F. C. Mackay
March 1995

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Introduction

Quantitative genetics is concerned with the inheritance of those differences between individuals that are of degree rather than of kind, quantitative rather than qualitative. These are the individual differences which, as Darwin wrote, 'afford materials for natural selection to act on and accumulate, in the same manner as man accumulates in any given direction individual differences in his domestic productions'. An understanding of the inheritance of these differences is thus of fundamental significance in the study of evolution and in the application of genetics to animal and plant breeding; and it is from these two fields of enquiry that the subject has received the chief impetus to its growth.

Virtually every organ and function of any species shows individual differences of this nature, the difference of size among ourselves or our domestic animals being an example familiar to all. Individuals form a continuously graded series from one extreme to the other and do not fall naturally into sharply demarcated types. Qualitative differences, in contrast, divide individuals into distinct types with little or no connexion by intermediates. Examples are the differences between blue-eyed and brown-eyed individuals, between the blood groups, or between normally coloured and albino individuals. The familiar Mendelian ratios, which display the mechanism of inheritance, can be seen only when a gene difference at a single locus gives rise to a readily detectable difference in some such property of the organism. Quantitative differences, in so far as they are inherited, depend on genes whose effects are small in relation to the variation arising from other causes. Furthermore, quantitative differences are usually, though not necessarily always, influenced by gene differences at many loci. Consequently the individual genes, whether few or many, cannot be identified by their segregation; the Mendelian ratios are not displayed, and the methods of Mendelian analysis cannot be applied.

It is, nevertheless, a basic premiss of quantitative genetics that the inheritance of quantitative differences depends on genes subject to the same laws of transmission and having the same general properties as the genes whose transmission and properties are displayed by qualitative differences. Quantitative genetics is therefore an extension of Mendelian genetics, resting squarely on Mendelian principles as its foundation.

The methods of study in quantitative genetics differ from those employed in Mendelian genetics in two respects. In the first place, since ratios cannot be observed, single progenies are uninformative, and the unit of study must be extended to 'populations', that is, larger groups of individuals comprising many progenies. And, in the second place, the nature of the quantitative differences to be studied requires the measurement, and not just the classification, of the individuals.

The extension of Mendelian genetics into quantitative genetics may thus be made in two stages, the first introducing new concepts connected with the genetic properties of 'populations' and the second introducing concepts connected with the inheritance of measurements. This is how the subject is presented in this book. In the first part, which occupies Chapters 1 to 5, the genetic properties of populations are described by reference to genes causing easily identifiable, and therefore qualitative, differences. Quantitative differences are not discussed until the second part, which starts in Chapter 6. These two parts of the subject are often distinguished by different names, the first being referred to as 'population genetics' and the second as 'quantitative genetics' or 'biometrical genetics'.

The theoretical basis of quantitative genetics was established round about 1920 by the work of Fisher (1918), Haldane (summarized 1932) and Wright (1921). The development of the subject over the succeeding years, by these and many other geneticists and statisticians, has been mainly by elaboration, clarification, and the filling in of details, so that today we have a substantial body of theory accepted by the majority as valid.

The theory consists of the deduction of the consequences of Mendelian inheritance when extended to the properties of populations and to the simultaneous segregation of genes at many loci. The premiss from which the deductions are made is that the inheritance of quantitative differences is by means of genes, and that these genes are subject to the Mendelian laws of transmission and may have any of the properties known from Mendelian genetics. The property of 'variable expression' assumes great importance and might be raised to the status of another premiss: that the expression of the genotype in the phenotype is modifiable by non-genetic causes. Other properties whose consequences are taken into account include dominance, epistasis, pleiotropy, linkage, and mutation. The theory then allows us to deduce what will be the genetic properties of a population if the genes have the properties postulated. It allows us also to predict the consequences of any specified breeding plan, including those of natural selection. It therefore forms the basis for understanding evolutionary change. The main practical use of the theory is in comparing the merits of alternative procedures for animal and plant improvement.

The experimental side of quantitative genetics has three roles, complementary to the theoretical side. First, experimental study of populations allows us to deduce the properties of the genes associated with quantitative variation. Second, experimental breeding allows us to test the validity of the theory. And third, there are some consequences of breeding procedures that cannot be predicted from the theory, and questions about these can be answered only by experiment. There is now a large body of experimental data which substantiates the theory in considerable detail, showing that the genes concerned with quantitative variation do have the properties known from Mendelian genetics, and that the outcome of most breeding procedures can be predicted with some confidence. The aim is to describe all that is reasonably firmly established and, for the sake of clarity, to simplify as far as is possible without being misleading. Consequently, the emphasis is on the theoretical side. Though conclusions will often be drawn directly from experimental data, the experimental side of the subject is presented chiefly in the form of examples, chosen with the purpose of illustrating the theoretical conclusions. These

examples, however, cannot always be taken as substantiating the postulates that underlie the conclusions they illustrate. Too often the results of experiments are open to more than one interpretation. The experimental work mentioned is only a very small, and far from random, sample of what has been done. In particular, a great deal more experimentation has been done with plants and farm animals than would appear from its representation among the work cited.

No attempt has been made to give exhaustive references to published work in any part of the subject; or to indicate the origins, or trace the history of the ideas. To have done this would have required a much longer book, and a considerable sacrifice of clarity. Most of the material in the book is covered more fully in one or other of the sources listed below. These sources are not regularly cited in the text. References are given in the text when any conclusion is stated without full explanation of its derivation. These references are not always to the original papers, but rather to the more recent papers where the reader will find a convenient point of entry to the topic under discussion. A selection of the original papers that have most influenced the development of the subject is reprinted with extensive commentaries by Hill (1984) in the Benchmark Papers in Genetics series (Vol. 15).

Chief sources

(For full bibliographical details see list of References)

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1 Genetic constitution of a population

Frequencies of genes and genotypes

To describe the genetic constitution of a group of individuals we should have to specify their genotypes and say how many of each genotype there were. This would be a complete description, provided the nature of the phenotypic differences between the genotypes did not concern us. Suppose for simplicity that we were concerned with a certain autosomal locus, A, and that two different alleles at this locus, A_1 and A_2 , were present among the individuals. Then there would be three possible genotypes, A_1A_1 , A_1A_2 , and A_2A_2 . (We are concerned here, as throughout the book, exclusively with diploid organisms.) The genetic constitution of the group would be fully described by the proportion, or percentage, of individuals that belonged to each genotype, or in other words by the frequencies of the three genotypes among the individuals. These proportions or frequencies are called *genotype frequencies*, the frequency of a particular genotype being its proportion or percentage among the individuals. If, for example, we found one-quarter of the individuals in the group to be A_1A_1 , the frequency of this genotype would be 0.25, or 25 per cent. Naturally, the frequencies of all the genotypes together must add up to unity, or 100 per cent.

Example 1.1

The M-N blood groups in man are determined by two alleles at a locus, and the three genotypes correspond with the three blood groups, M, MN, and N. The following figures, taken from the tabulation of Mourant (1954), show the blood group frequencies among Eskimos of East Greenland and among Icelanders as follows:

Frequency, %		<i>Blood group</i>			<i>Number of individuals</i>
		M	MN	N	
	Greenland	83.5	15.6	0.9	569
	Iceland	31.2	51.5	17.3	747

Clearly the two populations differ in these genotype frequencies, the N blood group being rare in Greenland and relatively common in Iceland. Not only is this locus a source of variation within each of the two populations, but it is also a source of genetic difference between the populations.

A population, in the genetic sense, is not just a group of individuals, but a breeding group; and the genetics of a population is concerned not only with the genetic constitution of the individuals but also with the transmission of the genes from one generation to the next. In the transmission the genotypes of the parents are broken down and a new set of genotypes is constituted in the progeny, from the genes transmitted in the gametes. The genes carried by the population thus have continuity from generation to generation, but the genotypes in which they appear do not. The genetic constitution of a population, referring to the genes it carries, is described by the array of *gene frequencies*; that is, by specification of the alleles present at every locus and the numbers or proportions of the different alleles at each locus. If, for example, A_1 is an allele at the A locus, then the frequency of A_1 genes, or the gene frequency of A_1 , is the proportion or percentage of all genes at this locus that are the A_1 allele. The frequencies of all the alleles at any one locus must add up to unity, or 100 per cent.

The gene frequencies at a particular locus among a group of individuals can be determined from a knowledge of the genotype frequencies. To take a hypothetical example, suppose there are two alleles, A_1 and A_2 , and we classify 100 individuals and count the numbers in each genotype as follows:

	A_1A_1	A_1A_2	A_2A_2	Total
Number of individuals	30	60	10	100
Number of genes	{ A_1 : 60 A_2 : 0}	{ A_1 : 60 A_2 : 60}	{ A_1 : 0 A_2 : 20}	{ 120 80 } 200

Each individual contains two genes, so we have counted 200 representatives of the genes at this locus. Each A_1A_1 individual contains two A_1 genes and each A_1A_2 contains one A_1 gene. So there are 120 A_1 genes in the sample, and 80 A_2 genes. The frequency of A_1 is therefore 60 per cent or 0.6, and the frequency of A_2 is 40 per cent or 0.4. To express the relationship in a more general form, let the frequencies of genes and of genotypes be as follows:

	Genes		Genotypes		
	A_1	A_2	A_1A_1	A_1A_2	A_2A_2
Frequencies	p	q	P	H	Q

so that $p + q = 1$ and $P + H + Q = 1$. Since each individual contains two genes, the frequency of A_1 genes is $\frac{1}{2}(2P + H)$, and the relationship between gene frequency and genotype frequency among the individuals counted is as follows:

$$\left. \begin{aligned} p &= P + \frac{1}{2}H \\ q &= Q + \frac{1}{2}H \end{aligned} \right\} \dots [1.1]$$

Example 1.2

To illustrate the calculation of gene frequencies from genotype frequencies we may take the M–N blood group frequencies given in Example 1.1. The M and N blood groups represent the two homozygous genotypes and the MN group the heterozygote. The frequency of the M gene in Greenland is, from equation [1.1], $0.835 + \frac{1}{2}(0.156) = 0.913$, and the frequency of the N gene is $0.009 + \frac{1}{2}(0.156) = 0.087$, the sum of the frequencies being 1.000 as it should be. Doing the same for the Iceland sample, we find the following gene frequencies in the two populations, expressed now as percentages:

<i>Gene</i>		
	M	N
Greenland	91.3	8.7
Iceland	57.0	43.0

Thus the two populations differ in gene frequency as well as in genotype frequencies.

Mendelian variation in natural populations

There are many different levels at which we can observe genetic variation in natural populations for discrete traits that segregate as Mendelian units. At one end of the spectrum are visible variants with large effects on the phenotype, such as plant flower colour, shell colours and patterns in snails, or major mutations such as dwarfism. Much variation between individuals does not give rise to obvious differences in phenotype, however. This cryptic variation is revealed by techniques that study differences in proteins and in the DNA itself. The MN blood group variation in Examples 1.1 and 1.2 illustrates one kind of cryptic variation, detectable by an antibody reaction. Protein electrophoresis is a technique that detects differences in mobility of soluble proteins on a gel, in the presence of an electric field. Variants detected in this manner are inherited as co-dominant alleles, called allozymes. They are caused by amino acid substitutions that give rise to a change in the electric charge of the protein. Protein electrophoresis thus detects about 25% of the amino acid differences between proteins, since 5 of the 20 amino acids are charged.

Variation in DNA sequences can be detected using restriction enzymes. These enzymes recognize specific 4- or 6-base DNA sequences and cut the DNA whenever these sequences occur. The DNA pieces are then separated by size by electrophoresis, and visualized by hybridization to a labelled probe DNA by a process called Southern blotting. If there is variation in restriction sites between individuals for the stretch of DNA recognized by the probe, this is revealed on the blot as a change in size of the restriction fragment, called restriction fragment length polymorphisms, or RFLPs. Unlike protein electrophoresis, which only detects changes in functional proteins, RFLP variation can be in non-coding as well as coding regions of the genome. Although cloned DNA is necessary to detect this variation, it is not necessary to know the function or chromosomal location of the cloned probe. Variation in restriction fragment lengths can also be caused by insertions and deletions of DNA sequences between two restriction sites. Large

insertions are usually transposable elements: DNA sequences that are present in multiple, dispersed copies in the genome and that are able to move from location to location. Other length variation is caused by variation in numbers of tandemly repeated DNA sequences at 'minisatellite' or 'microsatellite' loci. The former, also called VNTR (for variable number of tandem repeat) loci, consist of repeating units 10–60 base pairs long. Microsatellite (or simple sequence repeat, SSR) loci consist of shorter repeating units of 1–6 base pairs, such as $(CA)_n$ or $(AGC)_n$, where n , the number of repeat units, is variable. Finally, the ultimate level of resolution of variation between individuals is to compare their actual DNA sequences obtained by direct sequencing.

Allelic variation for discrete traits, whether phenotypically visible or cryptic, is known as polymorphism, about which more will be said in Chapters 2 and 4. Polymorphic loci give rise to the variation in quantitative characters, which is the subject of this book.

Causes of change

Several agencies affect gene and genotype frequencies in the process of transmission of genes from one generation to the next. To understand quantitative genetic variation fully we need to know how these factors, separately and together, influence genetic variation in populations over time, and what is their relative importance as agencies of gene frequency change. These agencies form the chief subject-matter of the next four chapters, but we may briefly review them here in order to have some idea of what factors are being left out of consideration in this chapter. The agencies through which the genetic properties of a population may be changed are these:

Population size The genes passed from one generation to the next are a sample of the genes in the parent generation. Therefore the gene frequencies are subject to sampling variation between successive generations, and the smaller the number of parents the greater is the sampling variation. The effects of sampling variation will be considered in Chapters 3–5, and meantime we shall exclude it from the discussion by supposing always that we are dealing with a 'large population', which means simply one in which sampling variation is so small as to be negligible. For practical purposes a 'large population' is one in which the number of adult individuals is in the hundreds rather than in the tens.

Differences of fertility and viability Though we are not at present concerned with the phenotypic effects of the genes under discussion, we cannot ignore their effects on fertility and viability, because these influence the genetic constitution of the succeeding generation. The different genotypes among the parents may have different fertilities, and if they do they will contribute unequally to the gametes out of which the next generation is formed. In this way the gene frequency may be changed in the transmission. Further, the genotypes among the newly formed zygotes may have different survival rates, and so the gene frequencies in the new generation may be changed by the time the individuals are adult and themselves become parents. These processes are called selection, and will be described in Chapter 2. Meanwhile we shall suppose they are not operating. Human blood-group genes may be taken

frequencies show two important features. First the frequency of the heterozygotes cannot be greater than 50 per cent, and this maximum occurs when the gene frequencies are $p = q = 0.5$. Second, when the gene frequency of an allele is low, the rare allele occurs predominantly in heterozygotes and there are very few homozygotes. This has important consequences for the effectiveness of selection, as will be seen in the next chapter.

Applications of the Hardy–Weinberg law

There are three ways in which the Hardy–Weinberg law is particularly useful, which will now be illustrated.

Gene frequency of recessive allele At the beginning of the chapter we saw, in equation [1.1], how the gene frequencies among a group of individuals can be determined from their genotype frequencies; but for this it was necessary to know the frequencies of all three genotypes. Consequently, the relationship in equation [1.1] cannot be applied to the case of a recessive allele, when the heterozygote is indistinguishable from the dominant homozygote. If the genotypes are in Hardy–Weinberg proportions, however, we do not need to know the frequencies of all three genotypes. Let a , for example, be a recessive gene with a frequency of q ; then the frequency of aa homozygotes is q^2 , and the gene frequency is the square-root of the homozygote frequency. Example 1.3 illustrates the calculation. For this way of estimating the gene frequency to be a valid one, it is obviously essential that there should be no selective elimination of homozygotes before they are counted. It should be noted also that the estimation of gene frequency in this way is rather sensitive to the effects of non-random mating.

Example 1.3

Phenylketonuria (PKU) is a human metabolic disease due to a single recessive gene. Homozygotes can be detected a few days after birth, and selective elimination before then will be assumed to be negligible. Tests of babies born in Birmingham, UK, over a 3-year period detected 5 cases in 55,715 babies (Raine *et al.*, 1972). The frequency of homozygotes in the sample is 90×10^{-6} or about 1/11,000. The Hardy–Weinberg frequency of homozygotes is q^2 , so the gene frequency is $q = \sqrt{(90 \times 10^{-6})} = 9.5 \times 10^{-3} = 0.0095$.

The frequency of heterozygotes in the whole population is $2q(1 - q)$, and among normal individuals is $2q/(1 + q)$. Both work out to be 0.019, approximately. Thus about 2 per cent of normal people, or 1 in 50, are carriers of PKU. It comes as a surprise to most people to discover how common heterozygotes of a rare recessive abnormality are. The point has already been noted as a conclusion drawn from Fig. 1.1.

Frequency of ‘carriers’ It is often of interest to know the frequency of heterozygotes, or ‘carriers’, of recessive abnormalities, and this can be calculated if the gene frequency is known. If Hardy–Weinberg equilibrium can be assumed, the frequency of heterozygotes among all individuals, including homozygotes, is given by $2q(1 - q)$. It is, however, often more relevant to know the frequency among normal individuals, though this will not be very different if homozygotes

are rare. The frequency of heterozygotes among normal individuals, denoted by H' , is the ratio of genotype frequencies $Aa/(AA + Aa)$, where a is the recessive allele. So, when q is the frequency of a ,

$$H' = \frac{2q(1-q)}{(1-q)^2 + 2q(1-q)} = \frac{2q}{1+q} \quad \dots [1.3]$$

Test of Hardy–Weinberg equilibrium If data are available for a locus where all the genotypes are recognizable, the observed frequencies of the genotypes can be tested for agreement with a population in Hardy–Weinberg equilibrium. According to the Hardy–Weinberg law, the genotype frequencies of progeny are determined by the gene frequency in their parents. If the population is in equilibrium, the gene frequency is the same in parents and progeny, so the gene frequency observed in the progeny can be used as if it were the parental gene frequency to calculate the genotype frequencies expected by the Hardy–Weinberg law. The procedure is illustrated in Example 1.4.

Example 1.4

The M–N blood group frequencies in Iceland were given in Example 1.1. The observed numbers in the sample were as in the following table. The gene frequencies in the sample are first calculated from the observed numbers by equation [1.1]. Then the Hardy–Weinberg genotype frequencies p^2 , $2pq$ and q^2 are calculated from the gene frequencies by equation [1.2], and each is multiplied by the total number to get the numbers expected. For example, the expectation for MM is $(0.5696)^2 \times 747$. Comparing the observed with expected numbers shows a deficiency of both homozygotes and an excess of heterozygotes. The χ^2 tests how well, or how badly, the observed numbers agree with the expected. The discrepancy is not significant and could easily have arisen by chance in the sampling. Note that this χ^2 has only 1 degree of freedom because the gene frequency has been estimated from the data, so that the observed and expected numbers must agree in their gene frequencies as well as in their totals.

	Genotypes				Gene frequencies	
	MM	MN	NN	Total	M	N
Numbers observed	233	385	129	747	0.5696	0.4304
Numbers expected	242.36	366.26	138.38	747		
$\chi^2_1 = 1.96$	$P \sim 0.2$					

The test for agreement with an equilibrium population is a test of whether the conditions for the production of Hardy–Weinberg genotype frequencies have been fulfilled. The conclusions that can be drawn from the test, however, are limited. When good agreement is found, the test gives no reason to doubt the fulfilment of all the conditions. Tests made with blood-group genes nearly always show very good agreement, as in Example 1.4. But there is one condition whose non-fulfilment will not lead to a discrepancy, and that is equal fertility among the parents. The reason

for this will be explained in a moment. If the test reveals a discrepancy between the observed and expected frequencies, we can conclude that one or more of the conditions has not been fulfilled. But the nature of the discrepancy does not allow us to identify its source, or decide which condition has not been met. The reason for this is that the same discrepancy can arise from different causes. For example, an excess of heterozygotes can result from selective elimination of homozygotes, or from the gene frequency being different in males and females of the parental generation. The test is not as simple as it seems, and we must look more closely at what it does.

The Hardy–Weinberg law relates genes in parents to genotypes in progeny. Therefore, to test it fully, we need to know the gene frequency in the parents and to calculate the expected genotype frequencies in the progeny from the parental gene frequency. But for the test described we have only the progeny. We find the gene frequency in them by counting. We then say: if this was the gene frequency among the gametes that produced these progeny, the genotypes should be in the Hardy–Weinberg proportions as calculated from the observed gene frequency. If the gene frequency was not the same in the parents as in the progeny, we have used the wrong gene frequency to calculate the expectations. Reference to Table 1.1 will show that the conditions tested are random mating, equal gene frequencies in the two sexes of parents, and equal viability among the progeny; but equal fertility among the parents is not tested. Selection could therefore be acting through fertility and not be detected by this test. Selection acting through the viability of the progeny will lead to disagreement between the observed and expected frequencies. It is not possible, however, to identify the genotype or genotypes that have reduced viability. The reason for this will be explained in the next chapter, after the effects of selection have been dealt with. For fuller discussions of the limitations of the test see Wallace (1958, 1968), Prout (1965); and for fuller consideration of its statistical aspects see Smith (1970).

Mating frequencies and another proof of the Hardy–Weinberg law

Let us now look more closely into the breeding structure of a random-mating population, distinguishing the types of mating according to the genotypes of the pairs, and seeing what are the genotype frequencies among the progenies of the different types of mating. This provides a general method for relating genotype frequencies in successive generations, which will be used in a later chapter. It also provides another proof of the Hardy–Weinberg law; a proof more cumbersome than that already given but showing more clearly how the Hardy–Weinberg frequencies arise from the Mendelian laws of segregation. The procedure is to obtain first the frequencies of all possible mating types according to the frequencies of the genotypes among the parents, and then to obtain the frequencies of genotypes among the progeny of each type of mating according to the Mendelian ratios.

Consider a locus with two alleles, and let the frequencies of genes and genotypes in the parents be, as before:

	Genes		Genotypes		
	A ₁	A ₂	A ₁ A ₁	A ₁ A ₂	A ₂ A ₂
Frequencies	p	q	P	H	Q

There are altogether nine types of mating, and their frequencies when mating is random are found by multiplying together the marginal frequencies as shown in Table 1.3. Since the sex of the parent is irrelevant in this context, some of the types of mating are equivalent, and the number of different types reduces to six. By summation of the frequencies of equivalent types, we obtain the frequencies of mating types in the first two columns of Table 1.4. Now we have to consider the genotypes of offspring produced by each type of mating, and find the frequency of each genotype in the total progeny, assuming, of course, that all types of mating are equally fertile and all genotypes equally viable. This is done in the right-hand side of Table 1.4. Thus, for example, matings of the type $A_1A_1 \times A_1A_1$ produce only A_1A_1 offspring. So, of the total progeny, a proportion P^2 are A_1A_1 genotypes derived from this type of mating. Similarly, one-quarter of the offspring of $A_1A_2 \times A_1A_2$ matings are A_1A_1 . So this type of mating, which has a frequency of H^2 , contributes a proportion $\frac{1}{4}H^2$ of the total A_1A_1 progeny. To find the frequency of each genotype in the total progeny we add the frequencies contributed by each type of mating. The sums, after simplification, are given at the foot of Table 1.4, and from the identity given in equation [1.1] they are seen to be equal to p^2 , $2pq$, and q^2 . These are the Hardy-Weinberg equilibrium frequencies, and we have shown that they are attained by one generation of random mating, irrespective of the genotype frequencies among the parents.

Table 1.3

Genotype and frequency of male parent	Genotype and frequency of female parent		
	A_1A_1	A_1A_2	A_2A_2
	P	H	Q
A_1A_1	P	P^2	PH
A_1A_2	H	PH	H^2
A_2A_2	Q	PQ	HQ
			Q^2

Table 1.4

Mating		Genotype and frequency of progeny		
Type	Frequency	A_1A_1	A_1A_2	A_2A_2
$A_1A_1 \times A_1A_1$	P^2	P^2	—	—
$A_1A_1 \times A_1A_2$	$2PH$	PH	PH	—
$A_1A_1 \times A_2A_2$	$2PQ$	—	$2PQ$	—
$A_1A_2 \times A_1A_2$	H^2	$\frac{1}{4}H^2$	$\frac{1}{2}H^2$	$\frac{1}{4}H^2$
$A_1A_2 \times A_2A_2$	$2HQ$	—	HQ	HQ
$A_2A_2 \times A_2A_2$	Q^2	—	—	Q^2
Sums		$(P + \frac{1}{2}H)^2$	$2(P + \frac{1}{2}H)(Q + \frac{1}{2}H)$	$(Q + \frac{1}{2}H)^2$
=		p^2	$2pq$	q^2

Multiple alleles

When there are more than two alleles at a locus the genotype frequencies are determined by the gene frequencies in exactly the same way as with two alleles. If A_1 and A_2 are any two of the alleles and they have frequencies q_1 and q_2 then the genotype frequencies under Hardy–Weinberg equilibrium are as follows:

Genotype		
A_1A_1	A_1A_2	A_2A_2
Frequency: q_1^2	$2q_1q_2$	q_2^2

These frequencies are also attained by one generation of random mating.

If all the alleles are co-dominant, so that all the genotypes are recognizable in the phenotypes, then the gene frequencies can be estimated from the phenotypes simply by counting. If, however, one or more alleles are recessive, then gene frequencies cannot be obtained by counting the alleles. For example, in the human ABO blood group system the O-allele is recessive to both A and B, so that the A blood group (phenotype) is made up of two genotypes, AA and AO, and the B group of BB and BO. The gene frequencies have to be estimated by maximum-likelihood methods, as described, for example, by Weir (1990).

Sex-linked genes

With sex-linked genes the situation is rather more complex than with autosomal genes. The relationship between gene frequency and genotype frequency in the homogametic sex is the same as with an autosomal gene, but the heterogametic sex has only two genotypes and each individual carries only one gene instead of two. For this reason two-thirds of the sex-linked genes in the population are carried by the homogametic sex and one-third by the heterogametic. For the sake of brevity the heterogametic sex will be referred to as male. Consider two alleles, A_1 and A_2 , with frequencies p and q , and let the genotypic frequencies be as follows:

Females			Males	
A_1A_1	A_1A_2	A_2A_2	A_1	A_2
Frequency: P	H	Q	R	S

The frequency of A_1 among the females is then $p_f = P + \frac{1}{2}H$, and the frequency among the males is $p_m = R$. The frequency of A_1 in the whole population is

$$\begin{aligned}\bar{p} &= \frac{2}{3}p_f + \frac{1}{3}p_m \\ &= \frac{1}{3}(2p_f + p_m) \\ &= \frac{1}{3}(2P + H + R)\end{aligned}\quad \left. \right\} \quad \dots [1.4]$$

Now, if the gene frequencies among males and among females are different, the population is not in equilibrium. The gene frequency in the population as a whole does not change, but its distribution between the two sexes oscillates as the population approaches equilibrium. The reason for this can be seen from the following

consideration. Males get their sex-linked genes only from their mothers; therefore p_m is equal to p_f in the previous generation. Females get their sex-linked genes equally from both parents; therefore p_f is equal to the mean of p_m and p_f in the previous generation. Using primes to indicate the progeny generation, we have

$$\begin{aligned} p'_m &= p_f \\ p'_f &= \frac{1}{2}(p_m + p_f) \end{aligned}$$

The difference between the frequencies in the two sexes is

$$\begin{aligned} p'_f - p'_m &= \frac{1}{2}(p_m + p_f) - p_f \\ &= -\frac{1}{2}(p_f - p_m). \end{aligned}$$

i.e. half the differences in the previous generation, but in the other direction. Therefore the distribution of the genes between the two sexes oscillates, but the difference is halved in successive generations and the population rapidly approaches an equilibrium in which the frequencies in the two sexes are equal. Figure 1.2 illustrates the approach to equilibrium with a gene frequency of 2/3, when the population is started by mixing females of one sort (all A_1A_1) with males of another sort (all A_2A_2) and letting them breed at random.

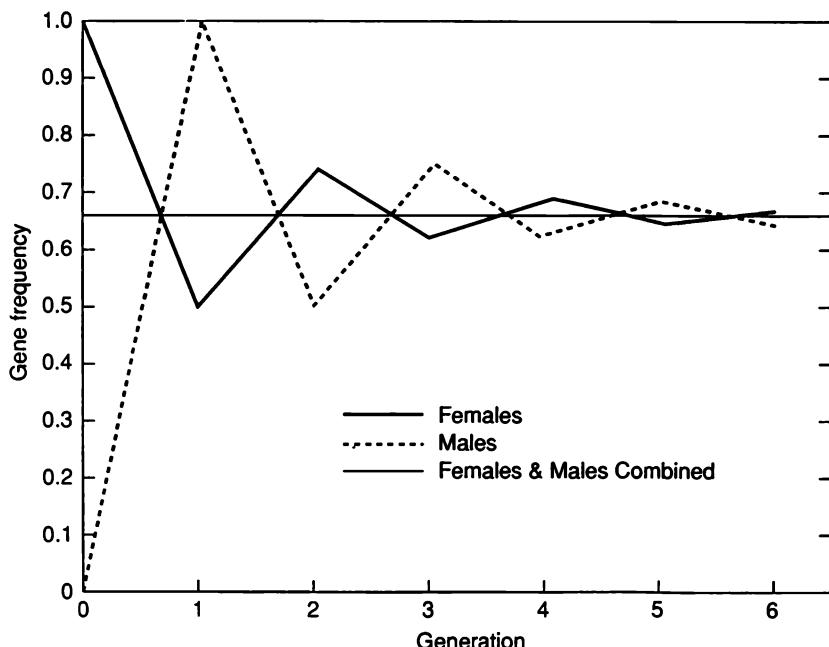


Fig. 1.2. Approach to equilibrium under random mating for a sex-linked gene, showing the gene frequency among females, among males, and in the two sexes combined. The population starts with females all of one sort ($q_f = 1$), and males all of the other sort ($q_m = 0$).

Example 1.5

Searle (1949) gives the frequencies of a number of genes in a sample of cats in London. The animals examined were sent to clinics for destruction; they were therefore not necessarily a random sample. Among the genes studied was the sex-linked gene formerly known as ‘yellow’ but now called ‘orange’ (O). All three genotypes in females are recognizable, the heterozygote being ‘tortoiseshell’ or ‘calico’. The data were tested against the Hardy–Weinberg expectations, to see particularly if there was any evidence of non-random mating. The first test is to see whether the gene frequency is the same in the two sexes. Then the genotypes in females are tested against the Hardy–Weinberg law in the same way as was done in Example 1.4. The numbers in each phenotypic class are shown in the table, with the gene frequencies calculated from them. The gene frequency is a little higher in males, but not significantly so. There is therefore no reason so far to think the population was not in equilibrium. The appropriate gene frequency for calculating the expected genotype frequencies in females is taken, for simplicity, to be the gene frequency observed in females. The expectations, calculated in the same way as in Example 1.4, are given in the table. The numbers observed do not agree very well with expectation, but with the small expected numbers the discrepancy is only doubtfully significant. The discrepancy, if real, might possibly have been due to non-random mating, but it might also have been due to human preferences for the colours having biased the sample and made it unrepresentative of the breeding population. For a more extensive analysis and discussion of cat populations, see Metcalfe and Turner (1971).

<i>Numbers of individuals</i>							
	<i>Females</i>				<i>Males</i>		
	++	+O	OO	Total	+	O	Total
Observed	277	54	7	338	311	42	353
Expected	273.4	61.2	3.4	338			
	$\chi^2_{[1]} = 4.6$; $P = 0.04$						
<i>Numbers of genes</i>							
	+	O	Total		<i>Frequencies of O-gene</i>		
	+	O	Total		q		
in females	608	68	676		0.101		
in males	311	42	353		0.119		

More than one locus

The attainment of the equilibrium in genotype frequencies after one generation of random mating is true of all autosomal loci considered separately. But it is not true of the genotypes with respect to two or more loci considered jointly. To illustrate the point, suppose there were two populations, one consisting entirely of $A_1A_1B_1B_1$ genotypes and the other entirely of $A_2A_2B_2B_2$ genotypes. Suppose that these two populations were mixed, with equal numbers of each sex, and allowed to mate at random. With two alleles at each of two loci there are nine possible genotypes, but

only three of these would appear in the first-generation progeny, the two original double homozygotes and the double heterozygote. There would be complete association between the traits determined by the two loci, and the two traits would appear to be determined by a single gene difference. With continued random mating the missing genotypes would appear in subsequent generations, but not immediately at their equilibrium frequencies, and the initial association between the traits would be progressively reduced. If the two loci were linked, the attainment of equilibrium frequencies would take longer because the appearance of the missing genotypes depends on recombination between the two loci. Disequilibrium with respect to two or more loci is called *gametic phase disequilibrium*, or *linkage disequilibrium*, irrespective of whether the loci are linked or not. Disequilibrium can arise from intermixture of populations with different gene frequencies, or from chance in small populations. Disequilibrium can also be produced, and maintained, by selection favouring one combination of alleles over another. The rate at which a random breeding population approaches equilibrium can be deduced as follows.

Table 1.5

Genes	A_1	A_2	B_1	B_2
Gene frequencies	p_A	q_A	p_B	q_B
Gametic types	A_1B_1	A_1B_2	A_2B_1	A_2B_2
Frequencies, equilibrium	p_Ap_B	p_Aq_B	q_Ap_B	q_Aq_B
Frequencies, actual	r	s	t	u
Difference from equilibrium	$+D$	$-D$	$-D$	$+D$

We first need a measure of the amount of disequilibrium. This is best expressed in terms of the frequencies of gametic types, rather than of zygotic genotypes. Consider two loci, each with two alleles, and gene frequencies as shown in Table 1.5. There are then four types of gamete. The population is in equilibrium if the gametes contain random combinations of the genes. The gametic frequencies at equilibrium therefore depend only on the gene frequencies, and are as shown in the table. Let the actual, non-equilibrium, frequencies be r , s , t , and u , as shown. Each of these differs from the equilibrium frequency by an amount D , two gametic types having a positive, and two a negative, deviation. The value of D for each gametic type is necessarily the same, except for the sign. The amount of disequilibrium is measured by D . The disequilibrium can be expressed by reference to genotypes by comparing the frequencies of coupling and of repulsion double heterozygotes. The genotype A_1B_1/A_2B_2 can be called a coupling heterozygote, whether the two loci are linked or not. Its frequency is $2ru$. The repulsion heterozygote is A_1B_2/A_2B_1 and its frequency is $2st$. If the population is in equilibrium, these two genotypes have equal frequencies. The relationship with D is

$$D = ru - st$$

Thus D is equal to half the difference in frequency between coupling and repulsion heterozygotes.

Example 1.6

Whole chromosomes of *Drosophila melanogaster* can be sampled from individuals in a natural population, and made completely homozygous by crossing to stocks containing dominantly marked balancer chromosomes that suppress recombination. The genotype for any number of loci on a chromosome is called a haplotype, since the chromosome is essentially one possible haploid gamete type. A total of 47 second chromosomes were sampled from a natural population in Raleigh, North Carolina, and assessed for restriction fragment length variation in the region of the *scabrous* gene (Lai *et al.*, 1994). The following data are numbers of chromosomes of each haplotype for two *PstI* restriction sites. *PstI*(−12.0) (Locus A) is located 12 kb 5' from the origin of transcription of the *scabrous* gene, and *PstI*(5.8) (Locus B) is 5.8 kb 3' from the origin of transcription. '+' indicates presence and ‘−’ absence of a site. We wish (i) to determine whether the two restriction sites are in linkage (dis)equilibrium, and (ii) to calculate D , the coefficient of linkage disequilibrium.

<i>Haplotype</i>		<i>Observed number</i>	<i>Observed frequency</i>	<i>Expected frequency</i>	<i>Expected number</i>
A	B				
+	+	4	0.085	$p_A p_B = 0.06$	2.8
+	−	4	0.085	$p_A q_B = 0.11$	5.2
−	+	13	0.277	$q_A p_B = 0.30$	14.1
−	−	26	0.553	$q_A q_B = 0.53$	24.9

(i) Using the terminology of Table 1.5, let p indicate the frequency of the + allele at each locus, and q denote the frequency of the − allele. Estimates of the gene frequencies at the two restriction site loci are $p_A = 8/47 = 0.17$; $q_A = 39/47 = 0.83$; $p_B = 17/47 = 0.36$; and $q_B = 30/47 = 0.64$. Expected haplotype frequencies and numbers are then as shown on the right of the table.

The expected numbers match the observed numbers very well, and the differences are not statistically significant ($\chi^2_{[1]} = 0.93$; $P > 0.5$). The sample therefore shows no evidence of the population being in linkage disequilibrium for these restriction sites. The sites are separated by 17.8 kb, which illustrates that very tightly linked loci are not necessarily in linkage disequilibrium.

(ii) Observed haplotype frequencies are given above, from which $D = ru - st = (0.085)(0.553) - (0.085)(0.277) = 0.023$. The absolute value of D depends on gene frequency. The absolute range of D is from −0.25 to 0.25; these values occur if $p_A = q_A = p_B = q_B = 0.5$, and either $r = u = 0$ and $s = t = 0.5$ ($D = -0.25$), or $s = t = 0$ and $r = u = 0.5$ ($D = 0.25$). If gene frequencies are not exactly equal, the absolute value of D will be within this range. Therefore D is often expressed as D/D_{MAX} , where D_{MAX} is the largest numerical value D could be, given the observed gene frequencies. From Table 1.5, $s = p_A q_B - D \geq 0$, and $t = q_A p_B - D \geq 0$, so D must be $\leq p_A q_B$ and $\leq q_A p_B$. Therefore D_{MAX} is the smaller of $p_A q_B$ or $q_A p_B$. For this example D_{MAX} is 0.11, so $D/D_{\text{MAX}} = 0.21$. The calculated value of D is 21 per cent of its maximal value, which is not trivial. Large sample sizes are necessary to detect linkage disequilibrium, particularly when gene frequencies are extreme.

When a population in linkage disequilibrium mates at random, the amount of disequilibrium is progressively reduced with each succeeding generation. The rate at which this happens depends on the frequency of gametic types in two successive generations. This is perhaps easiest to visualize if the two loci are thought of as

being linked on the same chromosome. The disequilibrium D in the progeny generation can be obtained from the frequency of any of the four gametic types, so let us consider only the A_1B_1 type. This can appear in the progeny gametes in two ways. First, it can be produced as a non-recombinant from the genotype A_1B_1/A_xB_x , the subscript x meaning that either of the two alleles can be present. The frequency with which A_1B_1 is produced in this way is $r(1 - c)$, r being the frequency of A_1B_1 in the parental gametes and c the recombination frequency. Or, second, it can be produced as a recombinant from the genotype A_1B_x/A_xB_1 . The frequency of the A_1B_x chromosome is p_A and that of the A_xB_1 chromosome is p_B . So the frequency with which A_1B_1 arises in this way is $p_A p_B c$. Therefore the frequency of A_1B_1 in the progeny gametes is

$$r' = r(1 - c) + p_A p_B c$$

and the disequilibrium in the progeny generation is

$$\begin{aligned} D' &= r' - p_A p_B \\ &= r(1 - c) - p_A p_B (1 - c) \\ &= (r - p_A p_B)(1 - c) \\ &= D(1 - c) \end{aligned}$$

If we take the process one generation further we get

$$D'' = D'(1 - c) = D(1 - c)^2$$

Thus, after any number t of generations, the disequilibrium is given by

$$D_t = D_0(1 - c)^t \quad \dots [1.5]$$

The loci do not have to be linked to be in disequilibrium. With unlinked loci $c = \frac{1}{2}$ and the amount of disequilibrium is halved by each generation of random mating. With linked loci the disequilibrium disappears more slowly. Figure 1.3 shows how the disequilibrium is reduced over 12 generations, with different degrees of linkage.

The approach to equilibrium given by the above equation applies equally to the disequilibrium of any number of loci considered jointly, provided $(1 - c)$ is defined as the probability of a gamete passing through a generation without recombination between any of the loci. The larger the number of loci the smaller is the probability of no recombination; with two unlinked loci it is $\frac{1}{2}$, with three $\frac{1}{4}$, and with four $\frac{1}{8}$. Thus the multilocus disequilibrium decays faster than the 2-locus, which soon comes to dominate the total disequilibrium among a number of loci. A practical consequence of this is that when a number of loci are available for study, disequilibrium is more likely to be found with pairs of loci than with larger numbers considered jointly. For details of three loci see Crow and Kimura (1970) and for methods of estimation see Weir and Cockerham (1979).

Linkage disequilibrium is commonly found in natural populations between loci for which recombination has not had sufficient time to dissipate the initial disequilibrium, for instance between disease loci and tightly linked RFLPs. Finding complete association (complete linkage disequilibrium) between a polymorphic site and a disease gene is indeed a first step to characterizing the disease gene at the molecular level, and can be very useful for genetic counselling. However, close linkage does

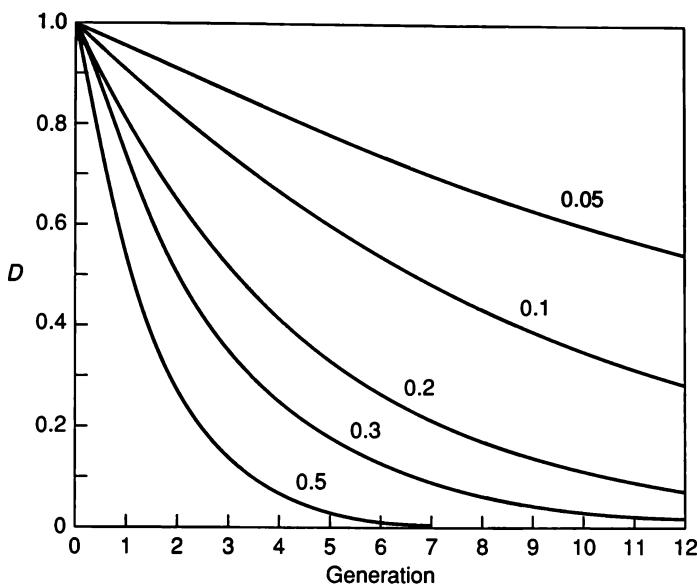


Fig. 1.3. Approach to equilibrium under random mating of two loci, considered jointly. The graphs show the amount of disequilibrium, D , relative to the disequilibrium in generation 0. The five graphs refer to different degrees of linkage between the two loci, as indicated by the recombination frequency shown alongside each graph. The graph marked 0.5 refers to unlinked loci.

not automatically mean the loci will be in linkage disequilibrium. Even closely linked loci may be in linkage equilibrium (see Example 1.6); and completely unlinked loci can be in linkage disequilibrium if, for example, two populations with different gene frequencies at the loci are mixed, as shown above. Thus knowledge of the disequilibrium in a population can tell us something about the breeding history of the population, which single loci cannot do because they come to Hardy–Weinberg frequencies after a single generation of random mating (see Crow, 1986, p. 23). Other causes of linkage disequilibrium are chance associations between alleles of different loci in small populations, and selection for particular allelic combinations. Linkage disequilibrium has consequences which will have to be taken into account in later chapters, particularly in connection with selection for quantitative characters.

Non-random mating

There are two distinct forms of non-random mating. The first is when mated individuals are related to each other by ancestral descent. This tends to increase the frequencies of homozygotes at all loci. Its effect will be described in Chapter 3. The second is when individuals tend to mate preferentially with respect to their genotypes at any particular locus under consideration. This form of non-random mating is dealt with briefly here.

Assortative mating

If mated pairs are of the same phenotype more often than would occur by chance, this is called *assortative mating*, and if less often, it is called *disassortative mating*.

To the extent that the phenotype reflects the genotype, assortative or disassortative mating affects the genotype frequencies. The effects are described by Crow and Kimura (1970) and will be only briefly outlined here. Assortative mating is of some importance in human populations, where it occurs with respect to stature, intelligence, and other characters. These, however, are not single gene differences such as can be discussed in the present context. Disassortative mating is widespread in the self-sterility systems of plants.

The consequences of assortative mating with a single locus can be deduced from Table 1.4 by appropriate modification of the frequencies of the types of mating to allow for the increased frequency of matings between like phenotypes. The effect on the genotype frequencies among the progeny is to increase the frequencies of homozygotes and reduce that of heterozygotes. In effect the population becomes partially subdivided into two groups, mating taking place more frequently within than between the groups. If assortative mating is continued in successive generations, the population approaches an equilibrium at which the genotype frequencies remain constant.

Disassortative mating has consequences that are, in general, opposite to those of assortative mating: it leads to an increase of heterozygotes and a reduction of homozygotes. Disassortative mating, however, usually has the additional consequence of changing the gene frequency. If mating is predominantly between unlike phenotypes, then the rarer phenotype has a better chance of success in mating than has the commoner phenotype. Consequently the rarer alleles are favoured, and the gene frequency changes toward intermediate values at which the phenotypes are equal in frequency. A familiar example of disassortative mating is the bisexual mode of reproduction, which leads immediately to a gene, or chromosome, frequency of 0.5. Self-sterility mechanisms of plants are based on multiple alleles, and the favouring of the rarer alleles results in the coexistence of a large number of alleles, all at more or less equal frequencies.

Problems

- 1.1 The following numbers of the human M-N blood groups were recorded in a sample of American Whites.

M	MN	N
1787	3039	1303

- (1) What are the genotype frequencies observed in this sample?
- (2) What are the gene frequencies?
- (3) With the gene frequencies observed, what are the genotype frequencies expected from the Hardy-Weinberg law?
- (4) How well do the observed frequencies agree with the expectation?

Data from Wiener, A.S. (1943) quoted by Stern, C. (1973) *Principles of Human Genetics*. Freeman, San Francisco. [Solution 1]

- 1.2 About 30 per cent of people do not recognize the bitter taste of phenyl-thio-carbamate (PTC). Inability to taste it is due to a single autosomal recessive gene. What is the frequency of the non-tasting gene, assuming the population to be in Hardy-Weinberg equilibrium?

[Solution 11]

1.3 Albinism occurs with a frequency of about 1 in 20,000 in European populations. Assuming it to be due to a single autosomal recessive gene, and assuming the population to be in Hardy–Weinberg equilibrium, what proportion of people are carriers? Only an approximate answer is needed.

[Solution 21]

1.4 As an exercise in algebra, work out the gene frequency of a recessive mutant in a random-breeding population that would result in one-third of normal individuals being carriers.

[Solution 31]

1.5 Three allelic variants, A, B, and C, of the red cell acid phosphatase enzyme were found in a sample of 178 English people. All genotypes were distinguishable by electrophoresis, and the frequencies in the sample were

Genotype	AA	AB	BB	AC	BC	CC
Frequency (%)	9.6	48.3	34.3	2.8	5.0	0.0

What are the gene frequencies in the sample? Why were no CC individuals found?

Data from Spencer, N., et al. (1964) *Nature*, 201, 299–300.

[Solution 41]

1.6 About 7 per cent of men are colour-blind in consequence of a sex-linked recessive gene. Assuming Hardy–Weinberg equilibrium, what proportion of women are expected to be (1) carriers, and (2) colour-blind? (3) In what proportion of marriages are both husband and wife expected to be colour-blind?

[Solution 51]

1.7 Sine oculis (*so*) and cinnabar (*cn*) are two autosomal recessive genes in *Drosophila melanogaster*. They are very closely linked and can be treated as if they were alleles at one locus. The ‘heterozygote’, *so/cn*, is wild-type and is distinguishable from both homozygotes; (*so/so* has no eyes; *cn/cn* has white eyes if the stock is made homozygous for another eye-colour mutant, brown, *bw*). In a class experiment 4 males and 4 females of an *so/so* stock were put in a vial together with 16 males and 16 females from a *cn/cn* stock and allowed to mate. There were 20 such vials. The total count of progeny, classified by genotype, was as follows.

<i>so/so</i>	<i>so/cn</i>	<i>cn/cn</i>
135	359	947

How do these numbers differ from the Hardy–Weinberg expectations? Suggest a reason for the discrepancy.

[Solution 61]

1.8 Suppose that *Drosophila* cultures are set up in vials as described in Problem 1.7, but this time with a gene frequency of 0.5. This is done by putting 10 males and 10 females of each stock in each vial. The supply of *so/so* females ran out and only 4 were left for the last vial. So, to preserve the intended gene frequency and numbers of parents, this vial was made up as follows: 16 ♂♂ + 4 ♀♀ of *so/so* with 4 ♂♂ + 16 ♀♀ of *cn/cn*. The student who got this vial was a bit surprised by what he found. What genotype frequencies would you expect in the progeny?

[Solution 71]

1.9 Prove that when there are any number of alleles at a locus the total frequency of heterozygotes is greatest when all alleles have the same frequency. What is then the total frequency of heterozygotes?

[Solution 81]

- 4 1.10 Suppose that a strain of genotype AA BB is mixed with another strain of genotype aa bb, with equal numbers of the two strains and equal numbers of males and females, which mate at random. Call this generation of parents generation 0. Subsequent generations also mate at random and there are no differences of fertility or viability among the genotypes. What will be the frequency of the genotype AA bb in the progeny of generation 2, i.e. after two generations of recombination, if the two loci are (1) unlinked, (2) linked with a recombination frequency of 20 per cent? [Solution 91]

1.11 How will the solutions of Problem 1.10 be altered if the two strains are crossed by taking males of one strain and females of the other? [Solution 101]

2 Changes of Gene Frequency

We have seen that a large random-mating population is stable with respect to gene frequencies and genotype frequencies, in the absence of agencies tending to change its genetic properties. We can now proceed to a study of the agencies through which changes of gene frequency, and consequently of genotype frequencies, are brought about. There are two sorts of process: *systematic processes*, which tend to change the gene frequency in a manner predictable both in amount and in direction; and the *dispersive process*, which arises in small populations from the effects of sampling, and is predictable in amount but not in direction. In this chapter we are concerned only with the systematic processes, and we shall consider only large random-mating populations in order to exclude the dispersive process from the picture. There are three systematic processes: *migration*, *mutation*, and *selection*. We shall study these separately at first, assuming that only one process is operating at a time, and then we shall see how the different processes interact.

Migration

The effect of migration is very simply dealt with and need not concern us much here, though we shall have more to say about it later, in connection with small populations. Let us suppose that a large population consists of a proportion m of new immigrants in each generation, the remainder, $1 - m$, being natives. Let the frequency of a certain gene be q_m among the immigrants and q_0 among the natives. Then the frequency of the gene in the mixed population, q_1 , will be

$$\begin{aligned} q_1 &= mq_m + (1 - m)q_0 \\ &= m(q_m - q_0) + q_0 \end{aligned} \quad \dots [2.1]$$

The change of gene frequency, Δq , brought about by one generation of immigration is the difference between the frequency before immigration and the frequency after immigration. Therefore

$$\begin{aligned} \Delta q &= q_1 - q_0 \\ &= m(q_m - q_0) \end{aligned} \quad \dots [2.2]$$

Thus the rate of change of gene frequency in a population subject to immigration depends, as must be obvious, on the immigration rate and on the difference of gene frequency between immigrants and natives.

Mutation

The effect of mutation on the genetic properties of the population differs according to whether we are concerned with a mutational event so rare as to be virtually unique, or with a mutational step that recurs repeatedly. The first produces no permanent change in a large population, whereas the second does.

Non-recurrent mutation

Consider first a mutational event that gives rise to just one representative of the mutated gene or chromosome in the whole population. This sort of mutation is of very little importance as a cause of change of gene frequency, because the product of a unique mutation has only a very small chance of surviving in a large population. The original mutated gene is present in a heterozygote and its chance of being lost in the next generation is one-half. If it survives, it may be represented by one or more copies, but each copy has only a one-half chance of surviving to the third generation. The loss is permanent, so the chance of indefinite survival is very small indeed, and is zero in an infinitely large population. Because real populations are not infinitely large, unique mutations must be expected very occasionally to survive indefinitely and lead to a change of gene frequency. More will be said about this later in this chapter and in Chapter 4.

Recurrent mutation

It is with the second type of mutation – recurrent mutation – that we are chiefly concerned as an agent for causing change of gene frequency, and in a large population the frequency of a mutant gene is never so low that complete loss can occur from sampling. We have, then, to find out what is the effect of this ‘pressure’ of mutation on the gene frequency in the population.

Suppose gene A_1 mutates to A_2 with a frequency u per generation. (u is the proportion of all A_1 genes that mutate to A_2 between one generation and the next.) If the frequency of A_1 in one generation is p_0 , the frequency of newly mutated A_2 genes in the next generation is up_0 . So the new gene frequency of A_1 is $p_0 - up_0$ and the change of gene frequency is $-up_0$. Now consider what happens when the genes mutate in both directions. Suppose for simplicity that there are only two alleles, A_1 and A_2 , with initial frequencies p_0 and q_0 . A_1 mutates to A_2 at a rate u per generation, and A_2 mutates to A_1 at a rate v . Then after one generation there is a gain of A_2 genes equal to up_0 due to mutation in one direction, and a loss equal to vq_0 due to mutation in the other direction. Stated in symbols, we have the situation:

Mutation rate	A_1	$\frac{u}{v}$	A_2
Initial gene frequencies	p_0		q_0

Then the change of gene frequency in one generation is

$$\Delta q = up_0 - vq_0 \quad \dots [2.3]$$

It is easy to see that this situation leads to an equilibrium in gene frequency at which no further change takes place, because if the frequency of one allele increases fewer of the other are left to mutate in that direction and more are available to mutate in

the other direction. The point of equilibrium can be found by equating the change of frequency, Δq , to zero. Thus at equilibrium

$$\begin{aligned} pu &= qv \\ \text{or} \quad \frac{p}{q} &= \frac{v}{u} \\ \text{and} \quad q &= \frac{u}{u+v} \end{aligned} \quad \left. \right\} \dots [2.4]$$

Two conclusions can be drawn from the effect of mutation on gene frequency. Mutation rates are generally very low – about 10^{-5} or 10^{-6} per generation for most loci in most organisms. This means that between about 1 in 100,000 and 1 in 1,000,000 gametes carry a newly mutated allele at any particular locus. With normal mutation rates, therefore, mutation alone can produce only very slow changes of gene frequency; on an evolutionary time-scale they might be important, but they could scarcely be detected by experiment except with microorganisms. The second conclusion concerns the equilibrium between mutation in the two directions. Studies of reverse mutation (from mutant to wild type) show that it is usually much less frequent than forward mutation (from wild type to mutant), (Muller and Oster, 1957; Schlager and Dickie, 1971). If reverse mutation were one-tenth as frequent as forward mutation, the equilibrium gene frequency resulting from mutation alone would be 0.1 of the wild type allele and 0.9 of the mutant; in other words the ‘mutant’ would be the common form and the ‘wild type’ the rare form. Since this is not the situation found in natural populations, it is clear that the frequencies of such genes are not the product of mutation alone. We shall see in the next section that the rarity of mutant alleles is attributable to selection.

Selection

Hitherto we have supposed that all individuals in the population contribute equally to the next generation. Now we must take account of the fact that individuals differ in viability and fertility, and that they therefore contribute different numbers of offspring to the next generation. The contribution of offspring to the next generation is called the *fitness* of the individual, or sometimes the *adaptive value*, or *selective value*. If the differences of fitness are in any way associated with the presence or absence of a particular gene in the individual’s genotype, then *selection* operates on that gene. When a gene is subject to selection its frequency in the offspring is not the same as in the parents, since parents of different genotypes pass on their genes unequally to the next generation. In this way selection causes a change of gene frequency, and consequently also of genotype frequency. The change of gene frequency resulting from selection is more complicated to describe than that resulting from mutation, because the differences of fitness that give rise to the selection are an aspect of the phenotype. We therefore have to take account of the degree of dominance shown by the genes in question. Dominance, in this connection, means dominance with respect to fitness, and this is not necessarily

2 Changes of gene frequency

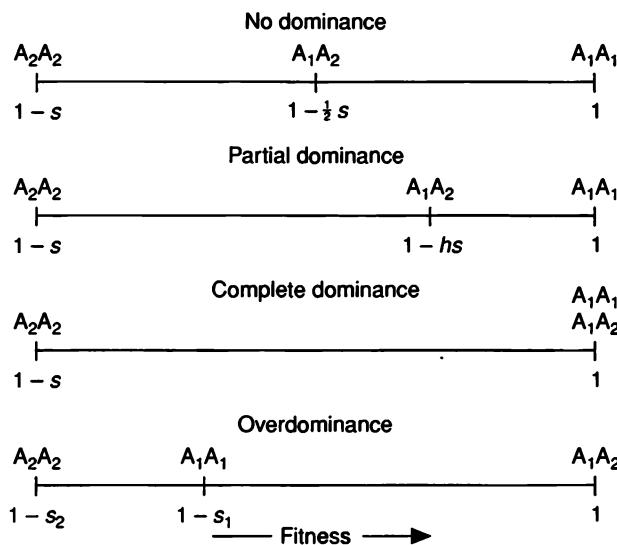


Fig. 2.1. Degrees of dominance with respect to fitness.

the same as the dominance with respect to the main visible effects of the gene. Most mutant genes, for example, are completely recessive to the wild type in their visible effects, but this does not necessarily mean that the heterozygote has a fitness equal to that of the wild-type homozygote. The meaning of the different degrees of dominance with which we shall deal is illustrated in Fig. 2.1.

It is most convenient to think of selection acting against the gene in question, in the form of selective elimination of one or other of the genotypes that carry it. This may operate either through reduced viability or through reduced fertility in its widest sense, including mating ability, or through both. In the life-cycle of individuals, selection acts first through viability, then through fertility. We therefore have to deduce the change of gene frequency from the zygote stage of one generation to the zygote stage of the progeny generation. Gene frequencies cannot be observed in zygotes, so there are practical difficulties in deducing the selective forces from observed changes of gene frequency, but we shall return to these later. The strength of the selection is expressed as the *coefficient of selection*, s , which is the proportionate reduction in the gametic contribution of a particular genotype compared with a standard genotype, usually the most favoured. The contribution of the favoured genotype is taken to be 1, and the contribution of the genotype selected against is then $1 - s$. This expresses the fitness of one genotype relative to the other. Suppose, for example, that the coefficient of selection is $s = 0.1$; the fitness is then 0.9, which means that for every 100 zygotes produced by the favoured genotype, only 90 are produced by the genotype selected against. Fitness, defined in this way as the proportionate contribution of offspring, should strictly speaking be called *relative fitness*, but it will be referred to as fitness throughout what follows.

The fitness of a genotype with respect to any particular locus is not necessarily the same in all individuals. It depends on the environmental circumstances in which the individual lives, and also on the genotype with respect to genes at other loci.

When we assign a certain fitness to a genotype, this refers to the average fitness of this genotype in the whole population. Though differences of fitness between individuals result in selection being applied to many, perhaps to all, loci simultaneously, we shall limit our attention here to the effects of selection on the genes at a single locus, supposing that the average fitness of the different genotypes remains constant despite the changes resulting from selection applied simultaneously to other loci. The conclusions we shall reach apply equally to natural selection occurring under natural conditions without the intervention of man, and to artificial selection imposed by the breeder or experimenter through his choice of individuals as parents and through the number of offspring he chooses to rear from each parent.

Change of gene frequency under selection

We have first to derive the basic formulae for the change of gene frequency brought about by one generation of selection. Then we can consider what they tell us about the effectiveness of selection. The different conditions of dominance have to be taken account of, but the method is the same for all, and it will be illustrated by reference to the case of complete dominance with selection acting against the recessive homozygote. Table 2.1 shows the genotypes with their Hardy-Weinberg frequencies before selection. A_2A_2 is the recessive homozygote with a coefficient of selection s acting against it. The next line gives the fitness of each genotype. Multiplying the initial frequency by the fitness gives the frequency of each genotype after selection. This is entered as the 'gametic contribution' in order to allow for selection to operate over the whole life-cycle. Note that after selection the total frequency is no longer unity, because there has been a proportionate loss of sq^2 due to the selection. To find the frequency of A_2 gametes produced – and so the frequency of A_2 genes in the progeny – we take the gametic contribution of A_2A_2 individuals plus half that of A_1A_2 individuals and divide by the new total, i.e., we apply equation [1.1]. Thus the new gene frequency is

$$q_1 = \frac{q^2(1-s) + pq}{1 - sq^2}$$

This can be simplified by substituting $p = (1 - q)$. Rearrangement then gives

$$q_1 = \frac{q - sq^2}{1 - sq^2} \quad \dots [2.5]$$

Table 2.1 Selection against a recessive gene.

	<i>Genotypes</i>			
	A_1A_1	A_1A_2	A_2A_2	<i>Total</i>
Initial frequencies	p^2	$2pq$	q^2	1
Coefficient of selection	0	0	s	
Fitness	1	1	$1 - s$	
Gametic contribution	p^2	$2pq$	$q^2(1 - s)$	$1 - sq^2$

The change of gene frequency, Δq , resulting from one generation of selection is

$$\Delta q = q_1 - q$$

Substituting for q_1 from equation [2.5], and after some rearrangement, this becomes

$$\Delta q = -\frac{sq^2(1-q)}{1-sq^2} \quad \dots [2.6]$$

From this we see that the effect of selection on gene frequency depends not only on the intensity of selection s , but also on the initial gene frequency. But both relationships are somewhat complex, and the examination of their significance will be postponed till after the other situations have been dealt with.

Expressions for the new gene frequency and for the change of gene frequency, with different conditions of dominance, are given in Table 2.2. The general expression (5) in the table allows Δq to be worked out for any degree of dominance with respect to fitness. Two expressions (3 and 4) are given for a completely dominant gene, according to the direction of selection. The first, which was derived above, is for selection against the recessive homozygote. If, in contrast, selection is against the dominant phenotype, Δq is not quite the same. The difference may best be appreciated by considering the effects of total elimination, when $s = 1$. The

Table 2.2 Change of gene frequency by one generation of selection, with different conditions of dominance for fitness, as specified below. The initial gene frequency of A_2 is q .

Initial frequencies and fitness of genotypes			New gene frequency	Change of gene frequency
A_1A_1 p^2	A_1A_2 $2pq$	A_2A_2 q^2	q_1	$\Delta q = q_1 - q$
(1) 1	$1 - \frac{1}{2}s$	$1 - s$	$\frac{q - \frac{1}{2}sq - \frac{1}{2}sq^2}{1 - sq}$	$-\frac{\frac{1}{2}sq(1-q)}{1 - sq}$
(2) 1	$1 - hs$	$1 - s$	$\frac{q - hspq - sq^2}{1 - 2hspq - sq^2}$	$-\frac{spq[q + h(p-q)]}{1 - 2hspq - sq^2}$
(3) 1	1	$1 - s$	$\frac{q - sq^2}{1 - sq^2}$	$-\frac{sq^2(1-q)}{1 - sq^2}$
(4) 1 - s	1 - s	1	$\frac{q - sq + sq^2}{1 - s(1 - q^2)}$	$+\frac{sq^2(1-q)}{1 - s(1 - q^2)}$
(5) $1 - s_1$	1	$1 - s_2$	$\frac{q - s_2q^2}{1 - s_1p^2 - s_2q^2}$	$+\frac{pq(s_1p - s_2q)}{1 - s_1p^2 - s_2q^2}$

(1) No dominance; selection against A_2 .

(2) Partial dominance of A_1 ; selection against A_2 .

(3) Complete dominance of A_1 ; selection against A_2 .

(4) Complete dominance of A_1 ; selection against A_1 .

(5) Overdominance; selection against A_1A_1 and A_2A_2 . (Applicable also to any degree of dominance with fitnesses expressed relative to A_1A_2 .)

formula for selection against the dominant phenotype then reduces to $q_1 = 1$, which expresses the fact that if only the recessive homozygotes breed the gene frequency goes to 1 immediately. Total elimination of the recessive homozygote, on the other hand, will leave all of the recessive genes that are present in heterozygotes. The difference between the effects of selection in opposite directions becomes less marked as the value of s decreases. All the forms of selection mentioned so far tend in the end to eliminate one or other allele from the population. Overdominance for fitness, where heterozygotes are superior in fitness, in contrast, tends to maintain both alleles in the population. This form of selection will be given more detailed attention later.

The expressions for Δq in Table 2.2 are rather cumbersome and it is often useful to simplify them by an approximation that is good enough for many purposes. If either the coefficient of selection s , or the gene frequency q , is small, then the denominators of the equations in Table 2.2 become very nearly unity, and we can use the numerators alone as expressions for Δq . Then for selection in either direction we have, with no dominance:

$$\Delta q = \pm \frac{1}{2} sq(1 - q) \text{ (approx.)} \quad \dots [2.7]$$

and with complete dominance:

$$\Delta q = \pm sq^2(1 - q) \text{ (approx.)} \quad \dots [2.8]$$

Effectiveness of selection

We see from the formulae that the effectiveness of selection, i.e., the magnitude of Δq , depends on the initial gene frequency q . The nature of this relationship is best appreciated from graphs showing Δq at different values of q . Figure 2.2 shows these graphs for the cases of no dominance and complete dominance. They also distinguish between selection in the two directions. A value of $s = 0.2$ was chosen for the coefficient of selection because, for reasons given in Chapter 12, this seems to be the right order of magnitude for the coefficient of selection operating on genes concerned with metric characters in laboratory selection experiments. First we may note that with this value of s there is never a great difference in Δq according to the direction of selection. The two important points about the effectiveness of selection that these graphs demonstrate are: (1) selection is most effective at intermediate gene frequencies and becomes least effective when q is either large or small; (2) selection for or against a recessive gene is extremely ineffective when the recessive allele is rare. This is the consequence of the fact, noted earlier, that when a gene is rare it is represented almost entirely in heterozygotes.

Another way of looking at the effect of the initial gene frequency on the effectiveness of selection is to plot a graph showing the course of selection over a number of generations, starting from one or other extreme. Such graphs are shown in Fig. 2.3. They were constructed directly from those of Fig. 2.2, and refer again to a coefficient of selection $s = 0.2$. They show that the change due to selection is at first very slow, whether one starts from a high or low initial gene frequency; it becomes more rapid at intermediate frequencies and falls off again at the end. In the case of a fully dominant gene one is chiefly interested in the frequency of the homozygous recessive genotype, i.e., q^2 . For this reason the graph shows the effect of selection on q^2 instead of on q .

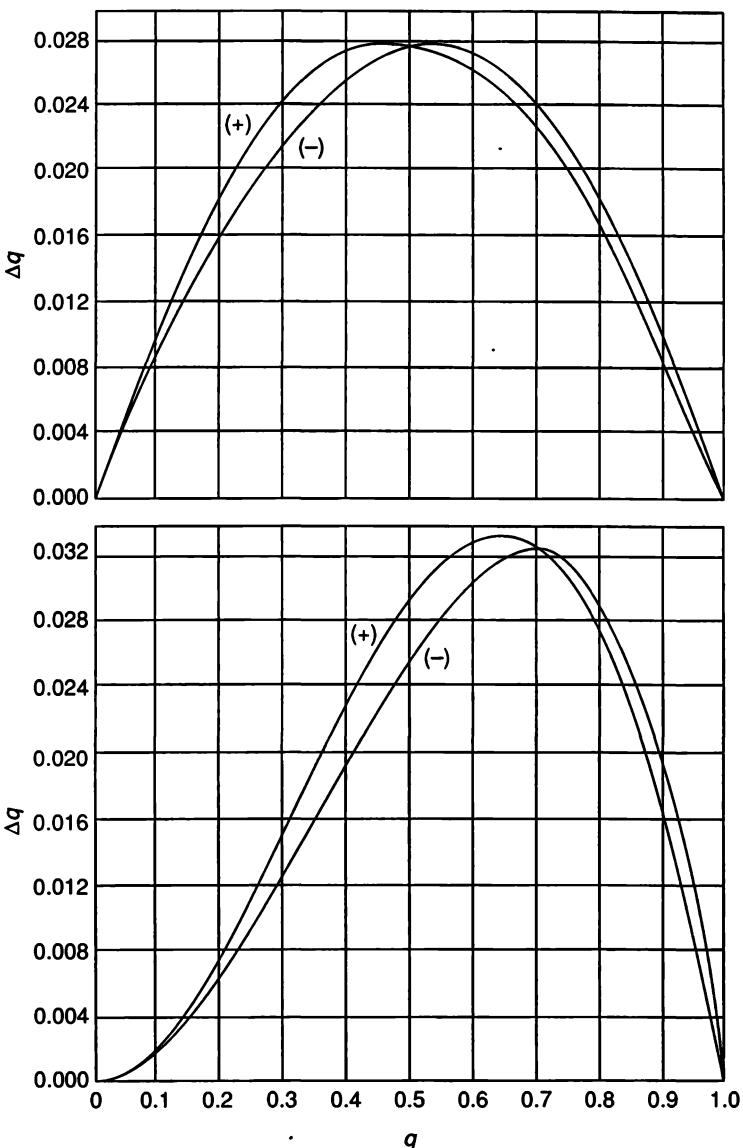


Fig. 2.2. Change of gene frequency, Δq , under selection of intensity $s = 0.2$, at different values of initial gene frequency, q . Upper figure: a gene with no dominance. Lower figure: a gene with complete dominance. The graphs marked $(-)$ refer to selection against the gene whose frequency is q , so that Δq is negative. The graphs marked $(+)$ refer to selection in favour of the gene, so that Δq is positive. (After Falconer, 1954.)

Example 2.1

Figure 2.4 shows the change of gene frequency of an autosomal recessive lethal in *Drosophila melanogaster* described by Wallace (1963). The population was started

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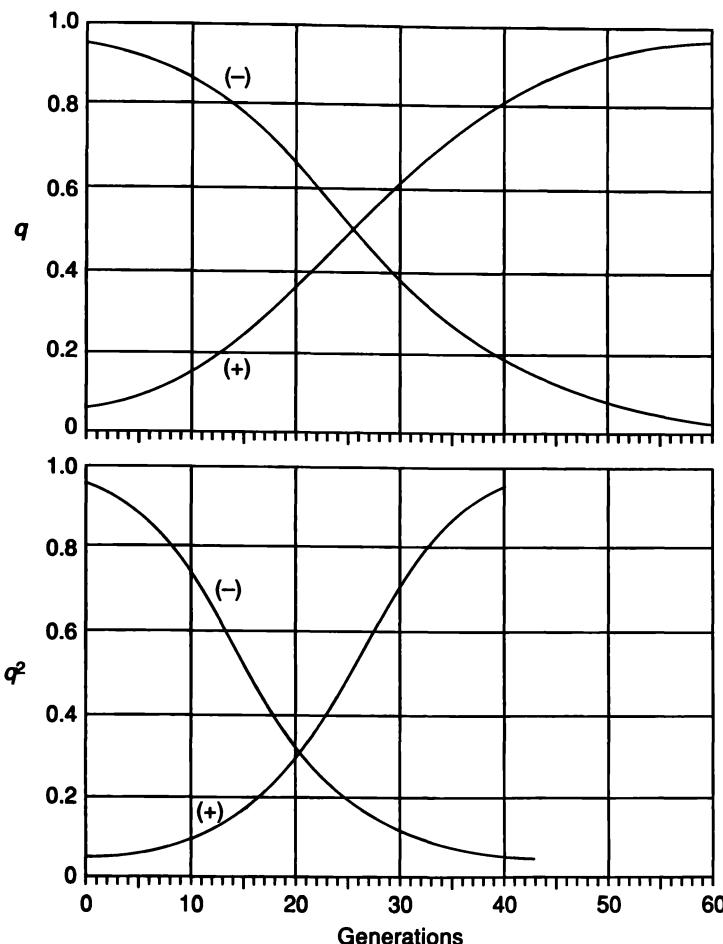


Fig. 2.3. Change of gene frequency during the course of selection from one extreme to the other. Intensity of selection, $s = 0.2$. Upper figure: a gene with no dominance. Lower figure: a gene with complete dominance, q being the frequency of the recessive allele and q^2 that of the recessive homozygote. The graphs marked $(-)$ refer to selection against the gene whose frequency is q , so that q or q^2 decreases. The graphs marked $(+)$ refer to selection in favour of the gene, so that q or q^2 increases. (After Falconer, 1954.)

Example 2.1 continued

from flies that were all heterozygotes, and the gene frequency in generation 0 was consequently $q = 0.5$. The parents of each subsequent generation were a random sample of the surviving progeny of the previous generation. Only heterozygotes and normal homozygotes survived. Heterozygotes were identified by test matings. About 100 to 200 flies were tested in each generation, giving a count of about 200 to 400 genes from which to estimate the gene frequency. The observed gene frequency \pm two standard errors is plotted for each of 10 successive generations.

Expected gene frequencies were calculated for each generation by the formulae for q_1 in Table 2.2. Two expectations were calculated. The first, shown by the

Continued

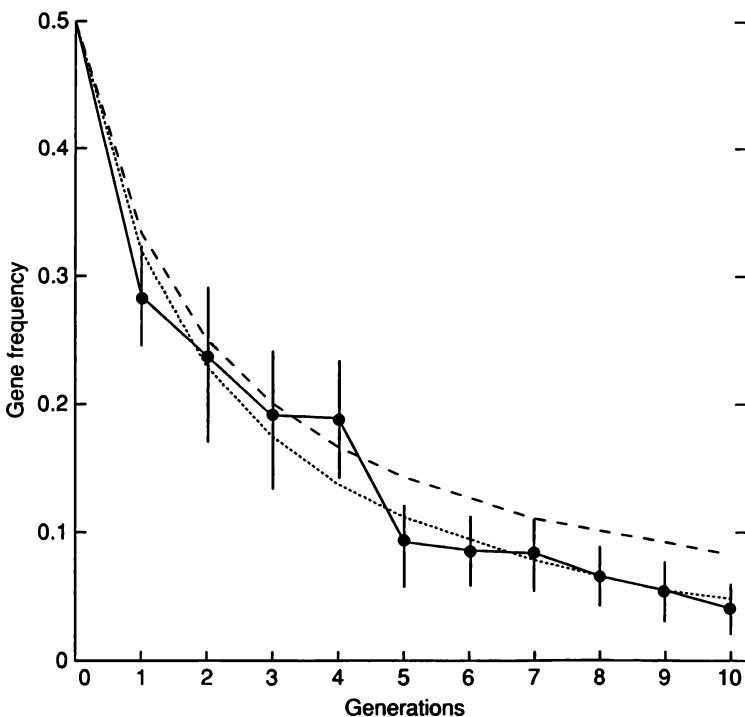


Fig. 2.4. Change of gene frequency under natural selection in the laboratory, as described in Example 2.1. (Adapted from Wallace, 1963.)

Example 2.1 continued

broken line, assumes the lethal to be completely recessive. With $s = 1$, the formula in line (3) of Table 2.2 reduces to $q_1 = q/(1 + q)$. The observed results suggest that the gene frequency was reduced a little faster than would be expected for a completely recessive lethal gene. The second expectation, shown by the dotted line, assumes the fitness of heterozygotes was reduced by 10 per cent. With $s = 1$, the formula in line (2) of Table 2.2 reduces to $q_1 = pq(1 - h)/[p^2 + 2pq(1 - h)]$, and this was evaluated with $h = 0.1$. The results agree well with this expectation.

Number of generations required

How many generations of selection would be needed to effect a specified change of gene frequency? An answer to this question may be required in connection with breeding programmes or proposed eugenic measures. We shall consider only the case of selection against a recessive when elimination of the unwanted homozygote is complete, i.e., $s = 1$. This would apply to natural selection against a recessive lethal, and to artificial selection against an unwanted recessive in a breeding programme. We shall also, for the moment, suppose that there is no mutation. The expression for the new gene frequency after one generation was given in equation [2.5] (and in line (3) of Table 2.2).

Substituting $s = 1$ in this equation and writing $q_0, q_1, q_2, \dots, q_t$ for the gene frequency after 0, 1, 2, ..., t generations of selection, we have

$$q_1 = \frac{q_0}{1 + q_0}$$

and

$$\begin{aligned} q_2 &= \frac{q_1}{1 + q_1} \\ &= \frac{q_0}{1 + 2q_0} \end{aligned}$$

by substituting for q_1 and simplifying. So in general

$$q_t = \frac{q_0}{1 + tq_0} \quad \dots [2.9]$$

and the number of generations, t , required to change the gene frequency from q_0 to q_t is

$$\begin{aligned} t &= \frac{q_0 - q_t}{q_0 q_t} \\ &= \frac{1}{q_t} - \frac{1}{q_0} \quad \dots [2.10] \end{aligned}$$

The example below illustrates the point, already made, that when the frequency of a recessive gene is low, selection is very slow to change it.

Example 2.2

It is sometimes suggested, as a eugenic measure, that those suffering from serious inherited defects should be prevented from reproducing, since in this way the frequency of such defects would be reduced in future generations. Before deciding whether the proposal is a good one, we ought to know what it would be expected to achieve. We cannot properly discuss this problem without taking mutation into account, as we shall do later; the answer we get, ignoring mutation, shows what is the best that could be hoped for. Albinism will serve as an example, though it is not a very serious defect. Supposing albinism to be due to a single recessive gene, how long would it take to reduce the frequency of albino individuals to half its present value? The present frequency among European people is about 1/20,000. This is q_0^2 , and it gives $q_0 = 1/141$. The objective is $q_t^2 = 1/40,000$, $q_t = 1/200$. So, from equation [2.10], $t = 200 - 141 = 59$ generations. With 25 years to a generation it would take nearly 1,500 years to achieve this modest objective. Albinism is not, in fact, a single genetic entity, but can be caused by at least two different recessive genes, each at a frequency lower than 1/141. So in reality the elimination would be even slower.

In domesticated species, of course, the elimination of deleterious genes can be greatly speeded up by progeny testing. Test-matings are made to known heterozygotes, and this identifies heterozygotes among those tested. The gene can then be eliminated very quickly. The gene persists only in heterozygotes that have been misclassified as normal through an inadequate number of progeny.

Average fitness and load

When the gene frequency is changed by selection, some individuals must suffer 'genetic death' by their failure to survive or to reproduce, and the average fitness of the population is thereby reduced. The proportion of the population that suffers genetic death is called the *load* borne by the population as a consequence of the presence of the deleterious gene in it. If L is the load, the average fitness of the population is $1 - L$. The average fitness and the load were deduced in Table 2.1 without being specifically pointed out. The average fitness is the total of the genotype frequencies after selection and is the denominator of all the expressions for q_1 or Δq given in Table 2.2. For a recessive gene, for example, the average fitness is $1 - sq^2$ and the load is sq^2 . The average fitness is again relative fitness, relative to a population that does not have the deleterious gene in it. The load is not necessarily a real detriment to the population, because most species produce more offspring than the resources of its environment can support, and the death of some individuals from genetic causes leaves room for others that would otherwise have died from lack of food or some other cause. There is a species of *Drosophila*, for example (*D. tropicalis*, from Central America), in which 50 per cent of individuals in a certain locality suffer genetic death, and yet the population flourishes (Dobzhansky and Pavlovsky, 1955).

Equilibria

Balance between mutation and selection

Having described the effects of mutation and selection separately, we must now compare them and consider them jointly. Which is the more effective process in causing change of gene frequency? Is it reasonable to attribute the low frequency of deleterious genes that we find in natural populations to the balance between mutation tending to increase the frequency and selection tending to decrease it? The expressions already obtained for the change of gene frequency under mutation or selection alone show that both depend on the initial gene frequency, but in different ways. Mutation to a particular gene is most effective in increasing its frequency when the mutant gene is rare (because there are more of the unmutated genes to mutate); but selection is least effective when the gene is rare. The relative effectiveness of the two processes depends therefore on the gene frequency, and if both processes operate for long enough a state of equilibrium will eventually be reached. So we must find what the gene frequency will be when equilibrium is reached. This is done by equating the two expressions for the change of gene frequency, because at equilibrium the change due to mutation will be equal and opposite to the change due to selection.

Let us consider a gene (A_2) with frequency q , mutation rate to it u , and from it v , and selection coefficient against it s . Then from equation [2.3] and the expression for gene frequency change in Table 2.2 with partial dominance, we have at equilibrium

$$up - vq = \frac{spq[q + h(p - q)]}{1 - 2hspq - sq^2} \quad \dots [2.11]$$

This equation is too complicated to give a clear answer to our question. But we can make two simplifications with only a trivial sacrifice of accuracy. We are specifically interested in genes at low equilibrium frequencies. If q is small, the term vq representing back mutation is relatively unimportant and can be neglected; and we can use the approximate expression for the selection effect (i.e., set the denominator to unity). Then $up = spq[q + h(p - q)]$, approximately. This expression can be further simplified for the special cases of A_2 recessive ($h = 0$), no dominance of A_2 ($h = 0.5$), and A_2 dominant ($h = 1$). Consider first the equilibrium condition for selection against a fully recessive gene:

$$u = sq^2 \text{ (approx.)} \quad \dots [2.12]$$

$$q = \sqrt{u/s} \text{ (approx.)} \quad \dots [2.13]$$

For a gene with no dominance, the expression simplifies to $u = 0.5sq$ (approx.), so at equilibrium

$$q = 2u/s \text{ (approx.)} \quad \dots [2.14]$$

For selection against a completely dominant gene the expression simplifies to $u = spq$ (approx.), and

$$qp = u/s \text{ (approx.)}$$

or

$$H = 2u/s \text{ (approx.)} \quad \dots [2.15]$$

where H is the frequency of heterozygotes, and u is the mutation rate to the dominant allele. If the mutant gene is rare, H is very nearly the frequency of the mutant phenotype in the population.

Example 2.3

If the equilibrium state is accepted as applicable, we can use it to get an estimate of the mutation rate of dominant abnormalities, for which the coefficient of selection is known. Among some human examples described by Haldane (1949) is the case of dominant dwarfism (chondrodyostrophy) studied in Denmark. The frequency of dwarfs was estimated at 10.7×10^{-5} , and their fitness ($1 - s$) at 0.196. The estimate of fitness was made from the number of children produced by dwarfs compared with their normal sibs. The mutation rate, by equation [2.15], comes out at 4.3×10^{-5} . Though there is a possibility of serious error in the estimate of frequency owing to prenatal mortality of dwarfs, the mutation rate is almost certainly estimated within the right order of magnitude. The mutation rate to recessives cannot be reliably estimated in this way because the estimate is very sensitive to small departures from equilibrium. (For more about mutation rates in man, see Stern, 1973.)

These expressions for the equilibrium gene frequency under the joint action of mutation and selection show that the gene frequency can have any value at equilibrium, depending on the relative magnitude of the mutation rate and the coefficient of selection. But if mutation rates are of the order of magnitude commonly accepted, i.e., 10^{-5} or thereabouts, then only a mild selection against the mutant

gene will be needed to hold it at a very low equilibrium frequency. For example, if a gene mutates at the rate of 10^{-5} , a selective disadvantage of 10 per cent is enough to hold the frequency of the recessive homozygote at 1 in 10,000; and a 50 per cent disadvantage will hold it at 1 in 50,000. It is quite clear therefore that the low frequency of deleterious mutants in natural populations is in accord with what would be expected from the joint action of mutation and selection.

Let us now consider the load, or proportion of genetic deaths, when a population is in equilibrium. The load from a recessive gene is sq^2 , as explained earlier. The equilibrium equation [2.12] therefore shows that the load at equilibrium is

$$L = u \quad \dots [2.16]$$

Thus the load depends only on the mutation rate and not at all on how seriously deleterious the gene is. The reason for this surprising conclusion is that a more deleterious gene comes to equilibrium at a lower gene frequency; there are therefore fewer homozygotes, though more of them die. With a less deleterious gene there are more homozygotes, but fewer of them die. Since the load from each locus does not depend on the selection coefficient, the total load from recessive alleles at all loci is simply the sum of the mutation rates, Σu . With deleterious dominant genes, the homozygotes are so rare that they can be neglected. The load therefore comes from the death of heterozygotes and is therefore $L = sH$, where H is the frequency of heterozygotes. Substituting the equilibrium frequency of heterozygotes from equation [2.15] gives the load at equilibrium as

$$L = 2u \quad \dots [2.17]$$

where u is the mutation rate to the dominant allele. Again the load is not affected by the harmfulness of the gene. Comparison of equations [2.16] and [2.17] raises another question. Why should the load from a dominant gene be twice that from a recessive with the same mutation rate? The reason is that the death of a mutant homozygote removes two genes from the population whereas the death of a heterozygote removes only one mutant gene. Equation [2.17] seems to suggest that the loss of one gene by the death of a heterozygote balances the introduction of two genes by mutation. This is not so because the loss by death is expressed per individual, whereas the gain by mutation is expressed per gamete: the mutation rate per individual is $2u$. The load from partially dominant alleles is between u and $2u$, and the total load from all loci is between Σu and $2\Sigma u$, where u is the mutation rate to alleles with any degree of dominance. If mutation rates are about 10^{-5} , an organism with 10,000 loci capable of mutation to deleterious alleles would have a total load of between 10 and 20 per cent; that is to say, about 1 or 2 zygotes in 10 would die as a result of mutation.

The fact that recessive genes at low frequencies respond only very slowly to selection makes it very unlikely that rare recessives are at their equilibrium frequencies in real populations. Unless the environmental conditions remain exceptionally constant over a long period, selection coefficients are likely to change faster than selection can adjust the frequency to each new equilibrium value. This, of course, would not apply to genes that are lethal under all conditions. There is also another reason, which applies to lethals too, for thinking that present-day

human populations are not in equilibrium. Modern civilization has reduced the subdivision into local, partially inbreeding, groups, and this has reduced the frequency of homozygotes as will be explained in the next chapter. In consequence, both the gene frequencies and the homozygote frequencies are below their equilibrium values, and must be presumed to be at present increasing slowly toward new equilibria at higher values. Deductions about rare recessives based on the supposition of equilibrium therefore cannot be made, particularly for human populations.

Changes of equilibrium

Mutation rates can be increased by artificially produced radiation or environmental chemicals; selection coefficients can be reduced by medical treatment or by domestication, or they can be increased by eugenic measures. What effects would be expected from these changes? Whatever the change, there will be a new equilibrium gene frequency toward which the population will start to move. The effect on the frequency of affected individuals, when the new equilibrium is reached, can readily be seen from equations [2.13] and [2.15]; for example, doubling the mutation rate, or halving the selection coefficient, would eventually double the frequency of affected individuals. The immediate effect of increasing the mutation rate depends on the coefficient of selection against the gene – the lower the selection coefficient, the slower the approach to equilibrium. The consequences of an increased mutation rate would unquestionably be harmful. (For an assessment of the consequences see Crow, 1957). The consequences of changing the selection coefficient one way or the other, however, need some comment.

Intensification of selection has sometimes been advocated as a eugenic measure for human populations. Example 2.2 showed how extremely slow such measures applied to a recessive gene would be to make a worthwhile reduction of its frequency. When mutation is taken into consideration the prospects are seen to be even worse. Not only is mutation hindering the selection, but it puts a limit – the equilibrium for $s = 1$ – below which the frequency cannot be reduced. Serious defects, moreover, have already a fairly strong natural selection working on them, and the addition of artificial selection can do no more than make the coefficient of selection s equal to 1. This would probably seldom do more than double the present coefficient of selection, and the incidence of defects would be reduced to not less than half their present values.

Perhaps the reduced intensity of natural selection under modern conditions should give us more concern. Minor genetic defects, such as colour-blindness, must presumably have had some selective disadvantage in the past but now have very little, if any, effect on fitness. Moreover, medical treatment removes, or reduces, the selection pressure against susceptibility to a variety of diseases that have at least some degree of genetic causation. This relaxation of natural selection suggests that the frequencies of the genes concerned will increase toward new equilibria at higher values. If this is true we must expect the incidence of minor genetic defects to increase in the future, and also the proportion of people who need medical treatment for a variety of diseases. By applying humanitarian principles for our own good now we are perhaps laying up a store of inconvenience for our descendants in the distant future.

Selection favouring heterozygotes

We have considered the effects of selection operating on genes that are partially or fully dominant with respect to fitness; but, though the appropriate formula was given in Table 2.2, we have not yet discussed the consequences of overdominance with respect to fitness; that is, when the heterozygote has a higher fitness than either homozygote. At first sight it may seem rather improbable that selection should favour the heterozygote of two alleles rather than one or other of the homozygotes. There is good evidence, however, that it does occur, though opinion is divided on how common a situation it is. Let us first examine the consequences of this form of selection, and then consider how it might operate.

Selection operating on a gene with partial or complete dominance tends toward the total elimination of one or other allele, the final gene frequency, in the absence of mutation, being 0 or 1. When selection favours the heterozygote, however, the gene frequency tends toward an equilibrium at an intermediate value, both alleles remaining in the population, even without mutation. The reason is as follows. The change of gene frequency after one generation was given in Table 2.2 as being

$$\Delta q = \frac{pq(s_1 p - s_2 q)}{1 - s_1 p^2 - s_2 q^2}$$

The condition for equilibrium is that $\Delta q = 0$, and this is fulfilled when $s_1 p = s_2 q$. The gene frequencies at this point of equilibrium are therefore

$$\frac{p}{q} = \frac{s_2}{s_1} \quad \dots [2.18]$$

or

$$q = \frac{s_1}{s_1 + s_2} \quad \dots [2.19]$$

Now, if q is greater than its equilibrium value (but not 1), and p therefore less, $s_1 p$ will be less than $s_2 q$, and Δq will be negative; that is to say q will decrease. Similarly, if q is less than its equilibrium value (but not 0) it will increase. Therefore when the gene frequency has any value, except 0 or 1, selection changes it toward the intermediate point of equilibrium given in equation [2.19], and both alleles remain permanently in the population. Three or more alleles at a locus can be maintained in the same way. The selective forces required are, however, less simple; see Crow and Kimura (1970, p. 277). A feature of the equilibrium worthy of note is that the gene frequency depends not on the degree of superiority of the heterozygote but on the relative disadvantage of one homozygote compared with that of the other. Therefore there is a point of equilibrium at some more or less intermediate gene frequency whenever a heterozygote is superior to both the homozygotes, no matter by how little.

The load resulting from overdominance for fitness is $s_1 p^2 + s_2 q^2$, from the denominator of the expression for Δq . Substituting the equilibrium value for q from equation [2.19], and the analogous value for p , leads to the following expression for the load at equilibrium:

$$L = \frac{s_1 s_2}{s_1 + s_2} \quad \dots [2.20]$$

Substitution of $s_2 = s_1 p/q$ and separately of $s_1 = s_2 q/p$ from equation [2.18] leads to

$$L = s_1 p = s_2 q \quad \dots [2.21]$$

Thus the load depends on the selection coefficients, unlike the load due to recurrent mutation, and the total load from all overdominant loci cannot be obtained in any simple way by summation.

An example of heterozygote advantage is described below, and the possible causes of overdominance for fitness are then discussed. First, however, we must examine the effects of selection on observed genotype frequencies.

Selection and the Hardy–Weinberg test One of the conditions for the generation of Hardy–Weinberg genotype frequencies is the absence of selection. It is tempting to think therefore that if a test of Hardy–Weinberg, as described in the previous chapter, gives a discrepancy between observed and expected genotype frequencies, this will reveal the action of selection and allow the relative fitnesses of the genotypes to be estimated. The conclusions that can be drawn about selection, however, are limited for the following reasons. (For a fuller treatment see Prout, 1965.)

Selection may, broadly speaking, take two forms: differences in viability and differences in fertility. The test is usually done by counting adults after selection for viability but before selection for fertility. The observed genotype frequencies in these counted adults are compared with Hardy–Weinberg expectations derived from the gene frequencies in these same adults. A valid test requires that the expectations be calculated from the gene frequencies before selection. If selection is for fertility only it will not cause a discrepancy and so the test will not reveal selection for fertility. If, however, selection is for viability which has already taken place, the expectations are calculated from the wrong gene frequencies. Selection for viability therefore causes a discrepancy, but the discrepancies between observed and expected genotype frequencies do not reveal which genotype has been selected; selection against either of the homozygotes, or against both, results in an excess of heterozygotes and a deficiency of both homozygotes over the wrongly calculated expectations. How this happens can be seen by working problem 2.10. Briefly stated, the source of the error is that the expectations should have been calculated from the gene frequencies in the previous generation. The error will not arise if the gene frequencies are not changing, as with a gene with heterozygote advantage at equilibrium frequencies.

Example 2.4

Sickle-cell anaemia in man is a well-known example of heterozygote advantage. It is particularly useful as an example because the data allow a test of observation with theory. The disease is caused by the abnormal haemoglobin-S. Homozygotes suffer from a severe anaemia from which many die, yet the gene is present among Africans and their descendants in America at frequencies much too high to be accounted for by mutation counterbalancing the selection against homozygotes. The explanation of the high frequencies is that heterozygotes have an advantage over normal homozygotes

Continued

Example 2.4 *continued*

through an increased resistance to malaria (Allison, 1954). The selective forces can be calculated from data given by Allison (1956) and one can then see how well these can account for the observed gene frequency. Allison classified 287 infants and 654 adults, from a district of Tanzania, for genotype. (Homozygotes are recognized by the presence of red blood cells with a characteristic 'sickle' shape; heterozygotes are recognized by the sickling of their cells when the blood sample is deoxygenated.) The observed numbers and frequencies are shown in the table, with the gene frequencies calculated from them by equation [1.1]. (AA denotes the normal homozygote, AS the heterozygote, and SS the anaemic homozygote.) Most of the differential selection is thought to take place before adulthood, i.e., the surviving genotypes do not differ much in fertility. The infants therefore represent the genotype frequencies before selection and the adults after selection, and so we can calculate the selection coefficients from the observed frequencies. First, however, note that if the gene frequency is in equilibrium it will be the same after selection as it was before, and the data agree well with this expectation. Dividing the frequency of each genotype after selection by its frequency before selection gives the relative fitness of that genotype, as shown in the table. The fitnesses of the homozygotes can then be expressed relative to the heterozygote by dividing each by the heterozygote fitness. The homozygote fitnesses are $1 - s_1$ and $1 - s_2$, from which the selection coefficients work out to be 0.24 against AA and 0.80 against SS, both relative to AS. The equilibrium gene frequency expected to result from this selection against both homozygotes, by equation [2.19], is $q_s = 0.23$, which is reasonably close to the observed value. Thus the selective forces observed in the differential viability do satisfactorily account for the frequency of the sickle-cell gene in this population.

	<i>Genotype</i>			<i>Frequency of S-gene</i>
	AA	AS	SS	
Numbers of infants	189	89	9	
adults	400	249	5	
Frequency in infants	0.6585	0.3101	0.0314	0.1864
adults	0.6116	0.3807	0.0076	0.1980
Relative fitness	0.9288	1.2277	0.2420	
Fitness relative to AS	0.7565	1	0.1971	
Selection coefficient	$s_1 = 0.2435$		$s_2 = 0.8029$	
Expected $q_s = \frac{s_1}{s_1 + s_2} = 0.2327$				

The selective values may be more interesting if expressed relative to the normal homozygote. The fitness of AS is then $1/(1 - s_1) = 1.32$, and that of SS is $(1 - s_2)/(1 - s_1) = 0.26$. Thus the resistance to malaria confers a 32 per cent advantage on the heterozygote, and this balances a 74 per cent disadvantage in the anaemic homozygote when the gene frequency is about 0.2.

Possible causes of overdominance for fitness Let us now consider some of the ways in which selection might operate so as to favour heterozygotes. One way is

through pleiotropy, i.e., the gene having more than one phenotypic effect. To produce overdominance for fitness, the alleles must affect two components of fitness in opposite directions. The heterozygote advantage of sickle-cell anaemia arises in this way; one homozygote reduces fitness through one component, the anaemia, while the other homozygote reduces fitness through another component, susceptibility to malaria. There are a few other genes in man where heterozygote advantage for similar reasons is proved or suspected. Another example is the resistance of wild rats to the anti-coagulant poison warfarin (Greaves *et al.*, 1977). The gene conferring resistance is dominant, so that heterozygotes and homozygotes are resistant. Homozygotes, however, have a much increased requirement for vitamin K, which is not met by the normal diet. So in areas where the poison is being used, one homozygote is selected against by the poison and the other by the vitamin K deficiency, leading to an equilibrium frequency of the resistance gene, which was about 0.34 in the area studied.

There are many ways in which a locus can affect different components of fitness. For example, the components can be different stages of the life-cycle, different environments encountered by the same individual at different times, or by different individuals in different places, the two sexes, different combinations of genes at other loci which modify the locus in question. The conditions that produce overdominance for fitness are that the alleles affect the components in opposite directions and that there is some degree of dominance on the scale in which the components combine to give fitness. The meaning of the last condition is this: if the components are multiplied together to give fitness, then there must be some degree of dominance on the geometric scale but not necessarily on the arithmetic scale. To take a simple example, a hypothetical locus with two alleles in mice might affect the number born per litter and the number of litters as follows:

	<i>Genotype</i>		
	A ₁ A ₁	A ₁ A ₂	A ₂ A ₂
Number per litter	6	7	8
Number of litters	8	7	6
Total number = fitness	48	49	48

Fitness is the product of the two components and there is overdominance for fitness. In their effects on the components separately, the alleles have no dominance on the arithmetic scale, but a small degree of dominance on the geometric scale, the geometric mean of the homozygous values being 6.9. Overdominance generated in this way is known as *marginal overdominance* (Wallace, 1968), meaning that the overdominance appears only in the margin of the table.

Gametic phase disequilibrium of linked loci can generate pseudo-overdominance in a similar way. If two loci are closely linked so that they appear to be one, and if the favourable alleles are dominant and linked in repulsion, then the heterozygote may be superior to either homozygote. The possibility of pseudo-overdominance being caused by linkage makes it extremely difficult to establish real overdominance at single loci from observations on populations derived from crosses between different strains, because it is formally impossible to exclude the presence of a

closely linked but unrecognized locus. Wild populations of many *Drosophila* species have chromosomes with different gene arrangements carried in inverted segments. Inversion heterozygotes are generally superior in fitness to homozygotes (see Wallace, 1968), and this heterozygote superiority is probably due to the linkage of the genes in the inversions.

Finally, overdominance can arise at the molecular level. If a locus codes for an enzyme, the products of the two alleles (allozymes) are likely to have different properties, such as enzymatic activity, heat-stability, or optima for environmental factors such as temperature or pH. The mixture of allozymes may therefore make the heterozygote more versatile than either of the homozygotes with single allozymes, i.e., less susceptible to the impairment of enzyme function by environmental circumstances. Or, if the allozymes differ in activity, the intermediate activity of the heterozygote may be more favourable than the higher or lower activities of the homozygotes. For further details and discussion of the evidence for overdominance at the molecular level, see Berger (1976).

We have seen that there are many ways by which overdominance for fitness could arise. It must be admitted, however, that the cases where it has been proved to occur are very few indeed.

Polymorphism

We saw earlier that the balance between mutation and selection satisfactorily accounts for the presence of deleterious genes at low frequencies, causing the appearance of rare abnormal, or mutant, individuals. Genes of this sort, however, are only a minor part of the genetic variation found in natural populations. There are many genes causing variants that are neither rare nor in any way abnormal, and the presence of these genes cannot easily be accounted for by the simple balance of selection against mutation. The blood-group genes used as examples in the first chapter are of this sort. More striking examples are the colour varieties found in many species, particularly among insects, snails, and fish.

When a locus has allelic variants at frequencies too high to be accounted for by selection-mutation balance, the locus is said to be *polymorphic* and the population to exhibit *polymorphism* for that locus. Operationally, a polymorphic locus is usually defined as one for which the frequency of the most common allele is less than 0.99. Otherwise, the locus is monomorphic; that is, all individuals are regarded as being homozygous for one allele.

The measure usually used to quantify the amount of genetic variation due to polymorphic loci is the *heterozygosity*, H , which is simply the frequency of heterozygotes. H can be expressed as an observed value, or as an expected value calculated from the observed gene frequencies. These two values will be different if the population is not in Hardy-Weinberg equilibrium. When a number of loci are assessed together, the amount of variation averaged over all loci can be expressed as the average heterozygosity (\bar{H}). The heterozygosity can be thought of as either the frequency of heterozygotes expected at any randomly chosen locus, or as the proportion of loci at which any individual is expected to be heterozygous. Another measure of variability sometimes used is the proportion of polymorphic loci among those tested. This measure, however, has disadvantages: it gives undue weight to

rare alleles, which contribute little to the variation; it depends on sample size because smaller samples will detect fewer loci with rare alleles; and the gene frequency chosen to define polymorphism is somewhat arbitrary.

Polymorphism is found in almost all natural populations, and occurs at all levels of genetic organization, from DNA sequences to major morphological traits. The amount of variation differs for different kinds of trait. Alleles causing visible morphological variants are rare. Blood group and allozyme variants are much more common, and are often caused by alleles at intermediate frequencies. The heterozygosity of allozymes varies among taxonomic groups. Averaged over a number of mammalian species \bar{H} is 0.04. It is higher in invertebrates than vertebrates, but rarely exceeds 0.3 (Kimura, 1983, p. 254). Allozyme polymorphisms differ also according to the function of the enzyme. In a survey of nine *Drosophila* species, for one functional group of 12 enzymes \bar{H} was 0.10, whereas for another functional group of 13 enzymes \bar{H} was 0.23 (Latter, 1981). Minisatellite (VNTR) loci each have multiple alleles and are very highly heterozygous with \bar{H} almost 1. When variation at several of these loci is considered, individuals can, with the sole exception of identical twins, be uniquely identified by their genotype. This is the genetic 'fingerprint' used in forensic identification. At the level of DNA sequence variation, heterozygosity is of the order of several nucleotide differences per kilobase pair (kb). In over 20 genes studied in *Drosophila* it averaged 3 per kb (Aquadro and Begun, 1993). Heterozygosity varies greatly depending on the position of the locus, being very low in regions of restricted recombination. Nucleotide heterozygosity also varies according to whether or not a polymorphism causes an amino acid change in a protein, and is greater for synonymous than non-synonymous codons.

Polymorphism is the source of the variation of quantitative characters, the subject of this book, so it, and its cause, are of fundamental interest to the later chapters. There are several possible causes, of which the following is a summary.

1. *Heterozygote advantage* We saw in the previous section that overdominance for fitness maintains an equilibrium gene frequency at intermediate levels, and that there are many ways in which overdominance for fitness can arise. Heterozygote advantage is therefore an attractive explanation for polymorphism. The paucity of proven cases need not be a difficulty, because an advantage of the heterozygote so small as to be quite undetectable in practice would be enough to maintain a polymorphism. There are, however, difficulties connected with the effects of inbreeding, and with the genetic load incurred if very many loci are kept polymorphic by heterozygote advantage. Also, isolates of haploid organisms have been found to have as much allozyme variability as diploid organisms, and this argues strongly against heterozygote advantage being an important cause of polymorphism. For further discussion of the problem, see Lewontin (1974), Berger (1976), Wills (1978) and Kimura (1983).

2. *Frequency-dependent selection* Having a phenotype that is rare may itself be an advantage, irrespective of what the phenotype is. The direction of selection is then dependent on the gene frequency: an allele at low frequency produces the rare phenotype and is favoured, but the same allele at a high frequency is selected

against. This leads to a stable equilibrium gene frequency and so to a balanced polymorphism. Many examples of frequency-dependent selection are known. Pollen grains bearing a rare self-sterility allele have a better chance of fertilizing an ovule because the same allele is seldom present in the stigmata of other plants. Birds and fish have been shown to take disproportionately more of the more common type of food when they are offered a choice (see, e.g., Allen, 1975), and this is thought to exert frequency-dependent selection on polymorphic prey, such as snails, giving an advantage to individuals with a rare pattern of coloration (see Clarke, 1969). In general, the development of special methods of attack and of defence in the relationships between predator and prey and between pathogen and host seem likely to result in frequency-dependent selection. Frequency-dependent selection is reviewed by Ayala and Campbell (1974) and by Clarke (1979).

3. Heterogeneous environment The environment experienced by individuals of a population is not constant; it differs from place to place and varies with time. If one allele is advantageous in one environment and another in a different environment, stable polymorphism can result without heterozygotes necessarily being on average superior. Selection can be thought of as tending to adapt different individuals to different environments. The situation is complex because the outcome depends on many factors such as the dominance relations, whether individuals choose to breed in the environments to which they are adapted, whether mating is preferentially between individuals from the same environment or random, what proportions of the whole population inhabit each of the different environments, whether individuals each encounter only one environment ('coarse-grained' environment) or more than one ('fine-grained'), and whether the heterogeneity of the environment is spatial or temporal. A relatively simple form of selection in a heterogeneous environment results in a *cline*. This is a gradient of gene frequency between one locality and another, one allele being at a high frequency at one end of the cline and at a low frequency at the other end. Clines are thought, or in many cases known, to be maintained by selection favouring one allele in one locality and another allele in another locality, with a limited amount of migration, which allows mating only between individuals from neighbouring parts of the cline. The selection in opposite directions at the two ends and the 'gene-flow' up and down the cline maintain the polymorphism. The role of heterogeneous environments in maintaining polymorphism is reviewed by Felsenstein (1976). Evidence that it has an important role was obtained from a survey of the polymorphism and ecology of 243 species (Nevo, 1978). Theoretical considerations, however, show that the conditions under which polymorphism would be maintained are rather restricted; see Hoekstra, Bijlsma, and Dolman (1985).

4. Transition Polymorphisms seen at present might possibly be transitional stages in the evolutionary replacement of one allele by another, which has become more advantageous through some environmental change in the past. This, however, is unlikely to be the explanation of more than a very small proportion of polymorphism.

5. Neutral mutation All the above mechanisms involve selection as the force responsible for the polymorphism. It is possible, however, that the selection coefficients may be very small indeed, so small that mutant alleles are effectively neutral with respect to fitness. Polymorphism then results from the balance between mutation and loss by chance, which depends on the population size. This theory will be described in Chapter 4, after the effects of population size have been described.

To obtain evidence that a polymorphism is maintained by any selective balance is difficult, for several reasons. Evidence that selection is operating might be sought from direct observation of selection coefficients; but selection coefficients of less than a few percent need huge samples for their detection. Changes of gene frequency might give evidence of selection; but if the polymorphism is stable, there will be no change of gene frequency from one generation to the next, and any change observed may be only a temporary change within one generation. The gene frequency can be changed artificially to see if natural selection will bring it back to its original value; but with such perturbation experiments it is essential to be sure the experimental conditions accurately mimic the natural environment. If selection is detected, by whatever means, it is very difficult to determine whether its target is the polymorphic locus of interest or some other locus in linkage disequilibrium with it.

Despite these difficulties, there are over 150 demonstrated cases of selection acting in natural populations (Endler, 1986). For example, there is evidence, both direct and indirect, in favour of balancing selection on the Fast/Slow polymorphism of the *Adh* allozymes in *Drosophila* (Clarke, 1975; Briscoe, Robertson and Malpica, 1975; Hudson, Kreitman and Aguadé, 1987). Most of the single-locus cases, however, involve polymorphisms with clear phenotypes, such as shell colours and banding patterns of snails, body colour, and resistance to chemicals and pathogens. Examples of selection on biochemical polymorphisms are less common.

Problems

2.1 Rare white-flowered plants occur in populations of a *Delphinium* species which normally has deep blue flowers. In an area in the Rocky Mountains the frequency of white-flowered plants was 7.4×10^{-4} . White-flowered plants were found to set an average of 143 seeds per plant while blue-flowered plants set 229, the reduction in seed-production being due to discrimination by pollinators, which are bumble-bees and humming-birds. On the assumption that white flowers are due to a single recessive gene, and that the population was in equilibrium, what rate of mutation would be needed to balance the selection?

Data from Waser, N. M. & Price, M. V. (1981) *Evolution*, 35, 376–90. [Solution 12]

2.2 If the white flowers in Problem 2.1 were due to a completely dominant gene, what would be the mutation rate needed to maintain equilibrium? [Solution 22]

2.3 If an allele, *A*, mutates to *a* with a frequency of 1 in 10,000 and back-mutates with a frequency of 1 in 100,000, and if the three genotypes have equal fitnesses, what will be the genotype frequencies at equilibrium in a random-mating population? [Solution 32]

2.4 Refer to Problem 2.3. What would be the consequences of doubling the mutation rate in both directions? [Solution 42]

2.5 Medical treatment is, or will be, available for several serious autosomal recessive diseases. What would be the long-term consequences if treatment allowed sufferers from such a disease to have on average half the number of children that normal people have, whereas without treatment they would have no children? Assume that the present frequency is the mutation versus selection equilibrium, that in the long term a new equilibrium will be reached, and that no other circumstances change.

[Solution 52]

2.6 Cystic fibrosis is an autosomal recessive human disease with an incidence of about 1 in 2,500 live births among Caucasians. What would be the consequence in the immediately following generation if the mutation rate were doubled? Assume that the present frequency is the mutation versus selection equilibrium, that back-mutation is negligible, and that affected individuals have no children. Express your result as a percentage increase of incidence and as the number of additional cases per million births.

[Solution 62]

2.7 A careless *Drosophila* stock-keeper allows a stock of a dominant autosomal mutant to be contaminated by wild-type flies. Originally all flies were homozygous for the mutant, but after 10 generations some wild-type flies were found in the stock. Precautions were then taken to prevent further contamination. Suppose that we make the following assumptions: (i) In every generation 1 per cent of flies were contaminants, (ii) all contaminants were homozygous wild type, (iii) mutant and wild-type flies have equal fitness. With these assumptions what would be (1) the proportion of wild-type flies in the generations after the last contamination, and (2) the proportion of heterozygotes among the flies with the mutant phenotype?

[Solution 72]

2.8 The two closely linked recessive genes of *Drosophila* described in Problem 1.7 can be treated as alleles. Two populations were set up with initial gene frequencies of *so* of 0.2 in one and 0.8 in the other. After 7 generations of random breeding the gene frequency of *so* was close to 0.35 in both populations. What does this tell us about the selection operating?

[Solution 82]

2.9 The gene that makes wild rats resistant to the anticoagulant poison warfarin exhibits heterozygote advantage because rats homozygous for the resistance gene suffer from vitamin K deficiency. Heterozygotes are resistant to the poison and do not suffer from vitamin K deficiency. The proportion of resistant homozygotes that die from vitamin K deficiency was estimated to be 63 per cent. Susceptible homozygotes are not all killed when poison is applied to an area. A population under continuous treatment with poison came to equilibrium with the resistance gene at a frequency of 0.34. What percentage of all rats in this population will die in consequence of the resistance gene and the poisoning?

Data from Greaves, J. H., et al. (1977) *Genet. Res.* **30**, 257–63.

[Solution 92]

2.10 Suppose that two mutant genes are used in a class experiment on selection in *Drosophila*. In both cases heterozygotes are distinguishable from homozygotes but the genes are recessive with respect to fitness. (These are not known genes.) With gene (a) mutant homozygotes of both sexes have their fertility reduced by 50 per cent relative to the other genotypes, but have unimpaired viability. With gene (b) mutant homozygotes are fully fertile but both sexes have their pre-adult mortality increased by 50 per cent relative to the other genotypes. In both cases a parental population is made up of 30 ♂♂ + 30 ♀♀ homozygous wild type and 20 ♂♂ + 20 ♀♀ homozygous mutant. What genotype frequencies will be found in the progeny? How do they compare with Hardy–Weinberg expectations based on

the observed gene frequency in the progeny? What conclusions about the selection can be drawn from the frequencies in the progeny? Why does Δq differ in the two cases?

[Solution 102]

2.11 Suppose a sex-linked trait due to a recessive gene has its genotypes in Hardy-Weinberg frequencies. A breeder then culls all affected individuals of both sexes. Derive an expression, in terms of the initial gene frequency, for the change of gene frequency resulting from one generation of selection.

[Solution 112]

2.12 What is the approximate equilibrium gene frequency of a deleterious sex-linked recessive gene, when selection is balanced by a mutation rate of u ? Human X-linked muscular dystrophy was found in a survey in England to have an incidence of 32.6 per 100,000 males. The mutation rate was estimated from the number of 'sporadic' cases to be 10.5×10^{-5} . Do these estimates agree with the expectation for a population in equilibrium when sufferers from the disease do not reproduce and carriers have normal survival and fertility?

Data from Gardner-Medwin, D. (1970) *J. Med. Genet.*, 7, 334–7.

[Solution 122]

2.13 Red coat colour in many breeds of cattle is due to an autosomal recessive gene, the dominant phenotype being black. Suppose that 1 per cent of red calves are born in a predominantly black breed, and suppose that it is desired to eliminate the red gene. Assuming the genotypes in the initial population to be in Hardy-Weinberg proportions, what proportion of red calves would there be after applying the following alternative selection procedures over two generations? (1) No red animals are used for breeding. (2) In addition to culling all red animals, all black bulls to be used for breeding are first tested by 6 progeny each from cows known to be heterozygotes. Any bull producing one or more red calves in the test is discarded. Cows used for breeding are not tested.

[Solution 132]

3 Small Populations:

I. Changes of Gene Frequency under Simplified Conditions

We have now to consider the last of the agencies through which gene frequencies can be changed. This is the dispersive process, which differs from the systematic processes in being random in direction, and predictable only in amount. In order to exclude this process from the previous discussions we have postulated always a 'large' population, and we have seen that in a large population the gene frequencies are inherently stable. That is to say, in the absence of migration, mutation, or selection, the gene and genotype frequencies remain unaltered from generation to generation. This property of stability does not hold in a small population, and the gene frequencies are subject to random fluctuations arising from the sampling of gametes. The gametes that transmit genes to the next generation carry a sample of the genes in the parent generation, and if the sample is not large the gene frequencies are liable to change between one generation and the next. This random change of gene frequency is the dispersive process.

In this chapter and the next we shall be concerned with the effects of the dispersive process on gene frequencies. If the deductions to be made about gene frequencies seem to be rather remote from reality, it should be remembered that the properties of a population with respect to any genetically determined character depend on gene frequencies. The conclusions are therefore fully relevant to quantitative characters to be dealt with in later chapters.

There are, broadly speaking, four consequences of the dispersive process, which are to be explained and quantified in this chapter. These are not really different consequences, but rather different ways in which the consequences may be seen. They are:

1. *Random drift* The random changes of gene frequency are called random drift. If the gene frequency in any one small population is followed, it may be seen to change in an erratic manner from generation to generation, with no tendency to revert to its original value.

2. *Differentiation between sub-populations* Random drift occurring independently in different sub-populations leads to genetic differentiation between the sub-populations. The inhabitants of a large area seldom in nature constitute a single large population, because mating takes place more often between inhabitants of the same region. Natural populations are therefore more or less subdivided into local

groups or sub-populations, and these come to differ in gene frequencies if the number of individuals in the groups is small. Domesticated or laboratory populations, in the same way, are often subdivided – for example, into herds or strains – and in them the subdivision and genetic differentiation are often more marked.

3. Uniformity within sub-populations Genetic variation within each sub-population becomes progressively reduced, and the individuals become more and more alike in genotype. This genetic uniformity is the reason for the widespread use of inbred strains of laboratory animals in many areas of biological research. (An inbred strain is one maintained as a small population over many generations.)

4. Increased homozygosity Homozygotes increase in frequency at the expense of heterozygotes. This, coupled with the general tendency for deleterious alleles to be recessive, is the genetic basis for the loss of fertility and viability that almost always results from inbreeding.

There are two different ways of looking at the dispersive process and of deducing its consequences. One is to regard it as a sampling process and to describe it in terms of sampling variance. The other is to regard it as an inbreeding process and describe it in terms of the genotypic changes resulting from matings between related individuals. Of these, the first is probably the simpler for a description of how the process works, but the second provides a more convenient means of quantifying its consequences. The plan to be followed here is first to describe the general nature of the dispersive process from the point of view of sampling. This will show how the four consequences come about. Then we shall approach the process afresh from the point of view of inbreeding, and show how the two viewpoints connect with each other. In all this we shall confine our attention to the simplest possible situation, with migration, mutation, and selection excluded. Thus we shall see what happens in small populations in the absence of other factors influencing gene frequency. In the next chapter we shall extend the conclusions to more realistic situations by removing the restrictive simplifications, and in Chapter 5 we shall consider the special cases of pedigree populations and very small populations maintained by regular systems of close inbreeding.

The idealized population

In order to reduce the dispersive process to its simplest form we imagine an idealized population as follows. We suppose there to be initially one large population in which mating is random, and this population becomes subdivided into a large number of sub-populations. The subdivision might arise from geographical or ecological causes under natural conditions, or from controlled breeding in domesticated or laboratory populations. The initial random-mating population will be referred to as the *base population*, and the sub-populations will be referred to as *lines*. All the lines together constitute the whole population, and each line is a 'small population' in which gene frequencies are subject to the dispersive process. When a single locus is under discussion we cannot properly understand what goes

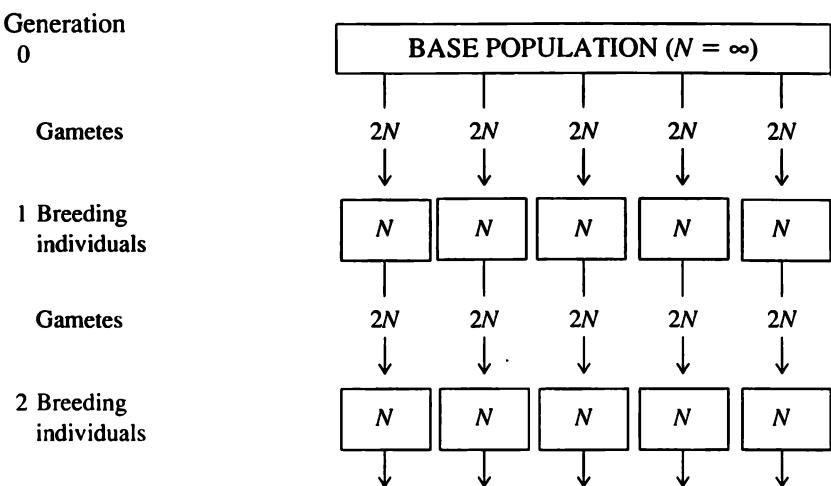


Fig. 3.1. Diagrammatic representation of the subdivision of a single large population – the base population – into a number of sub-populations, or lines.

on in one line except by considering it as one of a large number of lines. But what happens to the genes at one locus in a number of lines happens equally to those at a number of loci in one line, provided they all start at the same gene frequency. So the consequences of the process apply equally to a single line provided we consider many loci in it.

The simplifying conditions specified for the idealized population are the following:

1. Mating is restricted to members of the same line. The lines are thus isolated in the sense that no genes can pass from one line to another. In other words migration is excluded.
2. The generations are distinct and do not overlap.
3. The number of breeding individuals in each line is the same for all lines and in all generations. Breeding individuals are those that transmit genes to the next generation.
4. Within each line mating is random, including self-fertilization in random amount.
5. There is no selection at any stage.
6. Mutation is disregarded.

The situation implied by these conditions is represented diagrammatically in Fig. 3.1, and may be described thus: all breeding individuals contribute equally to a pool of gametes from which zygotes will be formed. Union of gametes is strictly random. Out of a potentially large number of zygotes, only a limited number survive to become breeding individuals in the next generation, and this is the stage at which the sampling of the genes transmitted by the gametes takes place. Survival of zygotes is random, and consequently the contribution of the parents to the next generation is not uniform, but varies according to the chances of survival of their progeny. Since the population size is constant from generation to generation, the average number of progeny that reach breeding age is one per individual parent or

two per mated pair of parents. In this scheme the sampling is seen as a single event, the reduction of a large number of gametes to a small number of breeding progeny. The reduction of numbers may take place in several stages. This makes no difference to the theoretical consequences deduced from the final number of breeding progeny, provided the sampling at each stage is random. The observed consequences, however, would be affected if a population were enumerated at stages before the reduction of numbers was complete.

The following symbols will be used in connection with the idealized population.

N = the number of breeding individuals in each line and generation. This is the *population size*.

t = time, in generations, starting from the base population at t_0 .

q = frequency of a particular allele at a locus.

$p = 1 - q$ = frequency of all other alleles at that locus. q and p refer to the frequencies in any one line; \bar{q} and \bar{p} refer to the frequencies in the whole population and are the means of q and p ; q_0 and p_0 are the frequencies in the base population.

Since all systematic processes tending to change the gene frequency have been excluded, the mean gene frequency among all lines at any stage must be the same as the initial frequency. Thus $\bar{q} = q_0$, and the two can be used interchangeably in this chapter.

It is obvious that the conditions specified for the idealized population do not hold in real populations. The conclusions to be drawn in this chapter, however, can be made applicable to real populations by the simple device of replacing the population size N by the 'effective' population size N_e , a concept to be introduced in the next chapter.

Sampling

Variance of gene frequency

The change of gene frequency resulting from sampling is random in the sense that its direction is unpredictable. But its magnitude can be predicted in terms of the variance of the change. Consider the formation of the lines from the base population. Each line is formed from a sample of N individuals drawn from the base population. Since each individual carries two genes at a locus, the subdivision of the population represents a series of samples each of $2N$ genes, drawn at random from the base population. The gene frequencies in these samples will have an average value equal to that in the base population, i.e. q_0 , and will be distributed about this mean with a variance $p_0q_0/2N$, which is the binomial variance of sample means, the sample size being in this case $2N$. This variance is the variance of q_1 , the gene frequency in the different lines after one generation. Since the initial gene frequency q_0 is the same for all lines, it is also the variance of $(q_1 - q_0)$, which is the change of gene frequency. Thus the change of gene frequency, Δq , resulting from sampling in one generation, can be stated in terms of its variance as

$$\sigma_{\Delta q}^2 = \frac{p_0 q_0}{2N} \quad \dots [3.1]$$

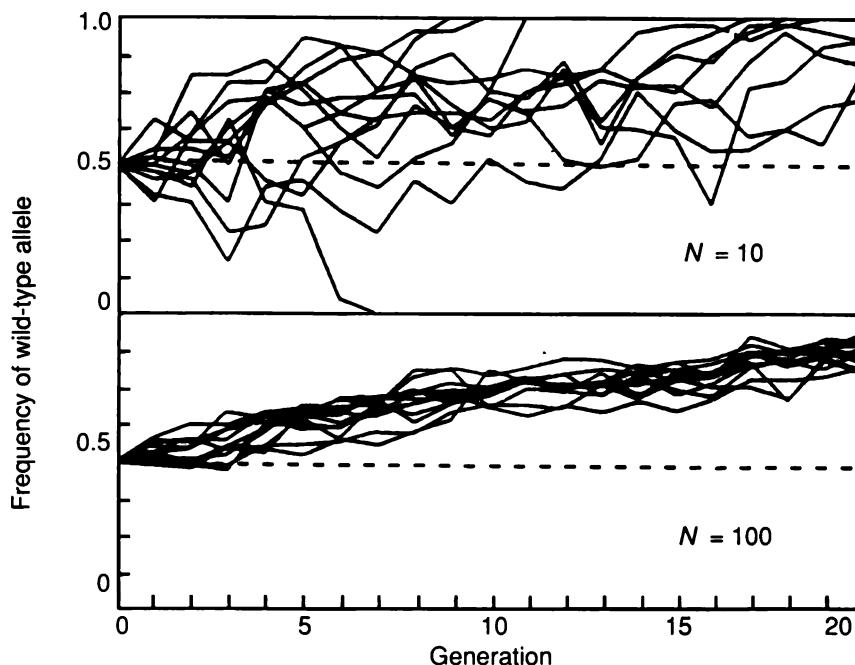


Fig. 3.2. Random drift of a colour gene ('black') in *Tribolium*. Heterozygotes were recognizable, so the gene frequencies were estimated exactly by counting. The figure shows the results with two population sizes, $N = 10$ and $N = 100$. There were 12 lines with each population size. Natural selection favoured the wild-type allele and led to an overall increase in its frequency, random drift causing variation of the lines around the mean, more marked in the smaller than in the larger populations. (After Rich, Bell, and Wilson, 1979.)

This variance of Δq expresses the magnitude of the change of gene frequency resulting from the dispersive process. It expresses the expected change in any one line, or the variance of gene frequencies that would be found among many lines after one generation. Its effect is a dispersion of gene frequencies among the lines; in other words, the lines come to differ in gene frequency, though the mean in the population as a whole remains unchanged.

In the next generation the sampling process is repeated, but each line now starts from a different gene frequency and so the second sampling leads to a further dispersion. The variance of the change now differs among the lines, since it depends on the gene frequency q_1 in the first generation of each line separately. The effect of continued sampling through successive generations is that each line fluctuates irregularly in gene frequency, and the lines spread apart progressively, thus becoming differentiated. These are the first two consequences of the process, and they are exemplified in Fig. 3.2. If there were only one small population or line, one would see only the random drift in the erratic changes of gene frequency from generation to generation. Having several lines, as in Fig. 3.2, one sees random drift in each line and also the progressive differentiation between them as they drift apart. The differentiation between lines is more clearly seen in Fig. 3.3, from a different experiment, showing the distributions of gene frequency in successive generations.

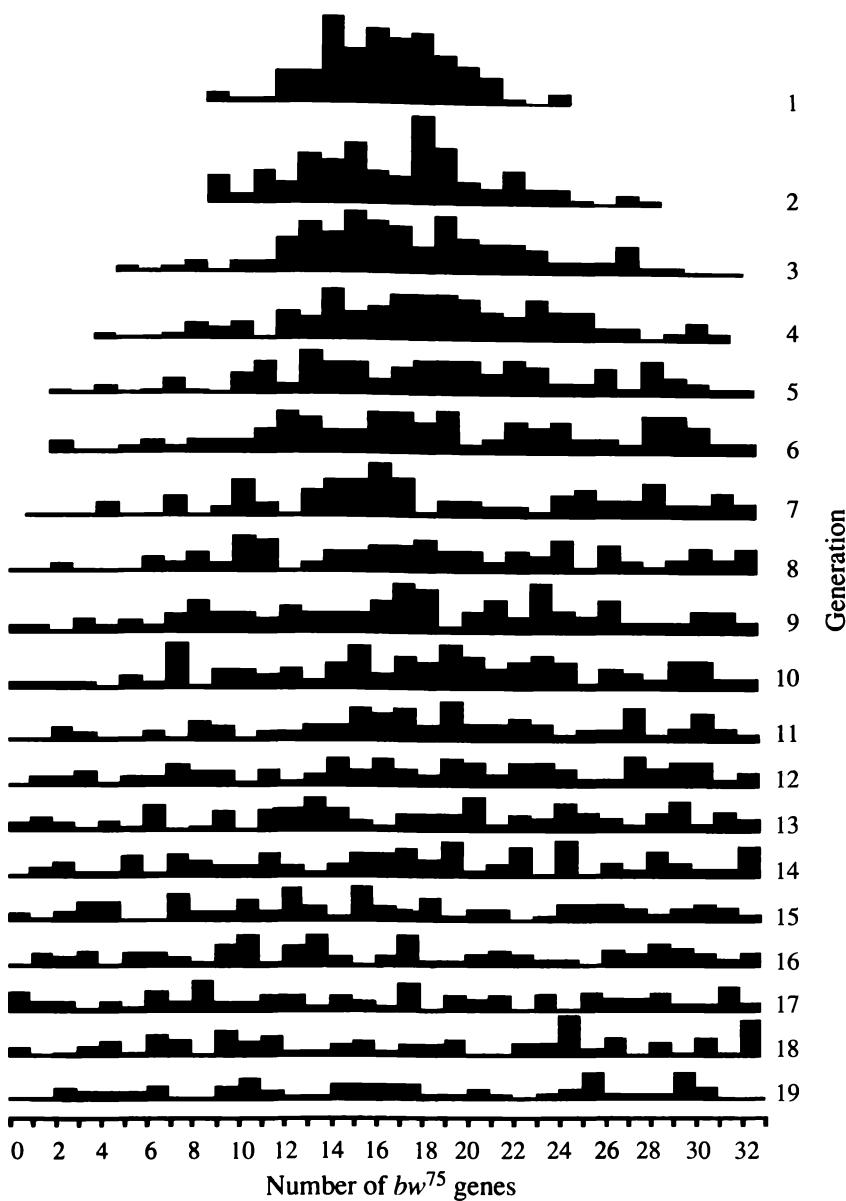


Fig. 3.3. Distributions of gene frequencies in 19 consecutive generations among 105 lines of *Drosophila melanogaster*, each of 16 individuals. The gene frequencies refer to two alleles at the 'brown' locus (bw^{75} and bw), with initial frequencies of 0.5. The height of each black column shows the number of lines having the gene frequency shown on the scale below, previously fixed lines being excluded. (After Buri, 1956.)

Increasing differentiation among the lines is equivalent to increasing variance of the gene frequency among them. The variance of the gene frequency, σ_q^2 , among the lines, at any generation t , is given by

$$\sigma_q^2 = p_0 q_0 \left[1 - \left(1 - \frac{1}{2N} \right)^t \right] \quad \dots [3.2]$$

(The derivation of this expression will be explained later because it is more easily understood by consideration of the inbreeding aspect of the process.) We may note here a fact that will be needed later, and is obvious from equation [3.2], namely that $\sigma_p^2 = \sigma_q^2$.

Examination of the distributions of gene frequencies in Fig. 3.3 shows that the distributions change in shape, becoming eventually quite flat, with all frequencies equally probable. (This is not true of the limiting frequencies of 0 and 1, which are discussed in the next section.) Theoretical considerations show that there are two phases in the dispersion. During the initial phase the gene frequencies are spreading out from the initial value. This phase is followed by a steady phase, when the gene frequencies are evenly spread out over the range and all gene frequencies except the two limits are equally probable. This uniform distribution of the steady phase is attained even if the initial gene frequency is not 0.5, though it takes longer to reach it. The duration, in generations, of the initial phase is a small multiple of the population size, depending on the initial gene frequency. With $q_0 = 0.5$ it lasts about $2N$ generations, and with $q_0 = 0.1$ it lasts about $4N$ generations (Kimura, 1955). The theoretical distributions of gene frequency during the initial phase, with $q_0 = 0.5$ and $q_0 = 0.1$, are shown in Fig. 3.4. The observed distributions in Fig. 3.3 agree well with the theoretical distributions for $q_0 = 0.5$.

Fixation

There are limits to the spreading apart of the lines that can be brought about by the dispersive process. The gene frequency cannot change beyond the limits of 0 or 1, and sooner or later each line must reach one or other of these limits. Moreover, the limits are 'traps' or points of no return, because once the gene frequency has reached 0 or 1 it cannot change any more in that line. When a particular allele has reached a frequency of 1 it is said to be *fixed* in that line, and when it reaches a frequency of 0 it is *lost*. When an allele reaches fixation, no other allele can be present in that line, and the line may then be said to be fixed. When a line is fixed, all individuals in it are of identical genotype with respect to that locus. Eventually all lines, and all loci in a line, become fixed. The individuals of a line are then genetically identical, and this is the basis of the genetic uniformity of highly inbred strains.

When the process has gone to completion and all lines are fixed, the mean gene frequency is still unchanged and equal to the initial gene frequency. Therefore the proportion of the lines in which different alleles at a locus are fixed is equal to the initial frequencies of the alleles. If the base population contains two alleles A_1 and A_2 at frequencies p_0 and q_0 respectively, then A_1 will be fixed in the proportion p_0 of the lines, and A_2 in the remaining proportion q_0 . The variance of the gene frequency among the lines is then $p_0 q_0$, as may be seen from equation [3.2] by putting t equal to infinity. (In Fig. 3.3 the lines in which fixation or loss has just occurred are shown, but not those in which it occurred earlier.)

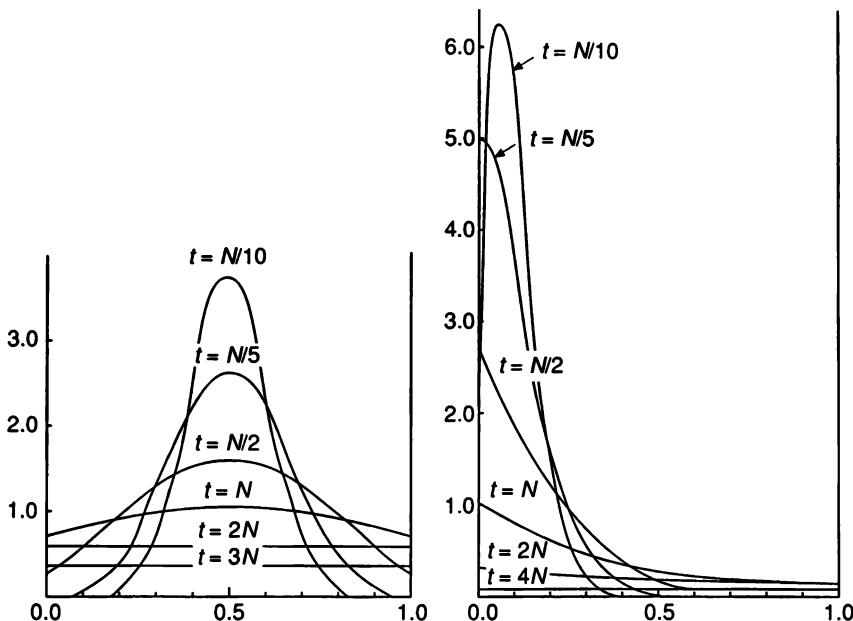


Fig. 3.4. Theoretical distributions of gene frequencies among lines, after different numbers of generations, t , expressed in terms of the population size of the lines, N . In the left-hand figure $q_0 = 0.5$; on the right $q_0 = 0.1$. Previously fixed lines (see next section) are excluded. The horizontal scale is the gene frequency, q , in any line. The vertical axis is the probability, scaled to make the area under each curve equal to the proportion of unfixed lines. (After Kimura, 1955.)

When concerned with the attainment of genetic uniformity one wants to know how soon fixation takes place; what is the probability of a particular locus being fixed, or what proportion of all loci in a line will be fixed, after a certain number of generations. Consideration of the progressive nature of the dispersion, as illustrated in Fig. 3.3, will show that fixation does not start immediately; the dispersion of gene frequencies must proceed some way before any line is likely to reach fixation. To deduce the probability of fixation is mathematically complicated and only an outline of the conclusions can be given here. After the steady phase has been reached fixation proceeds at a constant rate: a proportion of $1/N$ of the lines previously unfixed becomes fixed in each generation. After the earliest stages of fixation, the proportion of lines in which a gene with initial frequency q_0 is expected to be fixed, lost, or to be still segregating is approximately as follows (Wright, 1952):

$$\left. \begin{array}{ll} \text{fixed:} & q_0 - 3p_0 q_0 P \\ \text{lost:} & p_0 - 3p_0 q_0 P \\ \text{neither:} & 6p_0 q_0 P \end{array} \right\} \quad \text{where } P = \left(1 - \frac{1}{2N}\right)^t \quad \dots [3.3]$$

Genotype frequencies

Change of gene frequency leads to change of genotype frequencies; so the genotype frequencies in small populations follow the changes of gene frequency resulting from the dispersive process. In the idealized population, which we are still considering, mating is random within each of the lines. Consequently the genotype frequencies in any one line are the Hardy–Weinberg frequencies appropriate to the gene frequency in the previous generation of that line. (There is, in fact, a small deviation from Hardy–Weinberg frequencies within lines, which will be explained at the end of this chapter, but it can be ignored for the moment.) As the lines drift apart in gene frequency they become differentiated also in genotype frequencies. But differentiation is not the only aspect of the change: the general direction of the change is toward an increase of homozygous, and a decrease of heterozygous, genotypes. The reason for this is the dispersion of gene frequencies from intermediate values toward the extremes. Heterozygotes are most frequent at intermediate gene frequencies (see Fig. 1.1), so the drift of gene frequencies toward the extremes leads, on the average, to a decline in the frequency of heterozygotes. It also leads to a higher proportion of the individuals in a line having the same genotype, and so to an increased genetic uniformity within lines.

The genotype frequencies in the population as a whole can be deduced from a knowledge of the variance of gene frequencies in the following way. If an allele has a frequency q in one particular line, homozygotes of that allele will have a frequency of q^2 in that line. The frequency of these homozygotes in the population as a whole will therefore be the mean value of q^2 over all lines. We shall write this mean frequency of homozygotes as (q^2) . The value of (q^2) can be found from a knowledge of the variance of gene frequencies among the lines, by noting that the variance of a set of observations is found by deducting the square of the mean from the mean of the squared observations. Thus

$$\text{and } \begin{aligned} \sigma_q^2 &= (\bar{q}^2) - \bar{q}^2 && \dots [3.4] \\ (\bar{q}^2) &= \bar{q}^2 + \sigma_q^2 \end{aligned}$$

where σ_q^2 is the variance of gene frequencies among the lines, as given in equation [3.2], and \bar{q}^2 is the square of the mean gene frequency. Since the mean gene frequency \bar{q} is equal to the original q_0 , it follows that \bar{q}^2 or q_0^2 is the original frequency of homozygotes in the base population. Thus in the population as a whole the frequency of homozygotes of a particular allele increases, and is always in excess of the original frequency by an amount equal to the variance of the gene frequency among the lines. In a two-allele system the same applies to the other allele, and the frequency of heterozygotes is reduced correspondingly. Noting from equation [3.2] $\sigma_p^2 = \sigma_q^2$, we therefore find the genotypic frequencies for a locus with two alleles as follows:

Genotype	Frequency in whole population	
A_1A_1	$p_0^2 + \sigma_q^2$	
A_1A_2	$2p_0q_0 - 2\sigma_q^2$	
A_2A_2	$q_0^2 + \sigma_q^2$	

$\dots [3.5]$

These genotype frequencies are no longer the Hardy–Weinberg frequencies appropriate to the original or mean gene frequency. The Hardy–Weinberg relationships between gene frequency and genotype frequencies, though they hold good within each line separately, do not hold if the lines are taken together and regarded as a single population. This fact causes some difficulty in relating gene and genotype frequencies in natural populations, because they are often more or less subdivided and the degree of subdivision is seldom known.

The foregoing account of genotype frequencies describes the situation in terms of one locus in many lines. It can be regarded equally as referring to many loci in one line; then the change in any one line or small population is an increase in the number of loci at which individuals are homozygous and a corresponding decrease in the number at which they are heterozygous – in short, an increase of homozygotes at the expense of heterozygotes. This change of genotype frequencies resulting from the dispersive process is the genetic basis of the phenomenon of inbreeding depression, of which a full explanation will be found in Chapter 14.

We have now surveyed the general nature of the dispersive process and its four major consequences – random drift, differentiation of sub-populations, genetic uniformity within sub-populations, and overall increase in the frequency of homozygous genotypes. Let us now look at the process from another viewpoint, as an inbreeding process. Instead of regarding the increase of homozygotes as a consequence of the dispersion of gene frequencies, we shall now look directly at the manner in which the additional homozygotes arise.

Inbreeding

Inbreeding means the mating together of individuals that are related to each other by ancestry. That the degree of relationship between the individuals in a population depends on the size of the population will be clear by consideration of the numbers of possible ancestors. In a population of bisexual organisms every individual has two parents, four grand-parents, eight great-grandparents, etc., and t generations back it has 2^t ancestors. Not very many generations back, the number of individuals required to provide separate ancestors for all the present individuals becomes larger than any real population could contain. Any pair of individuals must therefore be related to each other through one or more common ancestors in the more or less remote past; and the smaller the size of the population in previous generations the less remote are the common ancestors, or the greater their number. Thus pairs mating at random are more closely related to each other in a small population than in a large one. This is why the properties of small populations can be treated as the consequences of inbreeding.

The essential consequence of two individuals having a common ancestor is that they may both carry replicates of one of the genes present in the ancestor; and if they mate they may pass on these replicates to their offspring. Thus inbred individuals – that is to say, offspring produced by inbreeding – may carry two genes at a locus that are replicates of one and the same gene in a previous generation. Consideration of this consequence of inbreeding shows that there are two sorts of identity among allelic genes, and two sorts of homozygote. The sort of identity we

have hitherto considered is a functional identity. If two genes cannot be distinguished by their phenotypic effects, or by any other functional criterion, they are regarded as being the same allele. An individual carrying a pair of such genes is a homozygote in the ordinary sense. The new sort of identity is one of origin by replication. Two genes that have originated from the replication of one single gene in a previous generation may be called *identical by descent*, or simply *identical*. Two genes that are not identical are *independent* in descent. Homozygotes of identical genes may be called *identical homozygotes*. Other terms in use are *autozygous* to describe identical homozygotes and *allozygous* to describe homozygotes that are not known to be autozygous. It is the production of identical homozygotes that gives rise to the increase of homozygotes as a consequence of inbreeding.

Identity by descent provides the basis for a measure of the dispersive process, through the degree of relationship between the mating pairs. The measure is the *coefficient of inbreeding*, which is the probability that the two genes at any locus in an individual are identical by descent. It refers to an individual and expresses the degree of relationship between the individual's parents. If the parents of any generation have mated at random then the coefficient of inbreeding of the progeny is the probability that two gametes taken at random from the parent generation carry identical genes at a locus. This is the average coefficient of inbreeding of all the progeny. Individuals of different families will have different inbreeding coefficients because with random mating some pairs of parents will be more closely related than other pairs. It is, however, with the average coefficient of inbreeding that we are concerned as a measure of the dispersive process. The coefficient of inbreeding is generally symbolized by F .

The degree of relationship expressed in the inbreeding coefficient is essentially a comparison between the population in question and some specified or implied base population. Without this point of reference it is meaningless, as the following consideration will show. On account of the limitation in the number of independent ancestors in any population not infinitely large, all genes now present at a locus in the population would be found to be identical by descent if traced far enough back into the remote past. Therefore the inbreeding coefficient only becomes meaningful if we specify some time in the past beyond which ancestries will not be pursued, and at which all genes present in the population are to be regarded as independent – that is, not identical by descent. This point is the *base population* and by its definition it has an inbreeding coefficient of zero. The inbreeding coefficient of a subsequent generation expresses the amount of the dispersive process that has taken place since the base population, and compares the degree of relationship between the individuals now, with that between individuals in the base population. Reference to the base population is not always explicitly stated, but is always implied. For example, we can speak of the inbreeding coefficient of a population subdivided into lines. The comparison of relationship is between the individuals of a line and individuals taken at random from the whole population. The base population implied is a hypothetical population from which all the lines were derived.

Inbreeding in the idealized population

Let us now return to the idealized population and deduce the coefficient of inbreeding in successive generations, starting with the base population and its progeny

constituting generation 1. The situation may be visualized by thinking of a hermaphrodite marine organism, capable of self-fertilization, shedding eggs and sperm into the sea. There are N individuals, each shedding equal numbers of gametes which unite at random. All the genes at a locus in the base population have to be regarded as being non-identical; so, considering only one locus, among the gametes shed by the base population there are $2N$ different sorts, in equal numbers, bearing the genes A_1, A_2, A_3 , etc., at the A locus. The gametes of any one sort carry identical genes; those of a different sort carry genes of independent origin. What is the probability that a pair of gametes taken at random carry identical genes? This is the inbreeding coefficient of generation 1. Any gamete had a $(1/2N)$ th chance of uniting with another of the same sort, so $1/2N$ is the probability that uniting gametes carry identical genes, and is thus the coefficient of inbreeding of the progeny. Now consider the second generation. There are now two ways in which identical homozygotes can arise, one from the new replication of genes and the other from the previous replication. The probability of newly replicated genes coming together in a zygote is again $1/2N$. The remaining proportion, $1 - 1/2N$, of zygotes carry genes that are independent in their origin from generation 1, but may have been identical in their origin from generation 0. The probability of their identical origin in generation 0 is what we have already deduced as the inbreeding coefficient of generation 1. Thus the total probability of identical homozygotes in generation 2 is

$$F_2 = \frac{1}{2N} + \left(1 - \frac{1}{2N}\right)F_1$$

where F_1 and F_2 stand for the inbreeding coefficients of generations 1 and 2 respectively. The same argument applies to subsequent generations, so that in general the inbreeding coefficient of individuals in generation t is

$$F_t = \frac{1}{2N} + \left(1 - \frac{1}{2N}\right)F_{t-1} \quad \dots [3.6]$$

Thus the inbreeding coefficient is made up of two parts: an ‘increment’, $1/2N$, attributable to the new inbreeding, and a ‘remainder’, attributable to the previous inbreeding and having the inbreeding coefficient of the previous generation. In the idealized population the ‘new inbreeding’ arises from self-fertilization, which brings together genes replicated in the immediately preceding generation. Exclusion of self-fertilization simply shifts the replication one generation further back, so that the ‘new inbreeding’ brings together genes replicated in the grand-parental generation; the coefficient of inbreeding is affected, but not very much, as we shall see later. The distinction between ‘new’ and ‘old’ inbreeding brings clearly to light a point which we note here in passing because it will be needed later and is often important in practice: if there is no ‘new inbreeding’, as would happen if the population size were suddenly increased, the previous inbreeding is not undone, but remains where it was before the increase of population size.

Let us call the ‘increment’ or ‘new inbreeding’ ΔF , so that

$$\Delta F = \frac{1}{2N} \quad \dots [3.7]$$

Equation [3.6] may then be rewritten in the form

$$F_t = \Delta F + (1 - \Delta F)F_{t-1} \quad \dots [3.8]$$

Further rearrangement makes clearer the precise meaning of the ‘increment’ ΔF .

$$\Delta F = \frac{F_t - F_{t-1}}{1 - F_{t-1}} \quad \dots [3.9]$$

From the equation written thus we see that the ‘increment’ ΔF measures the *rate of inbreeding* in the form of a proportionate increase. It is the increase of the inbreeding coefficient in one generation, relative to the distance that was still to go to reach complete inbreeding. This measure of the rate of inbreeding provides a convenient way of going beyond the restrictive simplifications of the idealized population, and it thus provides a means of comparing the inbreeding effects of different breeding systems. When the inbreeding coefficient is expressed in terms of ΔF , equation [3.8] is valid for any breeding system and is not restricted to the idealized population, though only in the idealized population is ΔF equal to $1/2N$.

So far we have done no more than relate the inbreeding coefficient in one generation to that of the previous generation. It remains to extend equation [3.8] back to the base population and so express the inbreeding coefficient in terms of the number of generations. This is made easier by the use of a symbol P for the complement of the inbreeding coefficient $1 - F$, which is known as the *panmictic index*. Substitution of $(1 - P)$ for F in equation [3.9], and rearrangement, leads to

$$\frac{P_t}{P_{t-1}} = 1 - \Delta F \quad \dots [3.10]$$

Thus the panmictic index is reduced by a constant proportion in each generation. Extension back to generation $t - 2$ gives

$$\frac{P_t}{P_{t-2}} = (1 - \Delta F)^2$$

and extension back to the base population gives

$$P_t = (1 - \Delta F)^t P_0 \quad \dots [3.11]$$

where P_0 is the panmictic index of the base population. The base population is defined as having an inbreeding coefficient of 0, and therefore a panmictic index of 1. The inbreeding coefficient in any generation t , referred to the base population, is therefore

$$F_t = 1 - (1 - \Delta F)^t \quad \dots [3.12]$$

The consequences of the dispersive process were described earlier from the viewpoint of sampling variance. Let us now look again at them, applying the rate of inbreeding and the inbreeding coefficient as measures of the process. Strictly speaking we should refer still to the idealized population, but the equating of the two viewpoints is generally valid, unless the population size is different in parent and offspring generations or there is non-random mating within lines.

Variance of gene frequency

First, the variance of the change of gene frequency in one generation, taken from equation [3.1] and expressed in terms of the rate of inbreeding, becomes

$$\sigma_{\Delta q}^2 = \frac{p_0 q_0}{2N} = p_0 q_0 \Delta F \quad \dots [3.13]$$

An equivalent way of writing equation [3.13] is in terms of the inbreeding coefficient and the variance of gene frequencies after one generation. It follows that the relationship is the same after any number of generations, so that after t generations

$$\sigma_q^2 = p_0 q_0 F_t \quad \dots [3.14]$$

Equation [3.14] can be shown to be equivalent to equation [3.2], which was given without explanation. Replacing F_t in equation [3.14] by $[1 - (1/2N)^t]$ from equations [3.12] and [3.7] gives equation [3.2].

Measures of the dispersive process based on inbreeding are more useful than those based on the variance of gene frequencies because they apply equally to any mean, or initial, gene frequency. Thus ΔF expresses the rate of dispersion, and F the cumulated effect of random drift.

Genotype frequencies

Let us consider next the genotype frequencies in the population as a whole. The genotype frequencies expressed in terms of the variance of gene frequency in equation [3.5] can be rewritten in terms of the coefficient of inbreeding from equation [3.14]. The frequency of $A_2 A_2$, for example, is

$$(\bar{q^2}) = q_0^2 + \sigma_q^2 = q_0^2 + p_0 q_0 F$$

The genotype frequencies expressed in this way are entered in the left-hand side of Table 3.1. As was explained before, this way of writing the genotype frequencies shows how the homozygotes increase at the expense of the heterozygotes. Recognition of identity by descent to which the inbreeding viewpoint led us means that we can now distinguish the two sorts of homozygote, identical and independent, among the $A_1 A_1$ and $A_2 A_2$ genotypes. The frequency of identical homozygotes among both genotypes together is by definition the inbreeding coefficient, F ; and the division between the two genotypes is in proportion to the initial gene frequencies. So $p_0 F$ is the frequency of $A_1 A_1$ identical homozygotes, and $q_0 F$ that of $A_2 A_2$ identical homozygotes. The remaining genotypes, both homozygotes and heterozygotes, carry genes that are independent in origin and are therefore the equivalent of pairs of gametes taken at random from the population as a whole. Their frequencies are therefore the Hardy-Weinberg frequencies. Thus, from the inbreeding viewpoint, we arrive at the genotype frequencies shown in the right-hand columns of Table 3.1. This way of writing the genotype frequencies shows how homozygotes are divided between those of independent and those of identical origin. The equivalence of the two ways of expressing the genotype frequencies can be verified from their algebraic identity. Both ways show equally clearly how the heterozygotes are reduced in frequency in proportion to $1 - F$.

The panmictic index, which was defined earlier as $P = 1 - F$, expresses the frequency of heterozygotes in a subdivided population relative to the Hardy–Weinberg frequency expected if the population as a whole mated at random. This can be seen by consideration of the frequency of heterozygotes given in Table 3.1. Let H_t and H_0 be the frequencies of heterozygotes in a subdivided and random-mating population respectively. Then $H_0 = 2p_0q_0$ and $H_t = 2p_0q_0(1 - F) = H_0(1 - F)$. The panmictic index at generation t is therefore

$$P_t = 1 - F_t = \frac{H_t}{H_0} \quad \dots [3.15]$$

Table 3.1 Genotype frequencies for a locus with two alleles, expressed in terms of the inbreeding coefficient F .

<i>Original frequencies</i>	<i>Change due to inbreeding</i>	<i>Origin:</i>	
		<i>Independent</i>	<i>Identical</i>
A_1A_1	p_0^2	$+ p_0q_0F$	$= p_0^2(1 - F)$
A_1A_2	$2p_0q_0$	$- 2p_0q_0F$	$= 2p_0q_0(1 - F)$
A_2A_2	q_0^2	$+ p_0q_0F$	$= q_0^2(1 - F)$

When a real population is sampled, a deficiency of heterozygotes may be the only indication that it is a subdivided population. The observed frequency of heterozygotes, H , relative to the Hardy–Weinberg frequency, $2\bar{p}\bar{q}$, then gives the panmictic index as $P = H/2\bar{p}\bar{q}$, \bar{p} and \bar{q} being the observed gene frequencies in the sample as a whole. Caution is needed, however, in regarding the value of P so calculated as anything more than a description of the sample. It is unlikely that all the sub-populations that really existed would be equally represented in the sample and, unless they were, P could not validly be used to estimate, for example, the variance of the gene frequency among the sub-populations by equation [3.14].

Genotype frequencies within lines Throughout this chapter it has been assumed that mating is at random within lines, and that consequently the genotype frequencies within any line are the Hardy–Weinberg frequencies appropriate to the gene frequency in that line. It was pointed out, however, that the genotype frequencies actually deviate slightly from the Hardy–Weinberg expectations. The reason for this deviation is that the sample of genes passed to the next generation consists, in fact, of two independent samples, one in male parents and the other in female parents, with N genes in each sample. The male and female parents therefore differ, on average, in their gene frequencies. A difference in gene frequency between male and female parents leads to an excess of heterozygotes in the progeny; or, in other words, an expectation calculated from the mean gene frequency is too low. By putting appropriate gametic frequencies in Table 1.2 it can be shown that the expected frequency of heterozygotes within any line is $H = 2pq + \frac{1}{2}D^2$, where p and q are the mean gene frequencies in the line, D is the difference in gene frequency between male and female parents, and D^2 is the mean squared difference. Since $D = 0$ it follows, by analogy with equation [3.4], that $D^2 = \sigma_D^2$. The variance σ_D^2

is the variance of the difference between two binomial samples of size N , which is $2pq/N$. Thus the expected frequency of heterozygotes within lines is

$$\begin{aligned} H &= 2pq + pq/N \\ &= 2pq\left(1 + \frac{1}{2N}\right) \end{aligned} \quad \left. \right\} \quad \dots [3.16]$$

(For further details see Robertson, 1965.) The excess of heterozygotes is trivial unless N , the number of parents of the sample, is very small. But it can have an appreciable effect if the frequencies observed in a small sample of a single population are tested for agreement with Hardy-Weinberg expectations.

The overall frequency of heterozygotes in the whole of a subdivided population is sometimes used to estimate the amount of inbreeding in the history of the population, rather than as a description of the present state of subdivision. This is done in Example 4.1. If the lines are separately identifiable, and the number of parents sampled in each line is known, correction can be made for the excess of heterozygotes. Substitution of H from equation [3.16] for H_0 in equation [3.15] gives

$$1 - F = \frac{H}{2pq(1 + 1/2N)} \quad \dots [3.17]$$

where H is the observed frequency of heterozygotes, p and q are the overall observed gene frequencies, and N is the number of parents in each line.

Problems

In working the problems on Chapter 3, treat the populations as if they were idealized populations.

3.1 Codfish have two forms of haemoglobin determined by alleles a and b at one locus. A sample of cod taken off the Norwegian coast had the following frequencies of the three genotypes.

aa	ab	bb	Total
130	763	1698	2591

Are these frequencies compatible with the sample having been drawn from a random-breeding population? What do they suggest about the breeding structure of the population?

Data from Møller, D. (1968) *Hereditas*, **60**, 1-32.

[Solution 3]

3.2 Among the cod described in Problem 3.1 two distinct races can be recognized by anatomical differences in the otoliths. When the sample was separated into the two races, called 'Arctic' and 'Coastal', the following numbers were found.

	aa	ab	bb	Total
Arctic	23	250	946	1219
Coastal	107	513	752	1372

What further light does this throw on the question in Problem 3.1?

[Solution 13]

3.3 If a population is maintained by random mating among 20 pairs of parents in every generation, what will be its inbreeding coefficient after 5 and after 10 generations?

[Solution 23]

3.4 Suppose that for a class experiment each student was given 10 pairs of unmated *Drosophila* taken at random from a large stock in which an electrophoretic variant was present at a gene frequency of 0.3. Each student then maintained his sub-population by taking 10 pairs at random to be parents of the next generation. After 5 generations each student determined the gene frequency in his own population by electrophoresis of a sample of 20 flies from the progeny. What would be the average gene frequency found? How much variation would you expect to find among the students in their estimated gene frequencies, assuming that all read their gels correctly?

[Solution 33]

3.5 If the numbers of the three genotypes counted by the students in the experiment of Problem 3.4 were put together, what would be the overall frequencies of the genotypes?

[Solution 43]

3.6 A stock of mice consisted of 18 lines all derived from the same base population but bred separately thereafter. The stock was polymorphic for an autosomal enzyme locus, *Got-1*, with two alleles, *a* and *b*. After 27 generations mice from all the lines were typed by electrophoresis for the genotypes at this locus and the following numbers were found.

<i>aa</i>	<i>ab</i>	<i>bb</i>	Total
42	76	448	566

What is the inbreeding coefficient indicated by these numbers?

Data from Garnett, I. (1973) Ph.D. Thesis, University of Edinburgh.

[Solution 53]

3.7 Suppose that a random-breeding population is sampled and the following genotype frequencies of a protein variant are found.

<i>aa</i>	<i>ab</i>	<i>bb</i>
0.34	0.52	0.14

(1) Ignoring the question of significance, do these frequencies give evidence of some form of selection operating on the genotypes? (2) How would the conclusion be altered by the knowledge that the individuals in the sample were the progeny of 4 pairs of parents?

[Solution 63]

3.8 Modify equation [3.16] so as to be applicable when there are different numbers of male and female parents, as is usually the case with domestic livestock.

[Solution 73]

4 Small Populations: II. Less Simplified Conditions

In order to simplify the description of the dispersive process we confined our attention in the last chapter to an idealized population, and to do this we had to specify a number of restrictive conditions, which could seldom be fulfilled in real populations. The purpose of this chapter is to adapt the conclusions of the last chapter to situations in which the conditions imposed do not hold; in other words, to remove the more serious restrictions and bring the conclusions closer to reality. The restrictive conditions were of two sorts, one sort being concerned with the breeding structure of the population and the other excluding mutation, migration, and selection from consideration. We shall first describe the effects of deviations from the idealized breeding structure, and then consider the outcome of the dispersive process when mutation, migration, or selection are operating at the same time.

Effective population size

If the breeding structure does not conform to that specified for the idealized population, it is possible to evaluate the dispersive process in terms of either the variance of gene frequencies or the rate of inbreeding. This can be done by the same general methods and no new principles are involved. We shall therefore give the conclusions briefly and without detailed explanation. For a comprehensive review of the matter see Caballero (1994). The most convenient way of dealing with any particular deviation from the idealized breeding structure is to express the situation in terms of the *effective number* of breeding individuals, or the *effective population size*, N_e . This is the number of individuals that would give rise to the calculated sampling variance, or rate of inbreeding, if they bred in the manner of the idealized population. Suppose, for example, that the rate of inbreeding, ΔF , had been calculated for a particular breeding structure from consideration of the probability of identical homozygotes being produced. In the idealized population, ΔF is related to the population size N by equation [3.7] as $\Delta F = 1/2N$. The effective size is related to ΔF in the same way and would therefore be obtained from the calculated ΔF as $N_e = 1/2\Delta F$. Thus all the conclusions drawn in the previous chapter are valid for any breeding structure, and the formulae deduced can be applied, if the effective number N_e is substituted for the actual number N . When the breeding structure is known, the effective number can be derived from the actual number, and the relationships between the two are given below for the most common departures from the idealized breeding structure. The exact expressions are often complicated, but

in most circumstances a simple approximation can be used with sufficient accuracy. It is important to note that in these relationships the actual number N is the number of breeding individuals, and it therefore cannot be obtained from a census, unless the different age-groups are distinguished. Knowing the effective population size N_e for any breeding structure, one can then obtain the rate of inbreeding as

$$\Delta F = \frac{1}{2N_e} \quad \dots [4.1]$$

and from ΔF any of the consequences of inbreeding can be calculated by the formulae of the previous chapter.

Exclusion of closely related matings

In bisexual organisms self-fertilization is, of course, impossible. Sib-mating is also excluded in man, and is often deliberately avoided in the maintenance of populations of laboratory and domesticated animals. The exclusion of closely related matings, however, does not make a great deal of difference to the rate of inbreeding for the following reason. The progeny of a closely related mating have a higher coefficient of inbreeding than those of less closely related matings. Their presence therefore raises the average coefficient of inbreeding of the population at any time. But their higher inbreeding is not permanent: mating at random, they themselves are likely to mate with less closely related individuals, and so their higher-than-average inbreeding is not passed on to their progeny. Thus the exclusion of closely related matings reduces the average coefficient of inbreeding throughout, but it does not much affect the rate at which the inbreeding accumulates. The effect of the exclusions can be quantified approximately in the effective number as follows (Wright, 1969, p. 212).

With self-fertilization excluded,

$$N_e = N + \frac{1}{2} \text{ (approx.)} \quad \dots [4.2a]$$

and so, by equation [4.1],

$$\Delta F = 1/(2N + 1) \text{ (approx.)} \quad \dots [4.2b]$$

With sib-mating also excluded,

$$N_e = N + 2 \text{ (approx.)} \quad \dots [4.3a]$$

and

$$\Delta F = 1/(2N + 4) \text{ (approx.)} \quad \dots [4.3b]$$

The approximations introduce very little error in calculating ΔF unless N is very small, as with close inbreeding; but then other methods of deducing ΔF are required, as will be explained in the next chapter.

Different numbers of males and females

In domestic and laboratory animals the sexes are often unequally represented among the breeding individuals, since it is more economical, when possible, to use fewer males than females. The two sexes, however, whatever their relative numbers, contribute equally to the genes in the next generation. Therefore the sampling variance attributable to the two sexes must be reckoned separately. Since

the sampling variance is proportional to the reciprocal of the number, the effective number is twice the harmonic mean of the numbers of the two sexes. It is twice the harmonic mean because the population size is $N = N_m + N_f$, where N_m and N_f are the numbers of males and females respectively. The harmonic mean is $1/\left[\frac{1}{2}(1/N_m + 1/N_f)\right]$, so

$$\frac{1}{N_e} = \frac{1}{4N_m} + \frac{1}{4N_f} \quad (\text{approx.}) \quad \dots [4.4a]$$

$$N_e = \frac{4N_m N_f}{N_m + N_f} \quad (\text{approx.}) \quad \dots [4.4b]$$

The rate of inbreeding is then

$$\Delta F = \frac{1}{8N_m} + \frac{1}{8N_f} \quad (\text{approx.}) \quad \dots [4.5]$$

This gives a close enough approximation unless both N_m and N_f are very small, as with close inbreeding. It should be noted that the rate of inbreeding depends chiefly on the numbers of the less numerous sex. For example, if a population were maintained with an indefinitely large number of females but only one male in each generation, the effective number would be only about 4.

Unequal numbers in successive generations

The rate of inbreeding in any one generation is given, as before, by $1/2N$. If the numbers are not constant from generation to generation, then the mean rate of inbreeding is the mean value of $1/2N$ in successive generations. The effective number is the harmonic mean of the numbers in each generation. Over a period of t generations, therefore,

$$\frac{1}{N_e} = \frac{1}{t} \left[\frac{1}{N_1} + \frac{1}{N_2} + \frac{1}{N_3} + \dots + \frac{1}{N_t} \right] \quad (\text{approx.}) \quad \dots [4.6]$$

Thus the generations with the smallest numbers have the most effect. The reason for this can be seen by consideration of the new and old inbreeding referred to in connection with equation [3.6]. An expansion in numbers does not affect the previous inbreeding; it merely reduces the amount of new inbreeding. So, in a population with fluctuating numbers, the inbreeding proceeds by steps of varying amount, and the present size of the population indicates only the present rate of inbreeding.

Non-random distribution of family size

This is the most important deviation from the breeding system of the idealized population. Its consequence is usually to render the effective number less than the actual, but in special circumstances it makes it greater. Family size means here the number of progeny of an individual that become breeding individuals in the next generation. It will be remembered that in the idealized population each breeding individual has an equal probability of contributing genes, or progeny, to the next

generation. The contribution of progeny is randomly distributed among the parents, and family sizes vary. In real populations the parents seldom have an equal chance of contributing progeny because they differ in fertility and in the survival of their progeny. This variation among parents leads to a greater variation of family size, and this has the consequence that a greater proportion of the next generation come from a smaller number of parents. The effective number is thus reduced. Conversely, the variation of family size may, by special breeding methods, be reduced below the random amount, with a consequent increase of the effective number. The relation of effective number to variation of family size is, briefly, as follows.

Attention will be restricted here to populations of constant size and with males and females in equal numbers. The mean family size \bar{k} of all individuals, whether male or female, must then be 2 because to replace the population each individual must on average have 1 male and 1 female offspring represented among the parents of the next generation. Random variation of family size, as in the idealized population, gives rise to a binomial distribution which, unless N is very small, differs little from a Poisson distribution. A Poisson distribution has a variance equal to the mean so the variance of family size when parents have an equal chance of contributing to the next generation is $V_k = \bar{k} = 2$. When parents do not have an equal chance of contributing to the next generation, through differences of fertility or other reasons, the variance of family size is greater than 2. The way in which the variance of family size influences the effective number can be deduced by consideration of the probability of a zygote being an identical homozygote, in a manner similar to that by which the inbreeding increment was deduced in the last chapter. The effective number is then obtained from the rate of inbreeding. The relationship to which this leads is approximately

$$N_e = \frac{4N}{V_k + 2} \quad (\text{approx.}) \quad \dots [4.7]$$

This reduces to $N_e = N$ for the idealized population in which $V_k = 2$. The relationship in equation [4.7] refers to monogamous mating, when V_k is the same for both sexes. If males can mate with more than one female, V_k is likely to be different for males and females. The effective number is then given by

$$N_e = \frac{8N}{V_{km} + V_{kf} + 4} \quad (\text{approx.}) \quad \dots [4.8]$$

where V_{km} and V_{kf} are the variances of family sizes of males and females respectively (Hill, 1979).

Variation of family size, V_k , above the random amount is one of the two most important causes of N_e being less than N , the other being variation in numbers over generations. The ratio N_e/N can be estimated in several different ways. A review of 192 estimates from 102 species of animals and plants (Frankham, 1995) shows that the estimates vary enormously, ranging from 10^{-6} in the Pacific oyster to 0.99 in humans. Some of this variation was due to which causes of N_e being less than N had been taken account of, and some to how the total, N , was obtained. The average of all estimates of N_e/N was 0.34, but the estimates that took account of all factors

averaged only 0.1, which is much lower than might have been expected. Estimates varied widely even within species, depending partly on the method of estimation. For example, in *Drosophila melanogaster* N_e/N ranged from 0.03 to 0.90, with a mean of 0.30; and in humans it ranged from 0.34 to 0.99 with a mean of 0.55.

Minimal inbreeding

It is often desirable to keep stocks of laboratory animals with the least possible inbreeding. Increasing the number of breeding individuals N as much as possible is not the only thing that can be done. By choice of the individuals to be used as parents, the variance of family size, V_k , can be reduced below its random amount, and the effective number consequently increased. If the individuals are chosen equally from all families, then there is no variation in family size, and $V_k = 0$. Substitution into equation [4.7] shows that the effective number then becomes $N_e = 2N$, approximately. The exact relationship is

$$N_e = 2N - 1 \quad \dots [4.9]$$

which is very nearly twice what it would be in an idealized population of the same size. Equation [4.9] refers to a population bred from equal numbers of males and females. Equalization of family size then means choosing two individuals from the progeny of each pair of parents.

If the sexes are unequal in numbers, the variance of family size can be made zero by choosing as parents one male from each sire's progeny and one female from each dam's progeny. The rate of inbreeding is then given by the following formula (Gewe, Robertson, and Latter, 1959):

$$\Delta F = \frac{3}{32N_m} + \frac{1}{32N_f} \quad \dots [4.10]$$

where N_m and N_f are the actual numbers of male and female parents respectively, and females are more numerous than males.

The avoidance of matings between close relatives, such as sibs or cousins, seems at first sight to be an easy way of reducing the rate of inbreeding. This delays the first increment of inbreeding, but very little reduction of the subsequent rate of inbreeding is achieved. The reasons for this were explained earlier and equation [4.3a] gives the effective population size with self-fertilization and sib-mating excluded. If family size is deliberately equalized then the avoidance of closely related matings achieves no further reduction in the rate of inbreeding (Robinson and Bray, 1965). The chief advantages of avoiding matings between close relatives are to make the rate of inbreeding more constant from generation to generation, and to make the inbreeding coefficients of individuals more uniform within generations.

Overlapping generations

In most natural populations, and in domesticated animals, the generations are not discrete but are overlapping. This means that the individuals present at any time are of different ages and at different stages of their life-cycles. Furthermore, individuals differ in length of life and consequently in their opportunities for reproduction. Differences of lifetime therefore add to differences of fertility in

increasing the variance of family size, the longer-lived individuals having a greater chance of contributing offspring to the next generation than the shorter-lived. The effect on N_e is dealt with by equations [4.7] or [4.8]. There is, however, a problem in finding what is the total number per generation, i.e., N in equation [4.7]. Provided the population has a stable age-structure the total number per generation can be found as follows. We need to know the number of individuals born within a specified time-interval, which might be one year or any convenient period. This number is the size of the cohort defined by the time-interval. The cohort size N_c is related to the total number alive at any time, N_T , i.e., the census count by $N_c = N_T/E$, where E is the expectation of life, or the mean age at death, expressed in units of the specified time-interval that defines the cohort (see Emigh and Pollak, 1979). We need to know also the generation length L in units of the specified time-interval, the generation length being the average age of parents at the birth of their offspring. Then the total number per generation is $N = N_c L$, and the effective number per generation is given approximately by

$$N_e = \frac{4N_c L}{V_k + 2} \quad (\text{approx.}) \quad \dots [4.11]$$

(Hill, 1979), where V_k is the variance of family size from all causes. If males and females differ in numbers or in generation length, as is often the case with farm animals, equation [4.11] has to be modified in a manner explained by Hill (1979).

The effective number in the human population of the USA has been estimated as $N_e = 0.41N_T$, but the ratio is probably somewhat lower than this because the estimate did not take account of all the possible sources of variation of fertility (Emigh and Pollak, 1979).

Example 4.1

Data from a mouse experiment (Garnett and Falconer, 1975, and unpublished) will serve to illustrate the use of several of the formulae deduced in this and the previous chapter. Furthermore, by calculating the effective population size independently from the variance and the inbreeding approaches, we can check on the validity of the theory. The population consisted of 18 lines, all originating from the same random-bred base and all maintained by minimal inbreeding with 8 pairs of parents mated in every generation (Falconer, 1973). The data consisted of gene and genotype frequencies at 5 polymorphic enzyme loci in each of the lines. The enzyme loci are listed in the table. There were two alleles present at all the loci; all the heterozygotes were distinguishable and the gene frequencies were obtained by counting (equation [1.1]). At generation 27 all the parents were typed, so the gene frequencies at that time were determined without error. For each locus, the variance of gene frequency among the 18 lines was calculated. The table gives, for each locus, the mean gene frequency, \bar{q} , the variance of gene frequency, σ_q^2 , and the overall frequency of heterozygotes in the population as a whole, H . There is no reason to think that the gene frequencies had changed from their values in the base population, so for calculations it is assumed that $q_0 = \bar{q}$.

Continued

Example 4.1 continued

The calculations to be made are: (1) the effective population size N_e , expected from the number of parents N , and the breeding structure; (2) the inbreeding coefficient F , from the variance of gene frequencies σ_q^2 , and then N_e from F at generation $t = 27$; (3) F at $t = 27$ from the frequency of heterozygotes H , and then N_e from F again.

1. With 8 pairs of parents, $N = 16$. With minimal inbreeding ($V_k = 0$), equation [4.9] gives $N_e = 2N - 1 = 31$. Equation [4.1] gives $\Delta F = 1/2N_e = 0.0161$, and equation [3.12] gives $F = 1 - (1 - 0.0161)^{27} = 0.355$. These expected values will be realized only if $V_k = 0$ is achieved. In practice some pairs will inevitably be sterile, so V_k will not be zero and N_e will be less than 31.

2. F is related to σ_q^2 by equation [3.14]. Taking *Dip-1* as an example, $F = \sigma_q^2/\bar{pq} = 0.077/(0.236 \times 0.764) = 0.427$. Each locus gives an independent estimate of F . They are given in the table in the column headed $F(2)$. The mean is $F = 0.378$. From this mean estimate of F , we get the rate of inbreeding ΔF from equation [3.12]. By rearrangement, $(1 - \Delta F)^t = 1 - F$, which with $t = 27$ yields $\Delta F = 0.0174$. The effective population size N_e is found from ΔF by equation [4.1]. This gives $N_e = 1/2\Delta F = 28.7$.

3. Equal numbers of individuals were classified in all lines, so F can be estimated from the overall frequency of heterozygotes, H . This could be done by equation [3.15], but the number of parents per line is small enough to make the expected chance differences of gene frequencies in males and females not negligible. Allowance for this is made in equation [3.17], which gives $(1 - F) = H/2pq(1 + 1/2N)$. Taking *Dip-1* again as an example, $(1 - F) = 0.240/(2 \times 0.236 \times 0.764 \times 1.03125) = 0.646$, and $F = 0.354$. Again, each locus gives an independent estimate of F , as given in the column headed $F(3)$. ΔF and N_e are calculated from F in the same way as under calculation 2 above, and the values are entered at the foot of the table.

Locus	\bar{q}	σ_q^2	H	$F(2)$	$F(3)$
<i>Dip-1</i>	0.764	0.077	0.240	0.427	0.355
<i>Id-1</i>	0.370	0.102	0.301	0.438	0.374
<i>Gpi-1</i>	0.297	0.072	0.283	0.345	0.343
<i>Gpd-1</i>	0.215	0.042	0.253	0.249	0.273
<i>Got-2</i>	0.141	0.052	0.134	0.429	0.464
Mean				0.378	0.362
Method			F	ΔF	N_e
1. Expected from breeding structure			0.355	0.0161	31
2. Variance of gene frequency. σ_q^2			0.378	0.0174	28.7
3. Frequency of heterozygotes, H			0.362	0.0165	30.3
4. Pedigrees			0.379	0.0175	28.6

The inbreeding coefficient can be calculated in yet another way – from the pedigree records, in a manner to be explained in the next chapter. This is an exact determination because it is based on the probabilities of identical homozygotes arising from the matings actually made. The calculation was made for each line, and the mean value was $F = 0.379$. This gives $\Delta F = 0.0175$ and $N_e = 28.6$. The ratio of N_e (achieved)/ N_e (expected) is $28.6/31 = 0.92$, and the ratio of N_e (achieved)/ N is $28.6/16 = 1.79$. Comparing the three estimates of N_e shown at the foot of the table,

Continued

Example 4.1 *continued*

we see that the estimates from the variance of gene frequencies and from the frequency of heterozygotes agree very well with the pedigrees. It may be noted that if the correction for unequal gene frequencies in male and female parents is not made, the estimate of N_e from the frequency of heterozygotes is 32.7 instead of 30.3.

Mutation, migration, and selection

The description of the dispersive process given so far in this chapter and the previous one is conditional on the systematic processes of mutation, migration, and selection being absent, and its relevance to real populations is therefore limited. So let us now consider the effects of the dispersive and systematic processes when acting jointly. The systematic processes, as we have seen in Chapter 2, tend to bring the gene frequencies to stable equilibria at particular values which would be the same for all populations under the same conditions. The dispersive process, in contrast, tends to scatter the gene frequencies away from these equilibrium values, and if not held in check by the systematic processes it would in the end lead to all genes being either fixed or lost in all populations not infinite in size. The tendency of the systematic processes to change the gene frequency toward its equilibrium value becomes stronger as the frequency deviates further from this value. For this reason there is a point of balance at which the dispersion of gene frequencies is held in check by the systematic processes. There is then a certain degree of differentiation between sub-populations which remains constant so long as the conditions remain unchanged. The problem is therefore to find the distribution of gene frequencies among the lines of a subdivided population when this steady state has been reached. It should be noted, however, that it may take a very long time after a change of conditions for a population to attain the steady state, so the distributions deduced are only approximately applicable to real populations. The solution is complicated mathematically and only the main conclusions will be given. For a more detailed account, see Crow (1986).

Non-recurrent neutral mutation

At the DNA sequence level, it is reasonable to think of mutations as non-recurrent since the probability of the same mutation occurring at a given nucleotide more than once is vanishingly small; i.e., there are an effectively infinitely large number of mutations that can potentially occur at each locus. This is the infinite alleles model of mutation, and the consequence is that a mutation occurs only once in a population.

We shall first consider briefly the fate of unique mutations that are effectively neutral with respect to fitness. The fate of such mutants forms the basis of the neutral theory of molecular evolution, of which a full account is given by Kimura (1983). Each mutant at an autosomal locus has only a half-chance of surviving in the next generation, and most are lost after a few generations, as was explained in Chapter 2. A few, however, will survive and spread through the population by the dispersive process. Some of these will later be lost, but some will eventually

become fixed. The fixation of a new allele that arose by mutation in an earlier generation is called an 'allelic substitution'. What is the chance that an allelic substitution at a particular locus will occur? In a diploid population of N individuals there are $2N$ representatives of that locus, and one of these will, in the absence of selection, eventually become fixed. Therefore the chance that any particular one becomes fixed is $1/2N$. Let u be the neutral mutation rate at the locus in question; i.e., the probability that a new neutral allele appears by mutation in any one generation. The total number of new mutants at the locus is then $2Nu$, assuming that each new mutant is initially present in only one copy. For each mutant separately, the chance of fixation is $1/2N$. Therefore the probability that one or another of the new mutants becomes fixed is $2Nu \times 1/2N = u$. This is the probability of an allelic substitution at a locus occurring in any particular generation, and it is simply equal to the mutation rate per generation at the locus in question. To get the rate of substitution at all loci together, we put u equal to the neutral mutation rate per gamete, i.e., the frequency of gametes carrying a new neutral mutant at any locus. The reason why the rate of allelic substitution is independent of the population size is that in a larger population the larger number of new mutants is balanced by the smaller individual chance of survival.

Selection, of course, increases or decreases the chance of fixation, according to whether the new mutant is favourable or unfavourable. The great majority of mutants are expected to be deleterious rather than beneficial. What is the chance that a deleterious mutant gives rise to an allelic substitution? By the same reasoning, this is equal to the mutation rate to 'effectively neutral' alleles; and, according to Kimura (1983), an 'effectively neutral' allele is one with a coefficient of selection s against it in the range from $s = 0$ (i.e. strictly neutral) up to $s = 1/2N_e$. Thus effective neutrality depends on the effective population size, and an effectively neutral allele is one for which the product $N_e s$ is less than $\frac{1}{2}$.

The expectation that some deleterious mutants will become fixed by random drift means that all populations must tend to decline in natural fitness over a long period of time, unless the conditions that determine fitness change or the decline is counter-balanced by the occurrence and fixation of favourable mutants (see Kimura, 1983, p. 248). There are important practical consequences of this expectation. Inbred lines of laboratory animals are maintained by brother-sister matings for which the effective population size is about 2.5 (equation [4.2a]). Deleterious mutants with a coefficient of selection of up to about 20 per cent could therefore become fixed and the consequent loss of reproductive fitness could be serious, unless counteracted by artificially intensified selection; favourable mutants are far too rare to counterbalance the loss of fitness in small populations. An experiment with *Drosophila* by Wright and Kerr (1954) exemplifies the fixation of a deleterious gene in small populations.

Recurrent mutation and migration

Recurrent mutation and migration can be dealt with together because they change the gene frequency in the same manner. Consider again a population subdivided into many lines, each with an effective size N_e ; and let a proportion m of the breeding individuals of every generation in each line be immigrants coming at random

from all other lines. Let u and v be the mutation rates in the two directions between two alleles at a locus. The state of dispersion between the sub-populations, when the balance between dispersion on the one hand and migration and mutation on the other is reached, can be expressed as the inbreeding coefficient as follows:

$$F = \frac{1}{4N_e(u + v + m) + 1} \quad (\text{approx.}) \quad \dots [4.12]$$

If the mean gene frequencies were known, the state of dispersion could be expressed as the variance of gene frequency by putting $\sigma_q^2 = F\bar{p}\bar{q}$, from equation [3.14].

The theoretical distributions of gene frequencies corresponding to four equilibrium values of F are shown in Fig. 4.1. These distributions are similar in general form to the distributions that a population goes through during the process of inbreeding without mutation or migration, shown in Fig. 3.4. The effect of mutation or migration can be thought of as arresting the process at a point corresponding to some value of F or of σ_q^2 , the variance of gene frequency among sub-populations. The chief difference here is that if F goes beyond 0.33, when all gene frequencies, including fixation, are equally probable, the distribution becomes U-shaped, with more sub-populations being at the extremes and fewer at intermediate gene frequencies. The reason for this is that, with mutation or migration, fixation in any one line is not permanent.

In order to see what equation [4.12] and the distributions in Fig. 4.1 mean, let us consider these questions: at what value of F will the population stabilize if there is mutation at the known rates, but no migration? and: how much migration, with no mutation, would be needed to produce the distributions shown? For this purpose it will be accurate enough to take equation [4.12] as $N_e = 1/4F(u + v + m)$. Substitute in this the usual mutation rate of $u + v = 10^{-5}$, with $m = 0$, and $F = 0.005$ corresponding to the least dispersed distribution in Fig. 4.1. This gives $N_e = 5 \times 10^6$, which means that sub-populations of size 5 million would differentiate as far as $F = 0.005$ before being stabilized by mutation. Smaller sub-populations would differentiate further. For example, the uniform distribution corresponding to $F = 0.333$ would be reached by sub-populations of size 75,000. For many species, perhaps most, even this is an unrealistically large size for sub-populations mating at random within themselves. The conclusion, therefore, is that recurrent mutation is negligible as a factor slowing down or arresting the differentiation of sub-populations by random drift. Migration, however, is quite a different matter. Rearrangement of equation [4.12], with $u + v = 0$, gives $F = 1/(4N_e m + 1)$. Thus the state of dispersion depends on the product $N_e m$, which is the actual number of immigrants per generation, irrespective of the population size. This conclusion, which may at first seem paradoxical, can be understood by noting that a smaller population needs a higher rate of immigration than a larger one to be held at the same state of dispersion. Substitution of the values of F corresponding to the distributions in Fig. 4.1 gives the values of $N_e m$ entered in the figure. For example, an average of one immigrant every two generations ($N_e m = \frac{1}{2}$) is sufficient to maintain the flat distribution of gene frequencies corresponding to $F = 0.333$. The conclusion is that quite small numbers of immigrants will prevent much differentiation by random drift. The reason why mutation and migration are so different in their

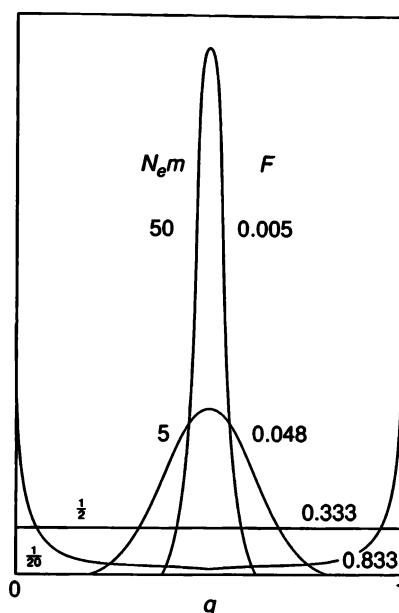


Fig. 4.1. Theoretical distributions of gene frequency among sub-populations when dispersion is balanced against mutation or migration, and the mean gene frequency is 0.5. The vertical axis is the probability, as in Fig. 3.4. The states of dispersion to which the curves refer are indicated by the values of F in the figure. The values of $N_e m$ are the numbers of immigrants per generation, as explained in the text. (Based on Wright, 1951.)

effects is the same as was pointed out in Chapter 2: realistic mutation rates are very much smaller than realistic migration rates.

The situation to which the foregoing consideration of migration refers is known as the 'island model'. It pictures a discontinuous population with immigrants to any sub-population coming from any other sub-population with equal probability. A more realistic model is the 'neighbourhood model' or 'isolation by distance'. The population is pictured as being continuously distributed over the area inhabited, but sub-divided into 'neighbourhoods' by the limited distance that individuals travel between birth and reproduction. A neighbourhood is the area within which mating is effectively random, and corresponds to a sub-population. Gene frequencies, however, vary continuously from neighbourhood to neighbourhood across the area. Since immigrants to a neighbourhood come from close by more often than from further away, they differ in gene frequency less than immigrants in the island model do. Therefore migration is less effective in counteracting random drift. The conclusion to which the neighbourhood model leads is that a large amount of local differentiation will take place if the effective number in the neighbourhoods is of the order of 20, a moderate amount if it is of the order of 200, but a negligible amount if it is larger than about 1,000.

Selection

Selection operating on a locus in a large population brings the gene frequency to an equilibrium at an intermediate value when selection favours heterozygotes and at a

low value when selection is balanced against mutation. The dispersive process tends to shift the gene frequency away from its equilibrium value. This reduces the average fitness of the population, because the load is minimal at the equilibrium, and some sub-populations may even become fixed for the deleterious allele. The effect of selection is stronger the further the gene frequency is away from the equilibrium value. So the opposing forces of selection and random drift reach a balance at which there is a stable distribution of gene frequencies among sub-populations. The question then is: how small must the sub-populations be to cause appreciable differentiation with its consequent deviations from the optimal gene frequency? The following illustrative cases will have to suffice for an answer, and for an understanding of the joint effects of mutation, selection, and dispersion the reader must consult other sources.

Consider first selection favouring heterozygotes. The effect depends on the equilibrium gene frequency. When the two homozygotes are at an equal disadvantage and the equilibrium gene frequency is consequently 0.5, the distributions of gene frequencies look roughly like those in Fig. 4.1. The least dispersed one, corresponding to $F = 0.005$, would be attained by a selection coefficient of $s = 0.1$ against both homozygotes in sub-populations of size $N_e = 1,000$. More dispersion would need less selection or smaller populations. The most dispersed distribution, with a substantial amount of fixation, would need very roughly $s = 0.01$ with $N_e = 100$. Thus selection for heterozygotes does not allow much random drift unless the selection is very weak (around 1 per cent) or the population size very small (around 100). If, however, the equilibrium gene frequency is not 0.5, the selection is less effective in preventing the random drift. When the equilibrium gene frequency is above roughly 0.8 or below 0.2 the selection actually accelerates the random drift (Robertson, 1962). The reason for this is that one homozygote is then much fitter than the other and the selection increases the probability of fixation of the more fit homozygote.

Next consider selection against a recessive allele balanced by recurrent mutation. This is difficult to illustrate because with realistic values of the selection coefficient, the equilibrium gene frequency will be very low, and the distributions are squeezed up against the limit near $q = 0$. Figure 4.2 shows three stable distributions for very weak selection with an equilibrium gene frequency of about $q = 0.2$. Mutation rate is taken to be the same in both directions, and the coefficient of selection s is 20 times the mutation rate. If we assume a mutation rate of 10^{-5} then $s = 20 \times 10^{-5}$ and the population sizes to which the distribution refer are (a) 250,000, (b) 25,000, and (c) 2,500. The conclusion is, again, that selection does not allow much random drift unless the selection is weak or the population size very small. The amount of random drift depends approximately on the product of the population size and the selection coefficient $N_e s$, and the three distributions in Fig. 4.2 correspond to values of $N_e s$ equal to 50, 5, and 0.5 respectively.

Random drift in natural populations

Having described the dispersive process and its theoretical consequences, we may now turn to the more practical question of how far these consequences are actually

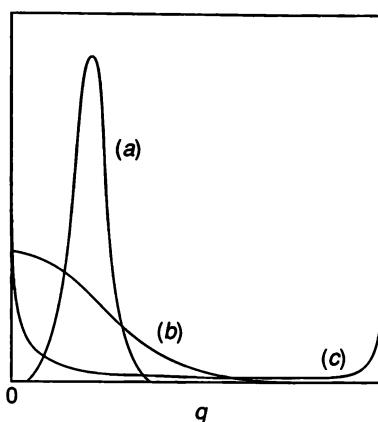


Fig. 4.2. Theoretical distributions of gene frequency among sub-populations when the dispersion is balanced by mutation and selection. The graphs refer to a recessive gene with $u = v = \frac{1}{2}s$, in populations of size: (a) $N_e = 50/s$, (b) $N_e = 5/s$, and (c) $N_e = 0.5/s$. (Based on Wright, 1942.)

seen in natural populations. The answering of this question is beset with difficulties, and the following comments are intended more to indicate the nature of these difficulties than to answer the question.

The theory of small populations, outlined in this and the preceding chapter, is essentially mathematical in nature and is unquestionably valid: given only the Mendelian mechanism of inheritance, the conclusions arrived at are a necessary consequence under the conditions specified. The question at issue, then, is whether the conditions in natural populations are often such as would allow the dispersion of gene frequencies to become detectable. The phenomena which would be expected to result from the dispersive process, if the conditions were appropriate, are differentiation between the inhabitants of different localities, and differences between successive generations. Both these phenomena are well known in subdivided or small isolated populations, and it is tempting to conclude that because they are the expected consequences of random drift, random drift must be their cause. But there are other possible causes: the environmental conditions probably differ from one locality to another and from one season to another; so the intensity, or even the direction, of selection may well vary from place to place and from year to year, and the differences observed could equally well be attributed to variation of the selection pressure. Before we can justifiably attribute these phenomena to random drift, therefore, we have to know: (1) that the effective population size is small enough; (2) that the sub-populations are well enough isolated (or the size of the 'neighbourhoods' sufficiently small); and (3) that the genes concerned are subject to very little selection.

The estimation of the present size of a population, though not technically easy, presents no difficulties of principle. But the present state of differentiation depends on the population size in the past, and this can generally only be guessed at. The population may have gone through one or more *bottlenecks* – generations in which its size has been much reduced by unfavourable conditions. The dispersion caused

by these generations of very low numbers is permanent and is not removed by subsequent increases in population size. (Equation [4.6] showed how the effective population size is influenced by variable numbers.) If a species colonizes a new territory, the founding members of the new sub-population may be very few in numbers, causing a substantial amount of random drift in the first generation. This is called the *founder effect*. If the sub-population then expands, its difference from the main population may seem much too great to be consistent with its present numbers. To attribute the difference to a founder effect may often be plausible but, in the absence of pedigree records, can seldom be other than a guess. One of the clearest and most interesting examples of isolated populations being differentiated as a result of founder effects is seen in the Amish communities in the USA, studied by McKusick (1978), the founder effects being established by genealogical records.

There is less difficulty in deciding whether the sub-populations are sufficiently well isolated. With a discontinuous population it is often possible to be reasonably sure that there is not too much immigration; and with a continuous population the size of the 'neighbourhoods' is, at least in principle, measurable. The greatest difficulty lies in estimating the intensity of natural selection acting on the genes concerned. Selection of an intensity far lower than could be detected experimentally is sufficient to check dispersion in all but the smallest populations. Many of the genes concerned with enzyme polymorphisms may have selection coefficients low enough to allow populations to become differentiated (see below). The genes concerned with quantitative differences may also be nearly enough neutral for random drift to take place. There is no doubt at all that genes of this sort do show random drift in laboratory populations, as will be shown in later chapters.

Polymorphism

We saw in Chapter 2 that there are ways in which polymorphism could be maintained by a balance of selective forces, but these do not seem likely to be the reason for all polymorphisms. An alternative to the selection model is a balance between mutation and random drift, with selection playing no part. This model will now be described.

Neutral theory

The neutral theory of molecular evolution assumes most new mutations are deleterious, a very few are advantageous, and some are selectively neutral (i.e., have no effect on fitness). The deleterious and advantageous mutations will be rapidly eliminated and fixed, respectively, and contribute little to polymorphism. At any one time variation in a population will be caused mostly by neutral alleles, destined for ultimate fixation or loss (Kimura, 1983). Polymorphism under this model is thus viewed as transient. However, neutral alleles can persist in the population for very long periods of time. For a neutral allele destined for ultimate fixation, this is on average $4N_e$ generations. Neutral alleles destined for loss do not last nearly as long on average, but the time to loss has a very high variance.

A population experiencing continual input of new unique neutral mutations and fixation or loss of existing variants from drift will eventually reach a steady state

where the rate of loss of variation exactly balances the rate of gain. Although the exact identity of alleles will vary over time as alleles arise and leave the population, a population at mutation–drift equilibrium will have a distribution of allele frequencies and average heterozygosity that is a function of the effective population size and the neutral mutation rate. The equilibrium average heterozygosity from a balance of neutral mutations and random drift is easy to derive by modifying equation [3.6] to include mutation. For the infinite alleles model of mutation each allele in a population of size N_e arises only once, at rate u . Homozygotes for any allele are thus identical by descent. The probability of two gametes carrying identical neutral alleles in a finite population was given by equation [3.6]. The two alleles will remain identical only if neither mutates, which has probability $(1 - u)^2$, so

$$F_t = \left[\frac{1}{2N_e} + \left(1 - \frac{1}{2N_e}\right) F_{t-1} \right] (1-u)^2 \quad \dots [4.13]$$

At equilibrium between random drift and mutation, $F_t = F_{t-1}$. Substituting the equilibrium value, \hat{F} , for F_t and F_{t-1} and rearranging leads to

$$\hat{F} = \frac{(1-u)^2}{2N_e - (2N_e - 1)(1-u)^2} \quad \dots [4.14]$$

The per-locus mutation rate, u , is very small, so the u^2 and $2u$ terms can be neglected. Equation [4.14] can then be simplified to

$$\hat{F} = \frac{1}{4N_e u + 1} \text{ (approx.)} \quad \dots [4.15]$$

\hat{F} is the expected homozygosity for a neutral allele in a population due to mutation–drift balance. The equilibrium heterozygosity, \hat{H} , is $1 - \hat{F}$:

$$\hat{H} = \frac{4N_e u}{4N_e u + 1} \text{ (approx.)} \quad \dots [4.16]$$

This is also the expected heterozygosity averaged over all loci. In Chapter 2, a polymorphic locus was defined as one for which the frequency of the most common allele does not exceed 0.99. The frequency of heterozygotes of the common allele and any other is then 0.02, and this is H because the frequency of heterozygotes for two rare alleles is negligible. This is the lowest value of H to be accounted for, because loci with lower values would not be counted as polymorphic. With $H = 0.02$, equation [4.16] shows that $4N_e u$ is approximately 0.02 also. Therefore, under this model polymorphism will be maintained if the reciprocal of the neutral mutation rate is more than 5,000 times the effective population size.

Tests The validity of the neutral theory has been tested by very many studies, of which only a brief outline can be given here. The neutral theory leads to expectations for the following observable properties of polymorphism, given values of N_e and u , and assuming the infinite allele model: the heterozygosity, the proportion of polymorphic loci, the distribution of allele frequencies among loci within a population, and the distribution of allele frequencies at one locus among populations or

closely related species (Kimura, 1983). The neutral theory can be evaluated by comparing the observed and expected values of these parameters.

Let us consider first inferences from observed heterozygosities. There is a huge body of data on allozyme frequencies for many loci, populations, and species with which to test accordance with neutral expectations. For example, allozyme heterozygosities range from 0 to 0.30, with a mode of approximately 0.05, over all species studied (Kimura, 1983, p. 254). Kimura (1983) argues that the neutral mutation rate for allozymes is probably of the order of 10^{-7} , allowing for only 1 in 10 mutations being neutral, with the rest being deleterious. With N_e of 10^5 , H would then be approximately 4 per cent, which is close to the observed mode. The problem is to know what the real value of N_e is, because any value of H could be accommodated under the neutral theory, given an appropriate choice of N_e and u . The neutral mutation rate of allozyme loci is not likely to vary among species. Therefore the heterozygosities of different populations should vary according to their population sizes. Organisms vary in population size by several orders of magnitude, but heterozygosities differ by little more than a factor of 10 in the species studied. This discrepancy is a reason for arguing that allozyme variants are subject to selection (Lewontin, 1974). However, population sizes obtained from a census are not an accurate estimate of N_e , as noted earlier in this chapter. The variation of N_e among species could be much less than it appears, as a result of bottlenecks in the past, particularly at the time of speciation (Kimura, 1983).

Observed allele frequency distributions generally agree well with the neutral expectation, except that an excess of rare alleles is often found in natural populations. Other statistical tests of neutrality are based on the expected relationships between the number of alleles and heterozygosity, the mean and variance of heterozygosity, and between the proportion of polymorphic loci and heterozygosity. For allozyme data there is good but not perfect accord with the neutral theory. Note, however, that the tests are based on strict neutrality, whereas the samples contain all alleles, including deleterious alleles at low frequencies. Some departure from strict neutrality may be expected, therefore, and the observed excess of rare alleles compared to neutral expectation is not inconsistent with the neutral theory. More powerful tests to distinguish selected from neutral polymorphisms are based on DNA sequence comparisons. The neutral theory predicts that sequence polymorphisms at silent sites (synonymous codons) and regions not coding for proteins should be more frequent than amino acid replacement polymorphisms, because the fraction of all mutations that are neutral should be greater for silent sites and introns than for mutations causing amino acid replacements. This is the concept of 'selective constraint', and observations are consistent with these expectations. The neutral theory also predicts a correlation between heterozygosity within species and divergence between species, which is in accord with data from 1500 species (Skibinski, Woodwork, and Ward, 1993). See Kimura (1983) and Hartl and Clark (1989) for more detailed descriptions of these tests and summaries of results.

The conclusion, after many years of vigorous debate, must be that much molecular polymorphism is attributable to the balance of neutral mutation and drift, although some undoubtedly is adaptive and is maintained by a balance of selective forces. Therefore no single mechanism is responsible for maintaining genetic

variation; rather, different forces operate on loci according to their function and at different levels of genetic organization. Since polymorphic loci are responsible for variation in quantitative characters, we shall return in Chapter 20 to the issue of near-neutrality of molecular polymorphisms and natural selection of phenotypes in the context of maintenance of variation for quantitative traits.

Problems

4.1 Suppose that four *Drosophila* stocks are maintained by putting a fixed number of unmated adults in a bottle and allowing them to mate at random. All stocks have 10 female parents but different numbers of male parents, the numbers of males being 10, 5, 2 and 1 respectively. Calculate the effective population size of each stock and the inbreeding coefficient after 10 generations. Assume that there are no differences of fertility among females or among males. [Solution 83]

4.2 The sex ratio among breeding individuals can be expressed as the number of females per male. Modify equation [4.4b] so as to express N_e in terms of the number of females, N_f , and the number of females per male, d . [Solution 93]

4.3 Suppose that an isolated natural population goes through a regular 5-year cycle of numbers, with the numbers of breeding pairs in successive generations being 500, 50, 100, 200, 400. What is the effective population size and the rate of inbreeding? [Solution 103]

4.4 Compare the (approximate) rates of inbreeding in two varieties of a plant, one of which is self-fertile and the other self-sterile, when both are propagated by random pollination among 20 individual plants. [Solution 113]

4.5 It is planned to keep a mouse stock with 8 pair-matings per generation and minimal inbreeding. The plan, however, cannot be strictly adhered to because some pairs fail to provide the two offspring required. In one particular generation the 8 matings provided the following numbers of offspring that were used as parents: 0, 1, 1, 2, 2, 3, 3, 4. What was the effective population size in this generation? [Solution 123]

4.6 The breeding plan for each of the lines of the mouse stock described in Problem 3.6 was to mate 8 pairs and to use 2 offspring from each pair as parents of the next generation. If this plan had been strictly adhered to, what would have been the effective population size of the lines? What was actually the effective population size indicated by the data in Problem 3.6? [Solution 133]

5 Small Populations: III. Pedigreed Populations and Close Inbreeding

In the two preceding chapters the genetic properties of small populations were described by reference to the effective number of breeding individuals; and expressions were derived, in terms of the effective number, by means of which the state of dispersion of the gene frequencies could be expressed as the coefficient of inbreeding. The coefficient of inbreeding, which is the probability of any individual being an identical homozygote, was deduced from the population size and the specified breeding structure. It expressed, therefore, the average inbreeding coefficient of all individuals of a generation. When pedigrees of the individuals are known, however, the coefficient of inbreeding can be more conveniently deduced directly from the pedigrees, instead of indirectly from the population size. This method has several advantages in practice. Knowledge is often required of the inbreeding coefficient of individuals, rather than of the generation as a whole, and this is what the calculation from pedigrees yields. In domestic animals, some individuals often appear as parents in two or more generations, and this overlapping of generations causes no trouble when the pedigrees are known. The first topic for consideration in this chapter is therefore the computation of inbreeding coefficients from pedigrees. The second topic concerns regular systems of close inbreeding. When self-fertilization is excluded, the rate of inbreeding expressed in terms of the population size is only an approximation, and the approximation is not close enough if the population size is very small. Under systems of close inbreeding, therefore, the rate of inbreeding must be deduced differently, and this is best done also by consideration of the pedigrees.

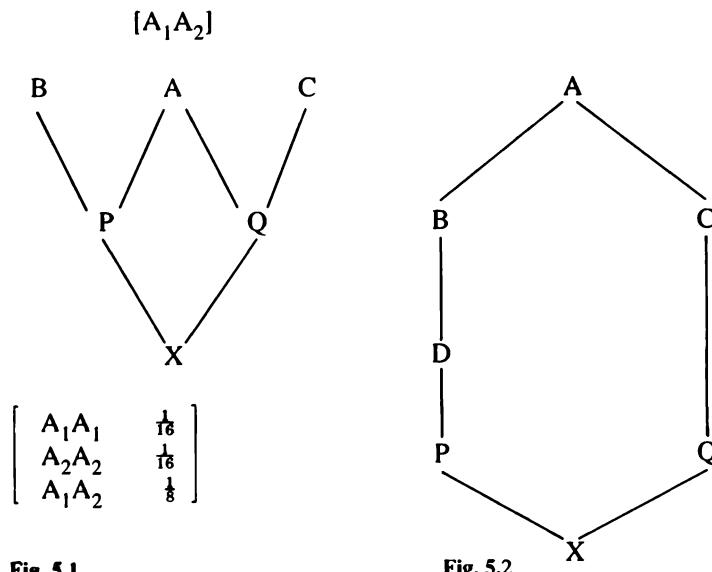
When the coefficient of inbreeding is deduced from the pedigrees of real populations, it does not necessarily describe the state of dispersion of the gene frequencies. It is essentially a statement about the pedigree relationships, and its correspondence with the state of dispersion is dependent on the absence of the processes that counteract dispersion, in particular on selection being negligible. We were able to use the coefficient of inbreeding as a measure of dispersion in the preceding chapters because the necessary conditions for its relationship with the variance of gene frequencies were specified.

Pedigreed populations

The inbreeding coefficient of an individual

This coefficient is the probability that the pair of alleles carried by the gametes that produced it were identical by descent. Computation of the inbreeding coefficient

therefore requires no more than the tracing of the pedigree back to common ancestors of the parents and computing the probabilities at each segregation. Consider the simple pedigree in Fig. 5.1, representing a mating between half sibs. X is the individual whose inbreeding coefficient F_X we want to know. Its parents P and Q are related through their common parent A. They are not related in any other way, so we only have to consider the transmission of A's genes through P and Q to X, and to calculate the probability of X being an identical homozygote. Let A_1 and A_2 symbolize the genes carried by A at any particular locus. The probability that X is A_1A_1 is $1/16 = (\frac{1}{2})^4$ because the chance that A_1 is transmitted through each of the four paths AP, PX, AQ, QX, is $\frac{1}{2}$ for each path. The probability that X is A_2A_2 is similarly $(\frac{1}{2})^4$, and the probability that X is either A_1A_1 or A_2A_2 is $2(\frac{1}{2})^4 = (\frac{1}{2})^3 = \frac{1}{8}$. This probability of X being an identical homozygote represents the new inbreeding arising from A as a common ancestor of P and Q. The common ancestor A may, however, itself be an identical homozygote through previous inbreeding, in which case X will be an identical homozygote also if it gets the genotype A_1A_2 or A_2A_1 (the two being distinguished according to whether A_1 comes through P or through Q). The probability of each of these genotypes is $(\frac{1}{2})^4$ for the same reason as before, and the probability of one or the other is $(\frac{1}{2})^3$. The probability of A being an identical homozygote is its inbreeding coefficient, F_A . The additional probability of X being an identical homozygote through the previous inbreeding is then $(\frac{1}{2})^3 F_A$. Putting the two parts of the inbreeding together gives the inbreeding coefficient of X as $F_X = (\frac{1}{2})^3 + (\frac{1}{2})^3 F_A = (\frac{1}{2})^3(1 + F_A)$. Note that the index 3 is the number of individuals in the path connecting the parents through their common ancestor, i.e., individuals P, A, and Q. This makes it easy to work out the probabilities simply by counting individuals in the path. In Fig. 5.1 there are only the parents and the common ancestor; in Fig. 5.2 the common ancestor is further back and the individuals to be counted are P, D, B, A, C, Q, making 6. F_X in Fig. 5.2 is therefore $(\frac{1}{2})^6(1 + F_A)$. In more complicated pedigrees, the parents may be related to each other



through more than one common ancestor, or from the same common ancestor through different paths, as illustrated in Example 5.1. Each common ancestor, and each path, then contributes an additional probability of the progeny being an identical homozygote, and the inbreeding coefficient is obtained by adding together the separate probabilities for each of the paths through which the parents are related.

Putting all this together gives the following general formula for the inbreeding coefficient of an individual:

$$F_X = \sum (\frac{1}{2})^n (1 + F_A) \quad \dots [5.1]$$

where n is the number of individuals in any path of relationship counting the parents of X , the common ancestor, and all individuals in the path connecting parents to common ancestor; summation is over all paths of relationship. When inbreeding coefficients are calculated in this way, it is necessary to define the base population to which the present inbreeding is referred. Individuals in the base population are assigned inbreeding coefficients of zero. In practice the individuals of the base population may be simply those at the head of the pedigree, whose ancestry further back is not known.

Example 5.1.

The pedigree in Fig. 5.3 will illustrate the use of the formula [5.1]. The individual whose inbreeding coefficient is to be calculated is X . We have to look for paths through which X 's parents, P and Q , are related to each other. Paths contributing nothing to the relationship are dotted. It is assumed that there are no relationships between any of the individuals other than those shown. There are four individuals that are common ancestors, A , B , F , and J , causing relationship between P and Q . The paths of relationship and the calculation of F_X (rounded to four decimal places) are shown in the table. The inbreeding coefficient of X works out to be 0.0606. The following points should be noted: (1) D and E are full sibs. Their relationship causes

Continued

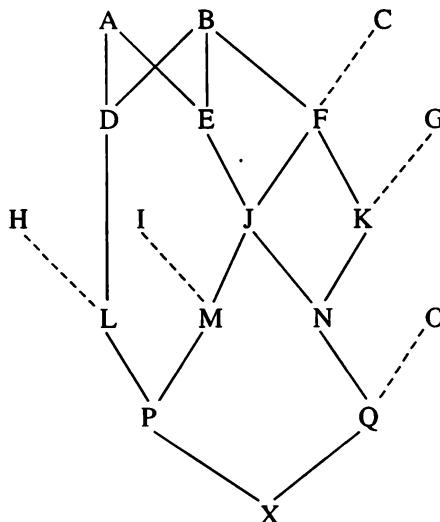


Fig. 5.3

Example 5.1 *continued*

some inbreeding in P, one of the parents of X, but it causes no relationship between P and Q and so contributes nothing to F_X . (2) E and F are half sibs, and the inbreeding coefficient of J, one of the common ancestors of P and Q, is therefore 1/8 as in Fig. 5.1. (3) There are four paths connecting P with Q through B as a common ancestor, and all four must be included in the calculation. (4) No individual can appear twice in the same path. For example, P M J E B F J N Q is not a valid path, because the inbreeding it produces is fully taken account of by the inbreeding coefficient of J in the shorter path P M J N Q. (5) Finally, care must be taken not to traverse paths in the wrong direction: for example, F cannot transmit genes to P through K and N.

<i>Paths of relationship</i>	<i>n</i>	<i>F of common ancestor</i>	<i>Contribution to F_X</i>
P L D A E J N Q	8	0	$(\frac{1}{2})^8 = 0.0039$
P L D B E J N Q	8	0	$(\frac{1}{2})^8 = 0.0039$
P L D B F J N Q	8	0	$(\frac{1}{2})^8 = 0.0039$
P L D B F K N Q	8	0	$(\frac{1}{2})^8 = 0.0039$
P M J E B F K N Q	9	0	$(\frac{1}{2})^9 = 0.0020$
P M J F K N Q	7	0	$(\frac{1}{2})^7 = 0.0078$
P M J N Q	5	$\frac{1}{8}$	$(\frac{1}{2})^5 \times \frac{1}{8} = 0.0352$ $F_X = 0.0606$

When pedigrees are long and complicated, it may not be practicable to trace all the paths of relationship. A sufficiently accurate estimate of the inbreeding coefficient can, however, be got by sampling a limited number of paths (Wright and McPhee, 1925).

Coancestry or kinship

There is another method of computing inbreeding coefficients which is often more convenient and is more readily adapted to a variety of problems. It will be used in the next section to work out the inbreeding coefficients under regular systems of close inbreeding. Its chief uses in practice are for planning matings to give the least inbreeding, and for calculating the inbreeding coefficient generation by generation in a fully pedigree population. The method does not differ in principle from the formula [5.1] given above, but instead of working from the present back to the common ancestors we work forward, keeping a running tally generation by generation, and compute the inbreeding that will result from the matings now being made. The inbreeding coefficient of an individual depends on the amount of common ancestry in its two parents. Therefore, instead of thinking about the inbreeding of the progeny, we can think of the degree of relationship by descent between the two parents. This is called the *coancestry*, or the *coefficient of kinship* or of *consanguinity*. It will be symbolized by f . The coancestry of any two individuals is identical with the inbreeding coefficient of their progeny if they were mated. Thus the coancestry of two individuals is the probability that two gametes taken at random, one from each, carry alleles that are identical by descent.

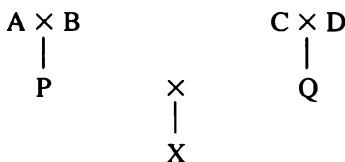


Fig. 5.4

Consider the generalized pedigree in Fig. 5.4. X is an individual with parents P and Q and grandparents A, B, C, and D. Now, the coancestry of P with Q is fully determined by the coancestries relating A and B with C and D, and if these are known we need go no further back in the pedigree. It can be shown that the coancestry of P with Q is simply the mean of the four coancestries AC, AD, BC, and BD. This will be clearer if stated in the form of probabilities, though the explanation is cumbersome when put into words. Take one gamete at random from P and one from Q, and repeat this many times. In half the cases, P's gamete will carry a gene from A and in half from B; similarly for Q's gamete. So the two gametes, one from P and one from Q, will carry genes from A and C in a quarter of the cases, from A and D in a quarter, from B and C in a quarter, and from B and D in a quarter of the cases. Now the probability that two gametes taken at random, one from A and the other from C, are identical by descent is the coancestry of A with C, i.e., f_{AC} , etc. So, reverting now to symbols,

$$f_{PQ} = \frac{1}{4}f_{AC} + \frac{1}{4}f_{AD} + \frac{1}{4}f_{BC} + \frac{1}{4}f_{BD}$$

This gives the basic rule relating coancestries in one generation with those in the next:

$$F_X = f_{PQ} = \frac{1}{4}(f_{AC} + f_{AD} + f_{BC} + f_{BD}) \quad \dots [5.2]$$

With this rule the experimenter can tabulate the coancestries generation by generation, and this gives a basis for planning matings and computing inbreeding coefficients. More detailed accounts of the operation are given by Plum (1954).

If there is overlapping of generations we may need to find the coancestry of individuals belonging to different generations, for which a supplementary rule is needed. Consideration of probabilities shows that the coancestry of two individuals is equivalent to the mean coancestry of one individual with the two parents of the other. Thus, referring to the same pedigree (Fig. 5.4), the rule giving the ancestry of P with C and with D is

$$\left. \begin{aligned} f_{PC} &= \frac{1}{2}(f_{AC} + f_{BC}) \\ f_{PD} &= \frac{1}{2}(f_{AD} + f_{BD}) \end{aligned} \right\} \dots [5.3]$$

This rule gives also

$$f_{PQ} = \frac{1}{2}(f_{PC} + f_{PD})$$

which by substitution from equation [5.3] reduces to the basic rule of equation [5.2].

Before we can apply the method to a pedigreed population, or to regular systems of inbreeding, we need to know the numerical values of some coancestries. The

parents of the first generation have to be assumed to be all unrelated, with $f = 0$. The first non-zero coancestries are among their progeny, and when all these have been determined all subsequent generations can be calculated by the rules given above. The relationships whose coancestries may be needed in the first generation are offspring and parent, full sibs, half sibs, and self. The coancestries of these relationships are needed also in the next section for working out the consequences of continued inbreeding. The coancestries are as follows, starting with self because this appears in all the others.

Self The coancestry of an individual with itself, f_{AA} , is the inbreeding coefficient of progeny that would be produced by self-mating. This is the probability that two gametes taken at random from A will carry identical alleles, which is $\frac{1}{2}(1 + F_A)$ for the following reason. Let A's genes be A_1 and A_2 . The probability that two gametes taken at random are both A_1 or both A_2 is $\frac{1}{2}$. The probability that one is A_1 and the other A_2 is $\frac{1}{2}$, but then the probability that A_1 and A_2 are identical by descent is the inbreeding coefficient of A, F_A . Thus the total probability that the two gametes carry identical alleles is $\frac{1}{2} + \frac{1}{2}F_A$, and so

$$f_{AA} = \frac{1}{2}(1 + F_A) \quad \dots [5.4]$$

If F_A is known (or assumed) to be zero, then $f_{AA} = \frac{1}{2}$.

Offspring and parent are in different generations, so the supplementary rule [5.3] is applicable. In Fig. 5.4 the coancestry of P with A is equal to the mean coancestry of P's parents with A, i.e.,

$$f_{PA} = \frac{1}{2}(f_{AB} + f_{AA}) \quad \dots [5.5]$$

If it is known or assumed that A and B are not related and A is not inbred, then $f_{AB} = 0$, $f_{AA} = \frac{1}{2}$, and the coancestry reduces to $f_{PA} = \frac{1}{4}$.

Full sibs are in the same generation, so the basic rule [5.2] applies. The application of the rule is more easily understood if the pedigree is written as in Fig. 5.5

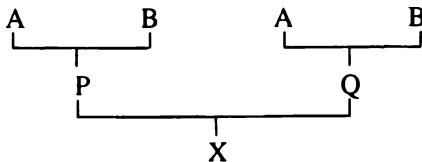


Fig. 5.5

A and B are the parents of both P and Q, which are full sibs and have an offspring X. Applying the basic rule [5.2] and noting that $f_{AB} = f_{BA}$, we have

$$f_{PQ} = \frac{1}{4}(2f_{AB} + f_{AA} + f_{BB}) \quad \dots [5.6]$$

With no previous inbreeding or relationship this reduces to $f_{PQ} = \frac{1}{4}$.

Half sibs Figure 5.1 gives a pedigree of half sibs. Applying the basic rule [5.2] and noting that A is a parent of both P and Q gives

$$f_{PQ} = \frac{1}{4}(f_{AB} + f_{AC} + f_{BC} + f_{AA}) \quad \dots [5.7]$$

With no previous inbreeding or relationship this reduces to $f_{PQ} = \frac{1}{8}$. This result has already been obtained as the inbreeding coefficient of X, the offspring of P and Q, in Fig. 5.1.

Regular systems of inbreeding

A regular system of inbreeding is one in which the same mating system is applied in all generations, and all individuals in the same generation have the same inbreeding coefficient. Regular systems are most often used to produce rapid inbreeding, and so the matings are between close relatives. We shall deal first with matings between the four sorts of relative already considered. (For other systems, see Wright, 1933, 1969.) Then we shall deal with the inbreeding produced by back-crossing and in the generations following a cross.

Close inbreeding

The inbreeding coefficients in successive generations can be calculated from the coancestries given in equations [5.4] to [5.7]. But it is more convenient first to derive recurrence equations, which relate the inbreeding coefficient in one generation to those of previous generations. The generation we are interested in is denoted by t , the previous one by $t - 1$, and the one before that by $t - 2$; $t - 3$ is as far back as we have to go with these four systems. The recurrence equations are derived as follows, and the inbreeding coefficients in successive generations are given in Table 5.1.

Self-fertilization If X in generation t is the offspring of A in generation $t - 1$, equation [5.4] gives

$$F_X = f_{AA} = \frac{1}{2}(1 + F_A)$$

and the recurrence equation is therefore

$$F_t = \frac{1}{2}(1 + F_{t-1}) \quad \dots [5.8]$$

In the first generation the parents are non-inbred and $F_{t-1} = 0$, which makes $F_{(t=1)} = \frac{1}{2}$. In the second generation $F_{t-1} = \frac{1}{2}$, and $F_{(t=2)}$ becomes $\frac{1}{2}(1 + \frac{1}{2}) = \frac{3}{4}$. Proceeding in this way allows one to write down the inbreeding coefficients in each successive generation. Note that in this case the rate of inbreeding is constant from the beginning and it corresponds exactly with equation [3.7]: $\Delta F = 1/2N = \frac{1}{2}$. This is not true of the other systems. Self-fertilization gives the most rapid inbreeding possible with a normal mating system. The inbreeding coefficient reaches 99.9 per cent after 10 generations. It is possible, however, to get complete homozygotes in one step by some forms of parthenogenesis and by manipulations such as doubling the chromosome complement of haploid cells.

We shall deal with full-sib mating next because it is the most often used of the other systems.

Full sibs From the coancestry in equation [5.6], referring to Fig. 5.5, we have

$$F_X = f_{PQ} = \frac{1}{4}(2f_{AB} + f_{AA} + f_{BB})$$

To get the recurrence equation we have to express the coancestries as inbreeding coefficients of previous generations. First, $f_{AB} = F_P = F_{t-1}$. Since individuals in the same generation have the same inbreeding coefficient, $f_{AA} = f_{BB} = \frac{1}{2}(1 + F_A)$ by equation [5.4], and $F_A = F_{t-2}$. Making these substitutions leads to the recurrence equation

$$F_t = \frac{1}{4}(1 + 2F_{t-1} + F_{t-2}) \quad \dots [5.9]$$

In the first generation, F_{t-1} and F_{t-2} are both zero and so $F_{(t=1)} = 0.25$. The inbreeding coefficients in the first four generations are 0.25, 0.375, 0.50, and 0.59. The rate of inbreeding is not constant in the first few generations, as may be seen by computing ΔF from equation [3.9]. For the first four generations ΔF is 0.25, 0.17, 0.20, and 0.19. It later settles down to a constant value of 0.191. The effective population size is then $N_e = 2.6$ by equation [4.1].

Offspring-parent We consider here only the mating of offspring with their younger parent; repeated backcrossing to the same parent will be considered later. Figure 5.6 shows as much of the pedigree as is needed, lettered to correspond with Fig. 5.4 and the coancestry in equation [5.5]. Each individual is an offspring in one generation and a parent in the next. The inbreeding of X is given by equation [5.5] as

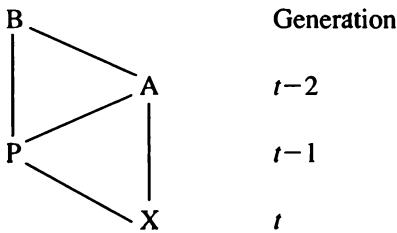


Fig. 5.6

$F_X = f_{PA} = \frac{1}{2}(f_{AB} + f_{AA})$. The recurrence equation is obtained by substituting $f_{AB} = F_P = F_{t-1}$, and $f_{AA} = \frac{1}{2}(1 + F_A) = \frac{1}{2} + \frac{1}{2}F_{t-2}$. The recurrence equation then becomes identical with that for full sibs in equation [5.9]. This is true, however, only for autosomal genes; for sex-linked genes, parent-offspring mating gives a slightly higher rate of inbreeding, with $\Delta F = 0.293$ after the first few generations (Wright, 1933).

Half sibs Figure 5.1 gives the individuals to which the coancestry in equation [5.7] refers. To get the recurrence equation for repeated half-sib matings we have to know the relationship between individuals B and C. These could be either half sibs to each other or full sibs. With animals, B and C are usually females, both mated to the same male A. To continue half-sib mating with the equivalents of B and C always half sibs, it is necessary to mate one of the females to a second male, making 4 individuals as parents in each generation. This is difficult in practice, but if it

is done the recurrence equation, obtained by substitutions in the same manner as above, becomes

$$F_t = \frac{1}{8}(1 + 6F_{t-1} + F_{t-2}) \quad \dots [5.10]$$

It is easier to continue half-sib mating with B and C being always full sibs, and the number of parents in each generation is then three. The inbreeding then goes a little faster and the recurrence equation is

$$F_t = \frac{1}{16}(3 + 8F_{t-1} + 4F_{t-2} + F_{t-3}) \quad \dots [5.11]$$

Table 5.1 Inbreeding coefficients under various systems of close inbreeding, and probability of fixation under full-sib mating.

Generation (<i>t</i>)	A	B (1)	B (2)	C	D
0	0	0	0	0	0
1	0.500	0.250	0	0.125	0.250
2	0.750	0.375	0.063	0.219	0.375
3	0.875	0.500	0.172	0.305	0.438
4	0.938	0.594	0.293	0.381	0.469
5	0.969	0.672	0.409	0.449	0.484
6	0.984	0.734	0.512	0.509	0.492
7	0.992	0.785	0.601	0.563	0.496
8	0.996	0.826	0.675	0.611	0.498
9	0.998	0.859	0.736	0.654	0.499
10	0.999	0.886	0.785	0.691	
11		0.908	0.826	0.725	
12		0.926	0.859	0.755	
13		0.940	0.886	0.782	
14		0.951	0.908	0.806	
15		0.961	0.925	0.827	
16		0.968	0.940	0.846	
17		0.974	0.951	0.863	
18		0.979	0.960	0.878	
19		0.983	0.968	0.891	
20		0.986	0.975	0.903	

Column	System of mating	Recurrence equation
A	Self-fertilization or repeated backcrosses to highly inbred line.	
B	Full brother × sister, or offspring × younger parent:	$\frac{1}{2}(1 + F_{t-1})$
(1)	Inbreeding coefficient.	$\frac{1}{4}(1 + 2F_{t-1} + F_{t-2})$
(2)	Probability of fixation (<i>from Schäfer, 1937</i>).	
C	Half sib (females half sisters).	$\frac{1}{8}(1 + 6F_{t-1} + F_{t-2})$
D	Repeated backcrosses to random-bred individual.	$\frac{1}{4}(1 + 2F_{t-1})$

Fixation

One is often more interested in the probability of fixation as a consequence of inbreeding than in the inbreeding coefficient. The inbreeding coefficient gives the

probability of an individual being a homozygote, which is $1 - 2p_0q_0(1 - F)$ from Table 3.1. But one wants to know also how soon all individuals in a line can be expected to be homozygous for the same allele at a particular locus. The probability of fixation depends on the number of alleles and their arrangement in the initial matings of the line. The probabilities of fixation at any one locus over the first 20 generations of full-sib mating are given in column B (2) of Table 5.1 when four alleles were present in the initial mating. There cannot, of course, be more than four alleles in a sib-mated line, and when there are fewer the probability of fixation is greater (see Haldane, 1955). After the first few generations the probability of fixation becomes only a little less than the inbreeding coefficient.

A question of more practical importance is the probability of fixation at all loci, or the proportion of the whole genome that is expected to be fixed. This is the degree of 'purity' implied by the term 'pure line', which is often used to mean a highly inbred line. We cannot get the probability of total fixation from the presumed number of loci and the probability of fixation at any one, because when one locus becomes fixed neighbouring loci linked to it become fixed too. Consequently the probability of total fixation depends on the total map length and, to a lesser extent, on the number of chromosomes. This is a complicated matter and cannot be explained here: for details see Stam (1980). Total fixation, as must be obvious, takes much longer than fixation at any one locus. For example, after 20 generations of sib-mating in an organism like the mouse virtually no individual can be expected to be completely homozygous and no line totally fixed. To reach the expectation that 95 per cent of individuals will be completely homozygous requires about 50 generations (Stam, 1980). After this number of generations the probability of total fixation is nearly the same. So, putting the matter the other way round, we can conclude that after 50 generations about 5 per cent of the genome is expected to be still heterogeneous in a sib-mated line of mice. New heterogeneity caused by mutation is described in Chapter 15.

Repeated backcrosses

Repeated backcrosses to an individual or to a highly inbred line are often made, for a variety of purposes. The resulting inbreeding is as follows. The pedigree (Fig. 5.7) shows an individual A, which will probably be a male, mated to his daughter C, his granddaughter D, etc. From the supplementary rule [5.5]

$$\begin{aligned} F_X = f_{AD} &= \frac{1}{2}(f_{AA} + f_{AC}) \\ &= \frac{1}{2}\{\frac{1}{2}(1 + F_A) + F_D\} \end{aligned}$$

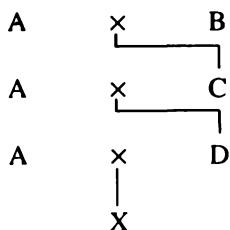


Fig. 5.7

The recurrence equation is therefore

$$F_t = \frac{1}{4}(1 + F_A + 2F_{t-1}) \quad \dots [5.12]$$

where F_A is the inbreeding coefficient of the individual to which the repeated backcrosses are made. If A is an individual from the base population and $F_A = 0$, the equation becomes

$$F_t = \frac{1}{4}(1 + 2F_{t-1}) \quad \dots [5.13]$$

The inbreeding coefficients over the first 9 generations are given in Table 5.1. If A is an individual from a highly inbred line and $F_A = 1$, the equation becomes

$$F_t = \frac{1}{2}(1 + F_{t-1}). \quad \dots [5.14]$$

which is identical with the equation for self-fertilization. In this case A need not be the same individual in successive generations: it can be any member of the inbred line.

The chief use of repeated backcrosses is to transfer a particular gene from one strain into the genetic background of another strain. A problem then arises as to the length of foreign chromosome that will be transferred along with the desired gene. A dominant gene can be transferred by successive crosses of the heterozygote to the strain into which it is to be introduced. It can be shown (see Crow and Kimura, 1970, p. 94) that in this case the mean length of chromosome introduced with the gene after t crosses is approximately $100/t$ cM on each side of the gene, or $200/t$ cM altogether. (1 centimorgan (cM) is the map distance corresponding to a recombination frequency of 1 per cent.) A recessive gene is commonly transferred by alternating backcrosses and intercrosses, from which the homozygote is extracted. The mean length of foreign chromosome in this case is about $200/t$ cM on each side, or $400/t$ cM altogether, after t cycles (Bartlett and Haldane, 1935). From the length of linked chromosome transferred and the total map length of the organism, we can arrive at the expected proportion of the total genome that is still heterogeneous. Suppose, for example, that a dominant gene is transferred to an inbred mouse strain by five backcrosses. The gene would carry with it a length of linked chromosome amounting to $200/5 = 40$ cM. Taking the total map length of the mouse to be 1,600 cM (Davisson and Roderick, 1989), this heterogeneous segment would represent 2.5 per cent of the total genome. In addition, some proportion of the genome not associated with the gene being transferred is expected to be still heterogeneous. This can be taken as approximately $1 - F$ which, from column A of Table 5.1, is 3 per cent after 5 backcrosses. So in all about 5.5 per cent of the genome is expected to be still heterogeneous. An exact treatment of the problem is given by Stam and Zeven (1981). The transference of histocompatibility genes has special problems, which are considered by Johnson (1981).

Crosses and subsequent generations

A standard procedure in genetical analysis and in breeding, particularly plant breeding, is to make crosses between highly inbred lines and to raise the F_1 , F_2 and subsequent generations. What is the inbreeding coefficient in the subsequent generations if these are maintained as a large random-bred population? This question is

easily answered by consideration of types of gamete, but it is not difficult to verify the solution by the rules of coancestry. We shall consider populations derived from a cross of two inbred lines (*2-way cross*) and from a cross of four inbred lines (*4-way cross*). All the lines are completely inbred, so all the gametes produced by any one line are identical. The population derived from a 2-way cross therefore starts from only two different gametes; the population is equivalent to one derived from the self-fertilization of one individual in a random breeding population and its inbreeding coefficient is therefore $F = 0.50$. A population derived from a 4-way cross starts from four different gametes, which is equivalent to full-sib mating and the inbreeding coefficient is $F = 0.25$.

These inbreeding coefficients of the derived populations have no meaning unless the base population to which they refer is defined. The base population implicit in the reasoning above is some real or hypothetical random-breeding population from which the inbred lines were derived. The inbred lines used in the crosses are assumed to be a random sample of all possible lines produced without any change of the mean gene frequencies, i.e., with no selection. With the base population defined in this way, the meaning of the inbreeding coefficient of the derived population is as follows. If we made a large number of 2-way, or of 4-way, crosses each with a different set of inbred lines, the populations derived from the crosses would constitute a set of lines or sub-populations. The inbreeding coefficient would then indicate the expected amount of dispersion of gene frequencies among these lines. Populations derived from 2-way crosses are equivalent to progenies of one generation of self-fertilization. The gene frequencies can therefore have only three values, 0, $\frac{1}{2}$, and 1. Populations derived from 4-way crosses are equivalent to progenies of one generation of full-sib mating, and the gene frequencies can have only five values, 0, $\frac{1}{4}$, $\frac{1}{2}$, $\frac{3}{4}$, and 1.

Mixed inbreeding and crossing

Many plants are 'inbreeders', reproducing normally by self-fertilization. In many of these, however, some cross-pollination regularly occurs. The proportion of crossing varies widely, ranging, for example in lima beans and sorghum varieties, from around 5 per cent up to 50 per cent (Allard, Jain, and Workman, 1968). How much heterozygosity will the crossing generate? It is assumed that the whole population is large, and that whether an individual selfs or crosses is random, being unrelated to what its parents did. In any generation there are two sorts of progeny, those produced by self-fertilization and those produced by crossing. Let C be the proportion of individuals produced by crossing; their inbreeding coefficient is zero. The proportion produced by selfing is $(1 - C)$, and their inbreeding coefficient is $F_i = \frac{1}{2}(1 + F_{i-1})$ by equation [5.8]. The average inbreeding coefficient is therefore

$$F_i = \frac{1}{2}(1 + F_{i-1})(1 - C)$$

If the rate of crossing remains constant, the average inbreeding coefficient reaches an equilibrium level at which it remains. Then $F_i = F_{i-1}$, and rearrangement of the above equation gives the average inbreeding coefficient at equilibrium as

$$F = \frac{1 - C}{1 + C} \quad \dots [5.15]$$

5 Small populations

where C is the proportion of individuals produced by cross-pollination. On the assumption that there is no selection for or against heterozygotes, the expected frequency of heterozygotes relative to a fully random breeding population is $1 - F$, by equation [3.15]. Application of equations [5.15] and [3.15] shows that 5 per cent of crossing generates heterozygosity amounting to 9.5 per cent of that of a random-breeding population, and 50 per cent of crossing generates 66.7 per cent. Studies of barley have shown the frequencies of heterozygotes at four esterase loci to be greater than expected from the known amount of crossing, which was 0.57 per cent, the excess being attributed to selection favouring heterozygotes (Allard, Kahler, and Weir, 1972).

The effect of crossing on the structure of a predominantly inbreeding population is more important than the generation of heterozygosity. With no crossing, an inbreeding population consists of completely homozygous lines, and natural selection operates through the elimination of the less well-adapted lines. Each local habitat is then inhabited by the line best adapted to it (Allard, Jain, and Workman, 1968), but no further adaptation can take place, nor new adaptation to different habitats, except by mutation. With some crossing, however, new lines are constantly generated, with genes recombined from the existing lines, and this allows continued, or new, adaptation to take place. Crossing also makes possible the elimination of deleterious genes that have arisen by mutation and been fixed by the inbreeding.

The converse problem is also of interest, namely a small amount of inbreeding in a predominantly outbreeding population. Substitution of high values of C (the proportion crossing) into equation [5.15] shows that a small amount of selfing raises the average inbreeding coefficient by very little. The reason for this is that the population does not become differentiated into permanent lines; the progeny of selfing are most likely themselves to cross-breed. If the inbreeding is by full-sib mating rather than selfing, the inbreeding coefficient expressed in a way analogous to equation [5.15] is $F = (1 - C)/(1 + 3C)$. Expressed in terms of the proportion of individuals produced by sib-mating, $S = (1 - C)$, the formula becomes

$$F = \frac{S}{4 - 3S} \quad \dots [5.16]$$

(see Li, 1976, for details). For example, 5 per cent of full-sib mating in a large population would raise the average inbreeding coefficient from 0 to 1.2 per cent, and 10 per cent would raise it to 2.3 per cent. The practical implication of this is that anyone keeping a stock by random breeding, or by minimal inbreeding, need not worry about the consequences of an occasional sib-mating, a point already noted in Chapter 4.

Change of base: structured population

The question to be considered here is not confined to pedigreed populations or close inbreeding. Having computed a coefficient of inbreeding with reference to a certain group of individuals as the base population, one may then want to know the inbreeding coefficient referred to a different base, either more or less remote in the ancestry. For example, an individual produced by a full-sib mating is 25 per cent

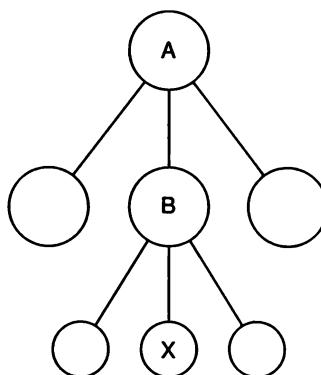


Fig. 5.8

inbred with reference to its parents. Its parents may themselves be inbred with reference to a more remote base. What is the inbreeding coefficient of the individual with reference to this more remote base population? This question implies a 'structured' population with a hierarchical subdivision into lines and sublines, as illustrated in Fig. 5.8. In Fig. 5.8, A represents the further-back base population with which we are concerned, B is a later stage, and X represents the individuals whose inbreeding coefficient is to be calculated. The unlettered circles contemporary with B represent the subdivision of A into lines in the manner of Fig. 3.1. In a real population only one of these lines, B, may actually exist. Line B is then further divided into sublines and X is an individual in one of these. The solution comes from a consideration of the relative frequencies of heterozygotes. Let H_X , H_B , and H_A be the frequencies of heterozygotes among the contemporaries of X, B, and A respectively. Then $H_X/H_A = (H_X/H_B)(H_B/H_A)$, and it follows from equation [3.15] that

$$P_{X \cdot A} = P_{X \cdot B} P_{B \cdot A} \quad \dots [5.17]$$

where $P_{X \cdot A} = 1 - F_{X \cdot A}$; $F_{X \cdot A}$ being the inbreeding coefficient of X referred to A as base, and similarly for the other subscripts. The relationship in equation [5.17] can be extended to any number of categories of subdivision, or stages of inbreeding.

Example 5.2.

A strain of mice was bred for 42 generations with an effective population size of about 40, and was then inbred by full-sib mating for a further 11 generations (Falconer, 1971). What was the inbreeding coefficient at the end? The inbreeding produced by the full-sib mating, i.e., from B to X in Fig. 5.8, was 0.908, from Table 5.1. Thus $P_{X \cdot B} = 1 - 0.908 = 0.092$. The inbreeding in the line when the sib-mating was started, i.e., from A to B, was as follows: with $N_e = 40$, equation [4.1] gives $\Delta F = 0.0125$, and after 42 generations equation [3.12] gives $F_{B \cdot A} = 0.410$. Thus $P_{B \cdot A} = 1 - 0.410 = 0.590$. By equation [5.17], $P_{X \cdot A} = 0.590 \times 0.092 = 0.054$. Thus the inbreeding coefficient at the end, referred to the origin of the line as base, was $F_{X \cdot A} = 1 - P_{X \cdot A} = 0.946$.

Equation [5.17] is an equivalent way of expressing what are known as *Wright's F-statistics*, used to describe structured populations. In the terminology of the *F*-statistics, F_{IS} is the inbreeding coefficient of an individual relative to its own sub-population and is equivalent to $1 - P_{X \cdot B}$ above; F_{ST} is the average inbreeding of the sub-population relative to the whole population, equivalent to $1 - P_{B \cdot A}$ above; and F_{IT} is the inbreeding coefficient of the individual relative to the whole population. The relationship equivalent to equation [5.17] is

$$(1 - F_{IT}) = (1 - F_{IS})(1 - F_{ST})$$

Mutation

After a long period of inbreeding, mutation may become an important factor in determining the frequency of heterozygotes. If u is the mutation rate of a gene that has reached near-fixation in the line, then the frequency of heterozygotes at this locus due to mutation is $4u$ under self-fertilization, and $12u$ under full-sib mating, for autosomal loci (Haldane, 1936). These are very small frequencies if we are concerned with only one locus, but if the effects of all loci are taken together, mutation is not entirely negligible as a source of heterozygosity in long-inbred strains such as the widely used strains of mice. The practical consequences of the origin of heterogeneity by mutation are that the characteristics of a line slowly change through the fixation of mutant alleles, and that sub-lines become differentiated. This matter is considered further in Chapter 15.

Selection favouring heterozygotes

When close inbreeding is practised, the object is generally to produce fixation, or homozygosis, within the lines. It is therefore a matter of some importance to know how selection will affect the progress toward fixation. Selection against a deleterious recessive may prevent the deleterious allele from becoming fixed, but it will not delay the fixation of the more favourable allele. Selection that favours heterozygotes, however, is another matter. A consequence of inbreeding almost universally observed is a reduction of fitness, the reasons for which will be given in Chapter 14. Thus selection resists the inbreeding, since the more homozygous individuals are the less fit, and this can only mean that selection favours heterozygotes – not necessarily heterozygotes of the loci taken singly, but heterozygotes of segments of chromosome. It is only necessary to have two deleterious genes, recessive or partially recessive, linked in repulsion, to confer a selective advantage on the heterozygotes of the segment of chromosome within which the genes are located. It is therefore important to find out how the opposing tendencies of inbreeding and selection in favour of heterozygotes balance each other, in order to assess the reliability of the computed inbreeding coefficient as a measure of the probability of fixation.

The outcome of the joint action of inbreeding and selection in favour of heterozygotes depends on whether there is replacement of the less fit lines by the more fit; in other words, on whether selection operates between lines or only within lines. Within any one line, selection against homozygotes only delays the progress toward fixation and cannot arrest it, unless both homozygotes are completely

inviable or sterile. The delay is roughly proportional to the coefficient of selection against the homozygotes and is least under the closest inbreeding (Reeve, 1955a). For example, if selection acted equally against both homozygotes, the 'real' rate of inbreeding, F , in a self-fertilized line would be reduced from 0.50 to 0.44 by a coefficient of selection of $s = 0.2$; and to 0.20 by $s = 0.75$. With full-sib mating, these coefficients of selection would reduce F from 0.19 to 0.15 and 0.03 respectively, all these values being only approximate. An example of delayed inbreeding is provided by an experiment with *Drosophila* (Rumball *et al.*, 1994). Two sib-mated lines and two lines inbred by double first-cousin mating were continued for 11 and 18 generations respectively, the real inbreeding being estimated from the genotype frequencies at six enzyme loci. In all four lines the real rate of inbreeding was about 80 per cent of the theoretical rate, and the delay could be unequivocally attributed to natural selection favouring heterozygous chromosome segments.

The consequences are different, however, if there are many lines and the breeding system allows the less fit lines to be replaced by sub-lines from the more fit. For example, replacement will result if seed from a population of self-pollinating plants is collected in bulk and a random sample is taken for planting; or, in a sib-mated population, if pairs of sibs for mating are taken at random from all the surviving progeny. The lines at any stage will differ by chance in the number of heterozygotes left, and those with more heterozygotes will leave more progeny and so will contribute most to the next generation. With this breeding system, selection against homozygotes, if sufficiently strong, leads to a state of balance between the opposing forces of inbreeding and selection, and the dispersive process is arrested. The coefficients of selection needed to arrest progress toward homozygosity are fairly high. For example, if both homozygotes are equally selected against, the minimum coefficient required to prevent complete homozygosis is $s = 0.50$ in a self-fertilizing population and $s = 0.24$ in a full-sib-mating population. The coefficients that would stop the process when the frequency of heterozygotes is half its original value, i.e., when $F = 0.5$, are $s = 0.67$ with self-fertilization and $s = 0.47$ with full-sib mating (Hayman and Mather, 1953).

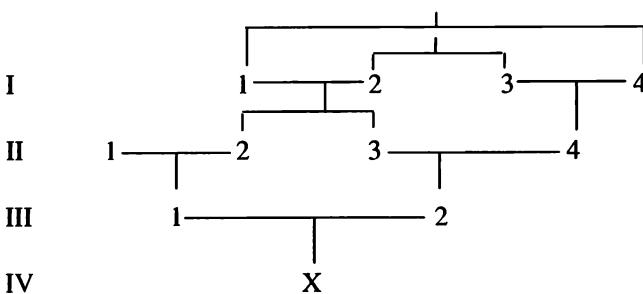
The conclusions outlined above refer to a single locus. If there were more than a few loci on different chromosomes all subject to selection against homozygotes of an intensity sufficient to arrest or seriously delay the progress of inbreeding, the total loss of fitness from all the loci would be very severe. Inbred lines of organisms with a high reproductive rate, such as plants and *Drosophila*, might well stand up to a total loss of fitness sufficient to keep several loci or segments of chromosome permanently unfixed. But the loss of fitness involved in preventing the fixation of more than two or three loci in an organism such as the mouse would be crippling. Under laboratory conditions the highly inbred strains of mice, after 100 or more generations of sib-mating, have a fitness not much less than half that of non-inbred strains. It is conceivable that they might have one locus permanently unfixed, but it is difficult to believe that they can have more. Complete lethality or sterility of both homozygotes at one locus means a 50 per cent loss of progeny; at two unlinked loci, a 75 per cent loss. A mouse strain with a mortality or sterility of 50 per cent can be kept going, but hardly one with 75 per cent.

Problems

5.1 What are the inbreeding coefficients in the offspring of marriages between the following relatives? (1) single first cousins, (2) double first cousins, (3) uncle–niece. [Solution 4]

5.2 What is the coancestry of the children of a pair of identical twins married to unrelated individuals? [Solution 14]

5.3 The following is a human pedigree of the absence of the corpus callosum. In generation I, individuals 1 and 4 are full sibs and so are 2 and 3. In generation IV, X represents a family of eight with two affected individuals. Calculate the inbreeding coefficient of this family and that of its parent, III 2.



Data from Shapira, Y. & Cohen, T. (1973) *J. Med. Genet.*, **10**, 266–9.

[Solution 24]

5.4 If a predominantly self-fertilizing plant regularly cross-pollinates with a frequency of 1 per cent, what will be the frequency of heterozygotes at a 2-allele locus with gene frequencies of 0.2 and 0.8, assuming no selection? [Solution 34]

5.5 Suppose that a population of a predominantly self-fertilizing plant is polymorphic for two alleles, *a* and *b*, and the frequencies of the three genotypes are

<i>aa</i>	<i>ab</i>	<i>bb</i>
0.54	0.12	0.34

What frequency of cross-pollination does this indicate, assuming there is no selection?

[Solution 44]

5.6 What would be the inbreeding coefficient of a population kept for 10 generations with an effective size of 16, and then for a further 10 generations with double that size? To how many generations of full-sib mating is it equivalent? [Solution 54]

5.7 Two highly inbred lines of a plant are crossed to produce an F_1 generation. The F_1 individuals are selfed to produce an F_2 . Individuals of the F_2 are then backcrossed to the F_1 and to one of the inbred lines. What are the inbreeding coefficients of the progeny of these two backcrosses? [Solution 64]

5.8 Consanguineous marriage increases the risk of the children suffering from recessive diseases. Work out how much the risk is increased by cousin marriage (single first cousins) for (1) cystic fibrosis with a population incidence of 1/2,500 and (2) phenylketonuria with an incidence of 1/11,000. [Solution 74]

5.9 Suppose that a proportion, y , of individuals in a population are produced by consanguineous matings giving them all an inbreeding coefficient of F , while the remainder, $1 - y$, are produced by random mating, e.g., a human population with some cousin marriages. If homozygotes of a recessive gene occur with an incidence of I in the population as a whole, show that the gene frequency, q , of the recessive allele is estimated from the overall incidence, I , by

$$(1 - yF)q^2 + yFq = I$$

[Solution 84]

6 Continuous Variation

It will be obvious, to biologists and laymen alike, that the sort of variation discussed in the foregoing chapters embraces but a small part of the naturally occurring variation. One has only to consider one's fellow men and women to realize that they all differ in countless ways, but that these differences are nearly all matters of degree and seldom present clear-cut distinctions attributable to the segregation of single genes. If, for example, we were to classify individuals according to their height, we could not put them into groups labelled 'tall' and 'short', because there are all degrees of height and a division into classes would be purely arbitrary. Variation of this sort, without natural discontinuities, is called *continuous variation*, and characters that exhibit it are called *quantitative characters* or *metric characters*, because their study depends on measurement instead of on counting. The genetic principles underlying the inheritance of metric characters are basically those of *population genetics* outlined in the previous chapters. But since the segregation of the genes concerned cannot be followed individually, new methods of study are needed and new concepts have to be introduced. The branch of genetics concerned with metric characters is called *quantitative genetics* or *biometrical genetics*. The importance of this branch of genetics need hardly be stressed; most of the characters of economic value to plant and animal breeders are metric characters, and most of the changes concerned in micro-evolution are changes of metric characters. It is therefore in this branch that genetics has its most important application to practical problems and also its most direct bearing on evolutionary theory.

How does it come about that the intrinsically discontinuous variation caused by genetic segregation is translated into the continuous variation of metric characters? There are two reasons: one is the simultaneous segregation of many genes affecting the character, and the other is the superimposition of truly continuous variation arising from non-genetic causes. Consider, for example, a simplified situation. Suppose there is segregation at 6 unlinked loci, each with 2 alleles at frequencies of 0.5. Suppose that there is complete dominance of one allele at each locus and that the dominant alleles each add one unit to the measurement of a certain character. Then if the segregation of these genes were the only cause of variation there would be 7 discrete classes in the measurements of the character, according to whether the individual had the dominant allele present at 0, 1, 2, . . . , or 6 of the loci. The frequencies of the classes would be according to the binomial expansion of $(\frac{1}{2} + \frac{1}{2})^6$, as shown in Fig. 6.1(a). If our measurements were sufficiently accurate we should recognize these classes as being distinct and we should be able to place any individual unambiguously in its class. If there were more genes segregating but each

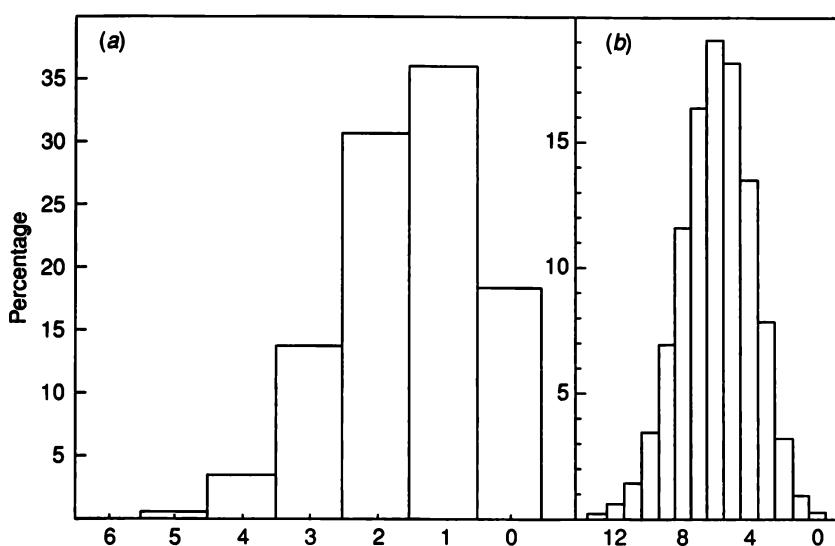


Fig. 6.1. Distributions expected from the simultaneous segregation of two alleles at each of several or many loci: (a) 6 loci, (b) 24 loci. There is complete dominance of one allele over the other at each locus, and the gene frequencies are all 0.5. Each locus, when homozygous for the recessive allele, is supposed to reduce the measurement by 1 unit in (a), and by $\frac{1}{4}$ unit in (b). The horizontal scale, representing the measurement, shows the number of loci homozygous for the recessive allele, and the vertical axis shows the probability, or the percentage of individuals expected in each class. The probabilities are derived from the binomial expansion of $(\frac{1}{4} + \frac{3}{4})^n$, where n is the number of loci.

had a smaller effect, there would be more classes with smaller differences between them, as in Fig. 6.1(b). It would then be more difficult to distinguish the classes, and if the difference between the classes became about as small as the error of measurement we should no longer be able to recognize the discontinuities. In addition, metric characters are subject to variation from non-genetic causes, and this variation is truly continuous. Its effect is, as it were, to blur the edges of the genetic discontinuity so that the variation as we see it becomes continuous, no matter how accurate our measurements may be.

Thus the distinction between genes concerned with Mendelian characters and those concerned with metric characters lies in the magnitude of their effects relative to other sources of variation. A gene with an effect large enough to cause a recognizable discontinuity even in the presence of segregation at other loci and of non-genetic variation can be studied by Mendelian methods, whereas a gene whose effect is not large enough to cause a discontinuity cannot be studied individually. This distinction is reflected in the terms *major gene* and *minor gene*. There are, however, all intermediate grades, genes that cannot properly be classed as major or as minor. And, furthermore, as a result of pleiotropy the same gene may be classed as major with respect to one character and minor with respect to another character. The distinction, though convenient, is therefore not a fundamental one, and there is no good evidence that there are two sorts of genes with different properties. Variation caused by the simultaneous segregation of many genes may be called

polygenic variation, and the minor genes concerned are sometimes referred to as *polygenes*.

Metric characters

The metric characters that might be studied in any higher organism are almost infinitely numerous. Any attribute that varies continuously and can be measured might in principle be studied as a metric character – anatomical dimensions and proportions, physiological functions of all sorts, and mental or psychological qualities. The essential condition is that they should be measurable. The technique of measurement, however, sets a practical limitation on what can be studied. Usually rather large numbers of individuals have to be measured and the study of any character whose measurement requires an elaborate technique therefore becomes impracticable. Consequently the characters that have been used in studies of quantitative genetics are predominantly anatomical dimensions, or physiological functions measured in terms of an end-product, such as lactation, fertility, or growth rate.

Some examples of metric characters are illustrated in Fig. 6.2. The variation is represented graphically by the frequency distribution of measurements. The measurements are grouped into equally spaced classes and the proportion of individuals falling in each class is plotted on the vertical scale. The resulting histogram is discontinuous only for the sake of convenience in plotting. If the class ranges were made smaller and the number of individuals measured were increased indefinitely, the histogram would become a smooth curve. The variation of some metric characters, such as bristle number or litter size, is not strictly speaking continuous because, being measured by counting, their values can only be whole numbers. Nevertheless, one can regard the measurements in such cases as referring to an underlying character whose variation is truly continuous though expressible only in whole numbers, in a manner analogous to the grouping of measurements into classes. For example, litter size may be regarded as a measure of the underlying, continuously varying character, fertility. For practical purposes such characters can be treated as continuously varying, provided the number of classes is not too small. When there are too few classes, as for example when susceptibility to disease is expressed as death or survival, different methods have to be employed, as will be explained in Chapter 18.

The frequency distributions of most metric characters approximate more or less closely to normal curves. This can be seen in Fig. 6.2, where the smooth curves drawn through the histograms are normal curves having means and variances calculated from the data. In the study of metric characters it is therefore possible to make use of the properties of the normal distribution and to apply the appropriate statistical techniques. Sometimes, however, the scale of measurement must be modified if a distribution approximating to the normal is to be obtained. The distribution in Fig. 6.2(d), for example, would be skewed if measured and plotted simply as the number of facets. But it becomes symmetrical, and approximates to a normal distribution, if measured and plotted in logarithmic units. The criteria on which the choice of a scale of measurement rests cannot be fully appreciated at this stage, and

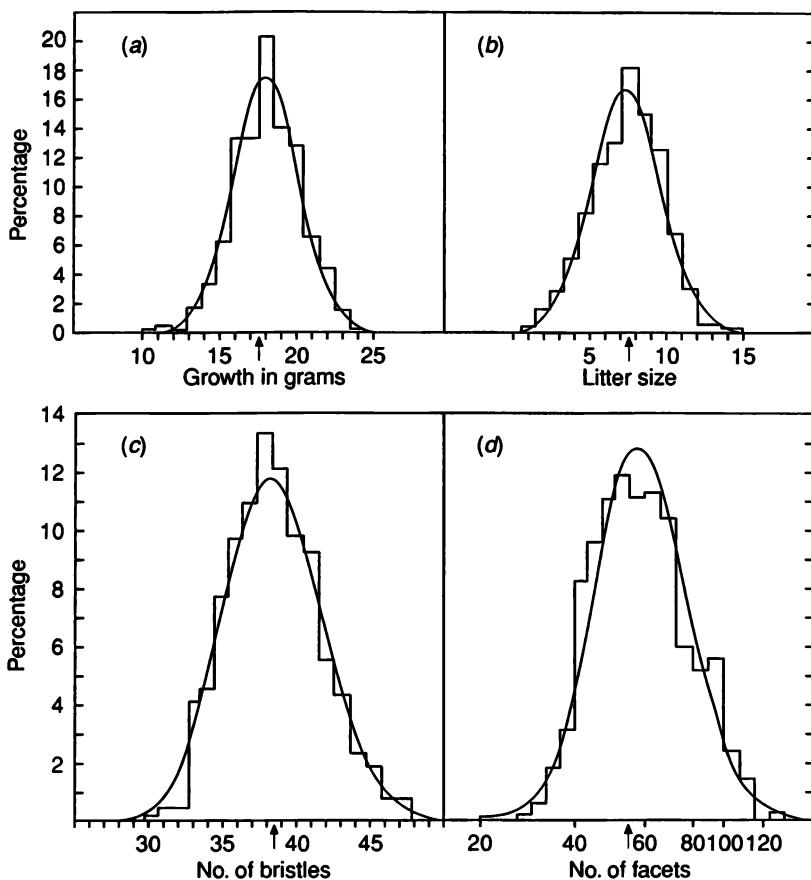


Fig. 6.2. Frequency distributions of four metric characters, with normal curves superimposed. The means are indicated by arrows. The characters are as follows, the number of observations on which each histogram is based being given in brackets:

- (a) Mouse ($\delta \delta$): growth from 3 to 6 weeks of age. (380)
 - (b) Mouse: litter size (number of live young in 1st litters). (689)
 - (c) *Drosophila melanogaster* ($\varphi \varphi$): number of bristles on ventral surface of 4th and 5th abdominal segments, together. (900)
 - (d) *Drosophila melanogaster* ($\varphi \varphi$): number of facets in the eye of the mutant "Bar". (488)
- (a), (b), and (c) are from original data; (d) is from data of Zeleny (1922).

will be explained in Chapter 17. Meantime it will be assumed that any metric character under discussion is measured on an appropriate scale and has a distribution that is approximately normal.

What are the grounds for believing that metric characters really are controlled by genes at many loci? There are two kinds of evidence. The first is indirect: observations in general agree well with what is expected from the theory of polygenic inheritance. The second is direct experimental evidence: loci affecting quantitative traits can be mapped on chromosomes by methods to be described in Chapter 21. Loci identified in this way are called *Quantitative Trait Loci*, or *QTLs*. *Drosophila melanogaster* has variable numbers of sensory bristles on the thorax and abdomen, called sternopleural and abdominal bristles, respectively. At least 17 QTLs affecting

sternopleural bristle number and 5 affecting abdominal bristle number have been mapped to the third chromosome (Shrimpton and Robertson, 1988b; Long *et al.*, 1995). Similarly, at least 6 QTLs affecting fruit mass have been found to differentiate the domestic tomato from a related wild species (Paterson *et al.*, 1988).

Properties of metric characters

There are two basic genetic phenomena concerned with metric characters, both more or less familiar to all biologists, and each forms the basis of a breeding method. The first is the resemblance between relatives. Everyone is familiar with the fact that relatives tend to resemble each other, and the closer the relationship, in general the closer the resemblance. Though it is only in our own species that resemblances are readily discernible without measurement, the phenomenon is equally present in other species. The degree of resemblance varies with the character, some showing more, some less. The resemblance between offspring and parents provides the basis for selective breeding. Use of the more desirable individuals as parents brings about an improvement of the mean level of the next generation, and just as some characters show more resemblance than others, so some are more responsive to selection than others. The degree of resemblance between relatives is one of the properties of a population that can be readily observed, and it is one of the aims of quantitative genetics to show how the degree of resemblance between different sorts of relatives can be used to predict the outcome of selective breeding and to point to the best method of carrying out the selection. The application of genetic principles to selective breeding of farm animals has led to very substantial improvements, with large economic benefits; the rates of improvement achieved have been between about 1 and 3 per cent per year (Smith, 1984, 1988). The principles underlying selective breeding form the central theme of the next seven chapters, the resemblance between relatives being dealt with in Chapters 9–10, and the effects of selection in Chapters 11–13.

Many quantitative characters are correlated with others. In mice, for example, body size and litter size, two of the characters illustrated in Fig. 6.2, are correlated; larger mice tend to have larger litters, as can be seen in Fig. 6.3. Correlations like this are partly due to pleiotropy: some of the genes that influence one character also influence the other. A correlated character may therefore be an aid to selection aimed at changing the character with which it is correlated. Correlated characters are dealt with in Chapter 19.

The second basic genetic phenomenon is inbreeding depression, with its converse hybrid vigour, or heterosis. This phenomenon is less familiar to the layman than the first, since the laws against incest prevent its more obvious manifestations in our own species; but it is well known to animal and plant breeders. Inbreeding tends to reduce the mean level of all characters closely connected with fitness in animals and in naturally outbreeding plants, and to lead in consequence to loss of general vigour and fertility. Since most characters of economic value in domestic animals and plants are aspects of vigour or fertility, inbreeding is generally deleterious. The reduced vigour and fertility of inbred lines is restored on crossing, and in certain circumstances this hybrid vigour can be made use of as a means of

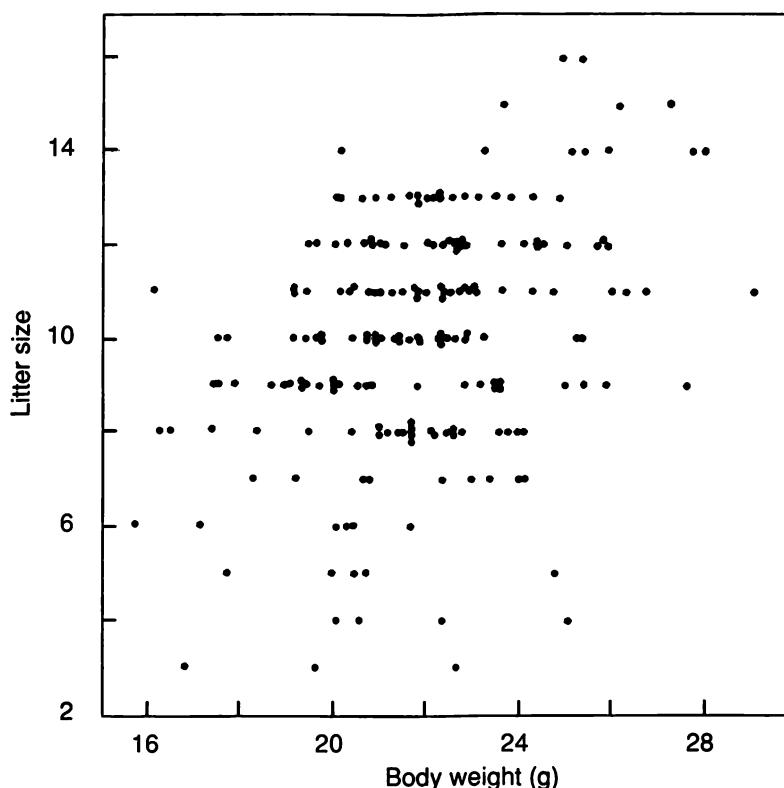


Fig. 6.3. Correlation between body weight and litter size in mice. Each point represents one individual female plotted according to its body weight at 6 weeks of age and the number of live young in its litter born some weeks later. The correlation among these 200 individuals is 0.3. (Data kindly provided by Dr Ian Hastings.)

improvement. The enormous improvement of the yield of commercially grown maize has been achieved by this means, yields having been approximately doubled in the USA since 1935 (Hallauer and Miranda, 1981, p. 408; for improvements in some other crop plants see Simmonds, 1979, p. 47). The effects of inbreeding and crossing are described in Chapters 14–16.

The properties of a population that we can observe in connection with a metric character are means, variances, and covariances. The natural subdivision of the population into families allows us to analyse the variance into components which form the basis for the measurement of the degree of resemblance between relatives. We can in addition observe the consequences of experimentally applied breeding methods, such as selection, inbreeding or cross-breeding. The practical objective of quantitative genetics is to find out how we can use the observations made on the population as it stands to predict the outcome of any particular breeding method. The more general aim is to find out how the observable properties of the population are influenced by the properties of the genes concerned and by the

various non-genetic circumstances that may influence a metric character. The chief properties of genes that have to be taken into account are the degree of dominance, the manner in which genes at different loci combine their effects, pleiotropy, linkage, and fitness under natural selection. To take account of all these properties simultaneously, in addition to a variety of non-genetic circumstances, would make the problems unmanageably complex. We therefore have to simplify matters by dealing with one thing at a time, starting with the simpler situations.

The plan to be followed in the succeeding chapters is this: we shall first show what determines the population mean, and then introduce two new concepts – average effect and breeding value – which are necessary to an understanding of the variance. Then we shall discuss the variance, its analysis into components, and the covariance of relatives, which will lead us to the degree of resemblance between relatives. In all this we shall take full account of dominance from the beginning: the other complicating factors will be more briefly discussed when they become relevant. The most important simplification that we shall make concerns the effect of genes on fitness: we shall assume that Mendelian segregation is undisturbed by differential fitness of the genotypes. The description of means, variances, and covariances will refer to a random-breeding population, with Hardy–Weinberg equilibrium genotype frequencies, with no selection and no inbreeding. That is to say, we shall describe the population before any special breeding method is applied to it. Then in Chapters 11–13 we shall describe the effects of selection, and in Chapters 14–16 the effects of inbreeding. This will cover the fundamentals of quantitative genetics, and in the final chapters we shall discuss some special topics, including correlated characters in Chapter 19, natural populations and evolution in Chapter 20, and the nature of the genes controlling metric characters in Chapter 21.

Problems

6.1 The figures tabulated are the number of leaves per plant in 25 F_1 and 25 F_2 plants from a cross of two cultivated varieties of tobacco, which had mean leaf numbers of 15.0 and 17.9 respectively. Tabulate (and plot if desired) the frequency distributions of the F_1 and F_2 generations. From each distribution calculate the mean, the variance, and the standard error of the mean. What is the main difference between the two distributions?

F_1					F_2				
18	15	16	18	15	16	20	19	17	14
16	14	16	18	17	16	14	14	15	17
16	13	16	14	16	20	13	12	15	16
15	16	15	15	16	21	18	15	14	18
15	16	16	15	16	14	17	13	15	13

Data from Johnson J. (1919) *Genetics*, 4, 307–40.

[Solution 5]

6.2 The table gives the weights (g) at 60 days of age of 50 male mice, bred from 12 pairs of parents, in one generation of a strain that had been bred selectively for small size.

Tabulate (and plot if desired) the frequency distribution and calculate the mean and variance. What is peculiar about the distribution?

12.8	15.7	13.7	5.7	6.1	13.2	12.5	7.0	6.6	14.8
12.8	14.1	14.0	17.8	14.7	11.8	13.5	14.1	16.2	6.6
5.7	11.7	13.4	6.6	6.8	15.6	13.0	11.5	12.1	15.4
11.8	11.4	10.7	15.6	14.9	4.7	13.1	13.4	14.5	13.4
11.8	17.2	15.0	15.1	14.6	14.8	15.1	14.9	18.4	16.5

Data kindly supplied by Dr J.W.B. King.

[Solution 15]

6.3 Work out the frequency distribution of the genotypic classes, from which to construct a histogram (like Fig. 6.1), when a metric character is affected by 4 independently segregating loci, each with 2 alleles and complete dominance. The recessive alleles when homozygous each reduce the measurement by 1 unit. All recessive alleles have a gene frequency of 0.3.

[Solution 25]

6.4 Work out the frequency distribution with everything the same as in Problem 6.3 except that the frequencies of the recessive alleles are 0.3 at two of the loci and 0.7 at the other two.

[Solution 35]

6.5 Work out the frequency distribution when there are three loci, each with 2 alleles and with no dominance. At all loci, homozygotes differ by 2 units of measurement and heterozygotes differ by 1 unit from both homozygotes. At all loci the gene frequency of the allele that decreases the measurement is 0.4.

[Solution 45]

6.6 What gene frequency would produce a perfectly symmetrical distribution of measurement classes under the conditions of (1) Problem 6.3 and (2) Problem 6.5? [Solution 55]

7 Values and Means

We have seen in the early chapters that the genetic properties of a population are expressible in terms of the gene frequencies and genotype frequencies. In order to deduce the connection between these on the one hand and the quantitative differences exhibited in a metric character on the other, we must introduce a new concept, the concept of *value*, expressible in the metric units by which the character is measured. The value observed when the character is measured on an individual is the *phenotypic value* of that individual. All observations, whether of means, variances, or covariances, must clearly be based on measurements of phenotypic values. In order to analyse the genetic properties of the populations we have to divide the phenotypic value into component parts attributable to different causes. Explanation of the meanings of these components is our chief concern in this chapter, though we shall also be able to find out how the population mean is influenced by the array of gene frequencies.

The first division of phenotypic value is into components attributable to the influence of genotype and environment. The *genotype* is the particular assemblage of genes possessed by the individual, and the *environment* is all the non-genetic circumstances that influence the phenotypic value. Inclusion of all non-genetic circumstances under the term ‘environment’ means that the genotype and the environment are by definition the only determinants of phenotypic value. The two components of value associated with genotype and environment are the *genotypic value* and the *environmental deviation*. We may think of the genotype conferring a certain value on the individual and the environment causing a deviation from this, in one direction or the other. Or, symbolically,

$$P = G + E \quad \dots [7.1]$$

where P is the phenotypic value, G is the genotypic value, and E is the environmental deviation. The mean environmental deviation in the population as a whole is taken to be zero, so that the mean phenotypic value is equal to the mean genotypic value. The term *population mean* then refers equally to phenotypic or to genotypic values. When dealing with successive generations we shall assume for simplicity that the environment remains constant from generation to generation, so that the population mean is constant in the absence of genetic change. If we could replicate a particular genotype in a number of individuals and measure them under environmental conditions normal for the population, their mean environmental deviations would be zero, and their mean phenotypic value would consequently be equal to the genotypic value of that particular genotype. This is the meaning of the genotypic value of an individual. In principle it is measurable, but in practice it is not, except

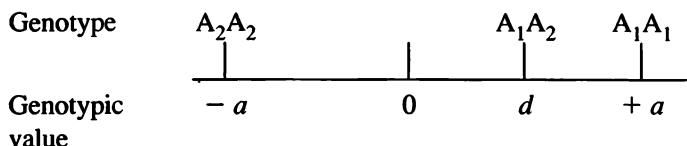


Fig. 7.1. Arbitrarily assigned genotypic values.

when we are concerned with a single locus where the genotypes are phenotypically distinguishable, or with the genotypes represented in highly inbred lines.

For the purposes of deduction we must assign arbitrary values to the genotypes under discussion. This is done in the following way. Considering a single locus with two alleles, A_1 and A_2 , we call the genotypic value of one homozygote $+a$, that of the other homozygote $-a$ and that of the heterozygote d . (We shall adopt the convention that A_1 is the allele that increases the value.) We thus have a scale of genotypic values as in Fig. 7.1. The origin, or point of zero value, on this scale is mid-way between the values of the two homozygotes. The value d of the heterozygote depends on the degree of dominance. If there is no dominance, $d = 0$; if A_1 is dominant over A_2 , d is positive, and if A_2 is dominant over A_1 , d is negative. If dominance is complete, d is equal to $+a$ or $-a$, and if there is overdominance, d is greater than $+a$ or less than $-a$. The degree of dominance may be expressed as d/a .

Example 7.1

For the purposes of illustration in this chapter, and also later on, we shall refer to a dwarfing gene in the mouse, known as 'pygmy' (symbol pg), described by King (1950, 1955), and by Warwick and Lewis (1954). This gene reduces body size and is nearly, but not quite, recessive in its effect on size. It was present in a strain of small mice (MacArthur's) at the time the studies cited above were made. The weights of mice of the three genotypes at 6 weeks of age were approximately as follows (sexes averaged):

	<i>Genotypes</i>		
	$++$	$+pg$	$pg pg$
Weight in grams	14	12	6

(The weight of heterozygotes given here is to some extent conjectural, but it is unlikely to be more than 1 g in error.) These are average weights obtained under normal environmental conditions, and they are therefore the genotypic values. The mid-point in genotypic value between the two homozygotes is 10 g, and this is the origin, or zero-point, on the scale of values assigned as in Fig. 7.1. The value of a on this scale is therefore 4 g, and that of d is 2 g.

Population mean

We can now see how the gene frequencies influence the mean of the character in the population as a whole. Let the gene frequencies of A_1 and A_2 be p and q respectively. Then the first two columns of Table 7.1 show the three genotypes and

their frequencies in a random breeding population, from formula [1.2]. The third column shows the genotypic values as specified above. The mean value in the whole population is obtained by multiplying the value of each genotype by its frequency and summing over the three genotypes. The reason why this yields the mean value may be understood by converting frequencies to numbers of individuals. Multiplying the value by the number of individuals in each genotype and summing over genotypes gives the sum of values of all individuals. The mean value would then be this sum of values divided by the total number of individuals. The procedure in working with frequencies is the same, but since the sum of the frequencies is 1, the sum of values \times frequencies is the mean value. In other words, the division by the total number has already been made in obtaining the frequencies. Multiplication of values by frequencies to obtain the mean value is a procedure that will be often used in this chapter and subsequent ones. Returning to the population mean, multiplication of the value by the frequency of each genotype is shown in the last column of Table 7.1. Summation of this column is simplified by noting that $p^2 - q^2 = (p + q)(p - q) = p - q$. The population mean, which is the sum of this column, is thus

$$M = a(p - q) + 2dpq \quad \dots [7.2]$$

This is both the mean genotypic value and the mean phenotypic value of the population with respect to the character.

The contribution of any locus to the population mean thus has two terms: $a(p - q)$ attributable to homozygotes, and $2dpq$ attributable to heterozygotes. If there is no dominance ($d = 0$), the second term is zero, and the mean is proportional to the gene frequency: $M = a(1 - 2q)$. If there is complete dominance ($d = a$), the mean is proportional to the square of the gene frequency: $M = a(1 - 2q^2)$. The *total range* of values attributable to the locus is $2a$, in the absence of overdominance. That is to say, if A_1 were fixed in the population ($p = 1$) the population mean would be a , and if A_2 were fixed ($q = 1$) it would be $-a$. If the locus shows overdominance, however, the mean of an unfixed population may be outside this range.

The genotypic values a and d are deviations from the mean value of the two homozygotes, as shown in Fig. 7.1. It follows that the population mean expressed in equation [7.2] is a deviation from the mid-homozygote value, which is the origin or zero-point of the scale. If the mean is to be expressed as a deviation from some other value, an appropriate constant must be added or subtracted. For example, one might want to express the mean as a deviation from the value of the lower homozygote. This would require the addition of a , and the mean would become, after some simplification, $M = 2p(a + dq)$. Or, expressed as a deviation from the upper homozygote, it would be $M = 2q(-a + dp)$.

Table 7.1

Genotype	Frequency	Value	Freq. \times Val.
A_1A_1	p^2	$+a$	p^2a
A_1A_2	$2pq$	d	$2pqd$
A_2A_2	q^2	$-a$	$-q^2a$
Sum =		$a(p - q) + 2dpq$	

Example 7.2

Let us take again the pygmy gene in mice, as described in Example 7.1, and see what effect this gene would have on the population mean when present at two particular frequencies. First, the total range is from 6 g to 14 g: a population consisting entirely of pygmy homozygotes would have a mean of 6 g, and one from which the gene was entirely absent would have a mean of 14 g. (These values refer specifically to MacArthur's Small Strain at the time the observations were made.) Now suppose the gene were present at a frequency of 0.1, so that under random mating homozygotes would appear with a frequency of 1 per cent. The values to be substituted in equation [7.2] are $p = 0.9$, $q = 0.1$, and $a = 4$, $d = 2$ g, as shown in Example 7.1. The population mean, by equation [7.2], is therefore: $M = 4 \times 0.8 + 2 \times 0.18 = 3.56$. This value of the mean, however, is measured from the mid-homozygote point, which is 10 g, as origin. Therefore the actual value of the population mean is 13.56 g. Next suppose the gene were present at a frequency of 0.4. Substituting in the same way, we find $M = 1.76$, to which must be added 10 g for the origin, giving a value of 11.76 g. Rough corroboration of these figures is given by the records of the strain carrying the gene. When the gene was present at a frequency of about 0.4 the mean weight was about 12 g. Two generations, later, when the pygmy gene had been deliberately eliminated, the mean weight rose to about 14 g.

Now we have to put together the contributions of genes at several loci and find their joint effect on the mean. This introduces the question of how genes at different loci combine to produce a joint effect on the character. For the moment we shall suppose that combination is by addition, which means that the value of a genotype with respect to several loci is the sum of the values attributable to the separate loci. For example, if the genotypic value of A_1A_1 is a_A and that of B_1B_1 is a_B , then the genotypic value of $A_1A_1B_1B_1$ is $a_A + a_B$. The consequences of non-additive combination will be explained at the end of this chapter. With additive combination, then, the population mean resulting from the joint effects of several loci is the sum of the contributions of each of the separate loci, thus:

$$M = \Sigma a(p - q) + 2\Sigma d p q \quad . . . [7.3]$$

This is again both the genotypic and the phenotypic mean value. The total range in the absence of overdominance is now $2\Sigma a$. If all alleles that increase the value were fixed, the mean would be $+\Sigma a$, and if all alleles that decrease the value were fixed, it would be $-\Sigma a$. These are the theoretical limits to the range of potential variation in the population. The origin from which the mean value in equation [7.3] is measured is the mid-point of the total range. This is equivalent to the average mid-homozygote point of all the loci separately.

Example 7.3

As an example of two loci that combine additively, we shall refer to two colour genes in mice, whose effects on the number of pigment granules have been described by Russell (1949). This is a metric character which reflects the intensity of pigmentation

Example 7.3 continued

in the coat. The two genes are ‘brown’ (b) and ‘extreme dilution’ (c^e), an allele of the albino series. Measurements were made of the number of melanin granules per unit volume of hair, in wild-type homozygotes, in the two single mutant homozygotes, and in the double mutant homozygote. We shall assume both wild-type alleles to be completely dominant, so that only these four genotypes need be considered. The mean numbers of granules in the four genotypes were as shown in the table.

	B^-	bb	$2a_B$
C^-	95	90	5
$c^e c^e$	38	34	4
$2a_c$	57	56	

The difference between the two figures in each row and in each column measures the homozygote difference, or $2a$ on the scale of values assigned as in Fig. 7.1. Apart from the trivial discrepancy of 1 unit, these differences are independent of the genotype at the other locus. In other words, the difference of value between B^- and bb is the same among C^- genotypes as it is among $c^e c^e$ genotypes; and similarly the difference between C^- and $c^e c^e$ is the same in B^- as it is in bb . Thus the two loci combine additively, and the value of a composite genotype can be rightly predicted from knowledge of the values of the single genotypes. For example, the bb genotype is 5 units less than the wild-type, and the $c^e c^e$ is 57 units less; therefore $bb\ c^e c^e$ should be 62 units less than the wild-type value of 95, namely 33, which is almost identical with the observed value of 34.

Average effect

In order to deduce the properties of a population connected with its family structure, we have to deal with the transmission of value from parent to offspring, and this cannot be done by means of genotypic values alone, because parents pass on their genes and not their genotypes to the next generation, genotypes being created afresh in each generation. A new measure of value is therefore needed which will refer to genes and not to genotypes. This will enable us to assign a ‘breeding value’ to individuals, a value associated with the genes carried by the individual and transmitted to its offspring. The new value associated with genes as distinct from genotypes is known as the average effect. Average effects depend on the genotypic values, a and d as previously defined, and also on the gene frequencies. Average effects are therefore properties of populations as well as of the genes concerned. The concept of average effects is not easy to grasp, but it is fundamental to understanding the inheritance of quantitative characters. There are several ways in which average effects can be defined. They are all equivalent under random mating but not otherwise (see Falconer, 1985); we are concerned here only with random breeding populations. One definition is this: the average effect of a particular gene (allele) is the mean deviation from the population mean of individuals which received that gene from one parent, the gene received from the other parent having come at random from the population. This may be stated in another way. Let a number of gametes all carrying A_1 unite at random with gametes from the

population; then the mean of the genotypes so produced deviates from the population mean by an amount which is the average effect of the A_1 gene.

Table 7.2

Type of gamete	Values and frequencies of genotypes produced			Mean value of genotypes produced	Population mean to be deducted	Average effect of gene
	A_1A_1	A_1A_2	A_2A_2			
A_1	p	q		$pa + qd$	$-(a(p-q) + 2dpq)$	$q[a+d(q-p)]$
A_2		p	q	$-qa + pd$	$-(a(p-q) + 2dpq)$	$-p[a+d(q-p)]$

Let us see how the average effect is related to the genotypic values a and d , in terms of which the population mean was expressed. This will help to make the concept clearer. The reasoning is set out in Table 7.2. Consider a locus with two alleles, A_1 and A_2 , at frequencies p and q respectively, and take first the average effect of the gene A_1 , for which we shall use the symbol α_1 . If gametes carrying A_1 unite at random with gametes from the population, the frequencies of the genotypes produced will be p of A_1A_1 and q of A_1A_2 . The genotypic value of A_1A_1 is $+a$ and that of A_1A_2 is d , and the mean of these, taking account of the proportions in which they occur, is $pa + qd$. The difference between this mean value and the population mean is the average effect of the gene A_1 . Taking the value of the population mean from equation [7.2], we get

$$\begin{aligned}\alpha_1 &= pa + qd - [a(p - q) - 2dpq] \\ &= q[a + d(q - p)]\end{aligned} \quad \dots [7.4a]$$

Similarly, the average effect of the gene A_2 is

$$\alpha_2 = -p[a + d(q - p)] \quad \dots [7.4b]$$

When there are more than two alleles the average effect of each allele can be expressed in a similar way. The reason why average effects depend on gene frequencies can be seen in the words 'taken at random' in the definition, because the content of a random sample depends on the gene frequency in the population.

When only two alleles at a locus are under consideration it is more convenient to express their average effects in terms of the *average effect of the gene substitution*. This is simply the difference between the average effects of the two alleles, but its meaning may be more clearly understood in the following way. Suppose that we could change A_2 genes chosen at random into A_1 genes, as if by directed mutation, and could then note the resulting change of value; the mean change so produced would be the average effect of the gene substitution. When A_2 genes are chosen at random a proportion p will be found in A_1A_2 genotypes (p being the gene frequency of A_1) and a proportion q in A_2A_2 genotypes. Changing A_1A_2 into A_1A_1 will change the value from d to $+a$, and the effect will therefore be $(a - d)$. Changing A_2A_2 into A_1A_2 will change the value from $-a$ to d , and the effect will be $(d + a)$. The average change is therefore $p(a - d) + q(d + a)$, which on

rearrangement becomes $a + d(q - p)$. Thus the average effect of the gene substitution (written as α , without subscript) is

$$\alpha = a + d(q - p) \quad \dots [7.5]$$

From equations [7.4] it can readily be seen that

$$\alpha = \alpha_1 - \alpha_2$$

and that the average effects of the two alleles, when expressed in terms of the average effect of the gene substitution, are

$$\left. \begin{array}{l} \alpha_1 = q\alpha \\ \alpha_2 = -p\alpha \end{array} \right\} \quad \dots [7.6]$$

The breeding values of genotypes can conveniently be expressed in these terms, as will be seen in the next section. Another definition of the average effect of a gene substitution will be given later, with a graphical representation in Fig. 7.2.

Example 7.4

Consider again the pygmy gene and its effect on body weight, which was found in Example 7.1 to be $a = 4$ g and $d = 2$ g. If the frequency of the pg gene were $q = 0.1$, the average effect of the gene substitution would be, by equation [7.5], $\alpha = 4 + 2(0.1 - 0.9) = 2.4$ g. And if the frequency were $q = 0.4$, the average effect of the gene substitution would be $\alpha = 4 + 2(0.4 - 0.6) = 3.6$ g. The average effects of the genes separately, by equation [7.6], are as follows.

	$q = 0.1$	$q = 0.4$
Average effect of +: $\alpha_1 =$	+0.24	+1.44
Average effect of pg: $\alpha_2 =$	-2.16	-2.16
$\alpha = \alpha_1 - \alpha_2 =$	2.40	3.60

Thus the average effect of the gene substitution, α , is greater when the gene frequency is greater. The identity of the average effects of pg at the two gene frequencies is only a coincidence.

Breeding value

The usefulness of the concept of average effect arises from the fact, already noted, that parents pass on their genes and not their genotypes to their progeny. It is therefore the average effects of the parents' genes that determine the mean genotypic value of its progeny. The value of an individual, judged by the mean value of its progeny, is called the *breeding value* of the individual. Breeding value, unlike average effect, can therefore be measured. If an individual is mated to a number of individuals taken at random from the population, then its breeding value is twice the mean deviation of the progeny from the population mean. The deviation has to be doubled because the parent in question provides only half the genes in the progeny, the other half coming at random from the population. Breeding values can be expressed in absolute units, but are usually more conveniently expressed in the

form of deviations from the population mean, as defined above. Just as the average effect is a property of the gene and the population, so is the breeding value a property of the individual and the population from which its mates are drawn. One cannot speak of an individual's breeding value without specifying the population in which it is to be mated.

Defined in terms of average effects, the breeding value of an individual is equal to the sum of the average effects of the genes it carries, the summation being made over the pair of alleles at each locus and over all loci. Thus, for a single locus with two alleles, the breeding values of the genotypes are as follows:

<i>Genotype</i>	<i>Breeding value</i>
A ₁ A ₁	2α ₁ = 2qα
A ₁ A ₂	α ₁ + α ₂ = (q - p)α
A ₂ A ₂	2α ₂ = -2pα

Example 7.5

Let us illustrate breeding values by reference to the pygmy gene in mice. The average effects of the + and pg genes were given in the last example. From these we may find the breeding values of the three genotypes as explained above. These breeding values, which are given below, are deviations from the population mean. The population means with gene frequencies of 0.1 and 0.4 were found in Example 7.2 and are shown again below in the column headed *M*.

<i>M</i>	<i>Breeding values</i>		
	++	+pg	pg pg
q = 0.1	13.56	+0.48	-1.92
q = 0.4	11.76	+2.88	-0.72

(The breeding values of pygmy homozygotes are only hypothetical because in fact pygmy homozygotes are nearly all sterile, but this complication may be overlooked in the present context.)

Extension to a locus with more than two alleles is straightforward, the breeding value of any genotype being the sum of the average effects of the two alleles present. If all loci are to be taken into account, the breeding value of a particular genotype is the sum of the breeding values attributable to each of the separate loci. If there is non-additive combination of genotypic values, a slight complication arises. We have given two definitions of breeding value, a practical one in terms of the measured value of the progeny and a theoretical one in terms of average effects. Non-additive combination renders these two definitions not quite equivalent. This point will be more fully explained in Chapter 9.

Consideration of the definition of breeding value will show that in a population in Hardy-Weinberg equilibrium the mean breeding value must be zero; or if breeding values are expressed in absolute units the mean breeding value must be equal to the mean genotypic value and to the mean phenotypic value. This can be verified

from the breeding values listed above. Multiplying the breeding value by the frequency of each genotype and summing gives the mean breeding value (expressed as a deviation from the population mean) as

$$2p^2q\alpha + 2pq(q-p)\alpha - 2q^2p\alpha = 2pq\alpha(p+q-p-q) = 0$$

The breeding value is sometimes referred to as the ‘additive genotype’, and variation in breeding value ascribed to the ‘additive effects’ of genes. Though we shall not use these terms we shall follow custom in using the term ‘additive’ in connection with the variation of breeding values to be discussed in the next chapter, and we shall use the symbol A to designate the breeding value of an individual.

Because the breeding value expresses the value transmitted from parents to offspring it follows that the expected breeding value of any individual is the average of the breeding values of its two parents; and it follows from the definition of breeding value that this is also the individual’s expected phenotypic value. Different offspring of the same parents will differ in breeding value according to which of each parent’s two alleles they receive; the ‘expected’ values are simply the mean values of a large number of offspring of the same parents. So the transmission of value from parents to offspring is expressed by

$$\bar{P}_o = \bar{A}_o = \frac{1}{2}(A_s + A_d) \quad \dots [7.7]$$

where the subscripts o , s , and d refer to offspring, sire, and dam respectively.

Dominance deviation

We have separated off the breeding value as a component part of the genotypic value of an individual. Let us consider now what makes up the remainder. When a single locus only is under consideration, the difference between the genotypic value G and the breeding value A of a particular genotype is known as the *dominance deviation* D , so that

$$G = A + D \quad \dots [7.8]$$

The dominance deviation arises from the property of dominance among the alleles at a locus, since in the absence of dominance, breeding values and genotypic values coincide. From the statistical point of view the dominance deviations are interactions between alleles, or within-locus interactions. They represent the effect of putting genes together in pairs to make genotypes; the effect not accounted for by the effects of the two genes taken singly. Since the average effects of genes, and the breeding values of genotypes, depend on the gene frequency in the population, the dominance deviations are also dependent on gene frequency. They are therefore partly properties of the population and are not simply measures of the degree of dominance.

Example 7.6

Continuing the example of the pygmy gene, we may now list the genotypic values and the breeding values, and so obtain the dominance deviations of the three

Continued

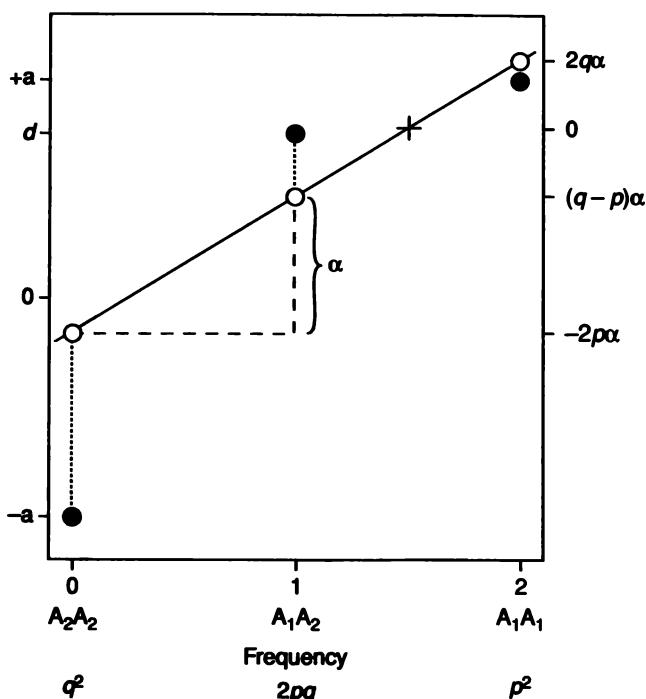


Fig. 7.2. Graphical representation of genotypic values (closed circles), and breeding values (open circles), of the genotypes for a locus with two alleles, A_1 and A_2 , at frequencies p and q , as explained in the text. Horizontal scale: number of A_1 genes in the genotype. Vertical scales of value: on left – arbitrary values assigned as in Fig. 7.1; on right – deviations from the population mean. The figure is drawn to scale for the values: $d = \frac{1}{2}a$, and $q = \frac{1}{4}$.

Example 7.6 continued

genotypes, by equation [7.8]. These values, all now expressed as deviations from the population mean M , are given in the table.

	$q = 0.1: M = 13.56$			$q = 0.4: M = 11.76$		
	$++$	$+pg$	$pg\ pg$	$++$	$+pg$	$pg\ pg$
Frequency	0.81	0.18	0.01	0.36	0.48	0.16
Genotypic value, G	+0.44	-1.56	-7.56	+2.24	+0.24	-5.76
Breeding value, A	+0.48	-1.92	-4.32	+2.88	-0.72	-4.32
Dominance dev., D	-0.04	+0.36	-3.24	-0.64	+0.96	-1.44

The relationship between genotypic values, breeding values and dominance deviations can be illustrated graphically, as in Fig. 7.2, and the meaning of the dominance deviation is perhaps more easily understood in this way. In the figure the genotypic values (closed circles) are plotted against the number of A_1 genes in the genotype. A straight regression line is fitted by least squares to these points, each point being weighted by the frequency of the genotype it represents. The position of this line gives the breeding values of each genotype, as shown by the open

circles. The differences between the breeding values and the genotypic values are the dominance deviations, indicated by vertical dotted lines. The cross marks the population mean. The average effect α of the gene substitution is given by the difference in breeding value between A_2A_2 and A_1A_2 , or between A_1A_2 and A_1A_1 , as indicated. The original definition of the average effect of a gene substitution was given by Fisher (1918, 1941) in terms of this linear regression of genotypic value on number of genes.

The dominance deviation can be expressed in terms of the arbitrarily assigned genotypic values a and d , by subtraction of the breeding value from the genotypic value, as shown in Table 7.3. The genotypic values must first be converted to deviations from the population mean, because the breeding values have been expressed in this way. The genotypic values, so converted, are given in two forms: in terms of a and in terms of α . Let us take the genotype A_1A_1 to show how these are obtained and how the dominance deviation is obtained by subtraction of the breeding value. The arbitrarily assigned genotypic value of A_1A_1 is $+a$, and the population mean is $a(p - q) + 2dpq$. Expressed as a deviation from the population mean, the genotypic value is therefore

$$a - [a(p - q) + 2dpq] = a(1 - p + q) - 2dpq = 2qa - 2dpq = 2q(a - dp)$$

This may be expressed in terms of the average effect α by substituting $a = \alpha - d(q - p)$ (from equation [7.5]), and the genotypic value then becomes $2q(\alpha - qd)$. Subtraction of the breeding value, $2q\alpha$, gives the dominance deviation as $-2q^2d$. By similar reasoning the dominance deviation of A_1A_2 is $2pqd$, and that of A_2A_2 is $-2p^2d$. Thus all the dominance deviations are functions of d . If there is no dominance, d is zero and the dominance deviations are also all zero. Therefore in the absence of dominance, breeding values and genotypic values are the same. Genes that show no dominance ($d = 0$) are sometimes called 'additive genes', or are said to 'act additively'.

Table 7.3 Values of genotypes in a two-allele system, measured as deviations from the population mean.

Population mean: $M = a(p - q) + 2dpq$

Average effect of gene substitution: $\alpha = a + d(q - p)$

<i>Genotypes</i>			
	A_1A_1	A_1A_2	A_2A_2
Frequencies	p^2	$2pq$	q^2
Assigned values	a	d	$-a$
Deviations from population mean:			
Genotypic value	$\left\{ \begin{array}{l} 2q(a - pd) \\ 2q(\alpha - qd) \end{array} \right.$		
Breeding value	$2q\alpha$	$(q - p)\alpha$	$-2p\alpha$
Dominance deviation	$-2q^2d$	$2pqd$	$-2p^2d$

Since the mean breeding value and the mean genotypic value are equal, it follows that the mean dominance deviation is zero. This can be verified by

multiplying the dominance deviation by the frequency of each genotype and summing. The mean dominance deviation is thus

$$-2p^2q^2d + 4p^2q^2d - 2p^2q^2d = 0$$

Interaction deviation

When only a single locus is under consideration, the genotypic value is made up of the breeding value and the dominance deviation only. But when the genotype refers to more than one locus, the genotypic value may contain an additional deviation due to non-additive combination. Let G_A be the genotypic value of an individual attributable to one locus, G_B that attributable to a second locus, and G the aggregate genotypic value attributable to both loci together. Then

$$G = G_A + G_B + I_{AB} \quad \dots [7.9]$$

where I_{AB} is the deviation from additive combination of these genotypic values. In dealing with the population mean, earlier in this chapter, we assumed that I was zero for all combinations of genotypes. If I is not zero for any combination of genes at different loci, those genes are said to 'interact' or to exhibit 'epistasis', the term epistasis being given a wider meaning in quantitative genetics than in Mendelian genetics. The deviation I is called the *interaction deviation* or *epistatic deviation*. If the interaction deviation is zero the genes concerned are said to 'act additively' between loci. Thus 'additive action' may mean two different things. Referred to genes at one locus it means the absence of dominance, and referred to genes at different loci it means the absence of epistasis.

Loci may interact in pairs or in threes or higher numbers, and the interactions may be of several different sorts, as the behaviour of major genes shows. The complex nature of the interactions, however, need not concern us, because in the aggregate genotypic value interactions of all sorts are treated together as a single interaction deviation. So for all loci together we can write

$$G = A + D + I \quad \dots [7.10]$$

where A is the sum of the breeding values attributable to the separate loci, and D is the sum of the dominance deviations.

The mean interaction deviation of all the genotypes in a population is zero when values are expressed as deviations from the population mean. That this must be so can be seen from equation [7.10], remembering that the mean G , A , and D are all zero. The interaction deviation is not just a property of the interacting genotypes, but depends also on the frequencies of the genotypes in the population, and so on the gene frequencies.

Example 7.7

As an example of non-additive combination of two loci we shall take the same two colour genes in mice that were used in Example 7.3 to illustrate additive combination;

Continued

but this time we refer to their effects on the size of the pigment granules, instead of their number (Russell, 1949). The mean size (diameter in μ) of the granules in each of the four genotypes was as shown in the table. This time the differences are not independent of the other genotype: the c^e gene, for example, has quite a large effect on the B– genotype, but none at all on the bb genotype. Thus the two loci show epistatic interaction and do not combine additively. The interaction deviations of the four genotypes in any particular population would depend on the gene frequencies at both loci.

	B–	bb	<i>Diff.</i>
C–	1.44	0.77	0.67
$c^e c^e$	0.94	0.77	0.17
<i>Diff.</i>	0.50	0.00	

Problems

- 7.1 Three allelic variants of the red cell acid phosphatase enzyme were present in a sample from the population in England. The table below gives the genotypes with their frequencies in the sample and the mean enzyme activity of each genotype. (CC individuals were not found.) What is the mean enzyme activity in this population?

Genotype	Frequency (%)	Enzyme activity
AA	9.6	122
AB	48.3	154
BB	34.3	188
AC	2.8	184
BC	5.0	212

Data from Spencer, N., *et al.* (1964) *Nature*, **201**, 299–300.

[Solution 6]

- 7.2 With the enzyme activities of the red cell acid phosphatase genotypes given in Problem 7.1 calculate the mean enzyme activities in populations with the C allele absent and the following gene frequencies of A: (1) 0.2, (2) 0.5, (3) 0.8. [Solution 16]

- 7.3 If there were a locus, overdominant with respect to a metric character, with the genotypic values given below, what gene frequency would give a random-mating population its maximum mean value, and what would the mean be?

$A_1 A_1$	$A_1 A_2$	$A_2 A_2$
110	150	90

[Solution 26]

- 7.4 Example 7.3 describes the effects of two colour genes on the number of pigment granules in the hairs of mice. The brown gene, b, when homozygous, reduced the number of granules from 95 to 90, and the extreme dilute gene, c^e , reduced the number from 95 to 38. The genes' effects in combination were additive. Assuming both genes to be completely recessive, find what would be the mean granule number in a population with the b gene at a frequency of 0.5 and the c^e gene at a frequency of 0.2. [Solution 36]

7.5 What are the average effects of the two alleles, and the average effect of the gene substitution, in the populations specified in Problem 7.2? [Solution 46]

7.6 What are the breeding values of the three genotypes in the three populations specified in Problem 7.2? [Solution 56]

7.7 Find the breeding values and dominance deviations of the three genotypes in the population specified in Problem 7.3 when the mean is at its maximal value. [Solution 66]

7.8 Calculate the breeding value and the dominance deviation of the genotype $bb\ c^e c^e$ in the population specified in Problem 7.4. Give the breeding value both as a deviation from the population mean and in absolute units of granule number. [Solution 76]

7.9 Problem 7.4 dealt with the effects of two colour genes on the number of pigment granules in mouse hairs. Example 7.7 describes the effects of the same two genes on the size of the pigment granules, and in this case the effects are not additive. Work out the interaction deviations of the genotypes in a population in which the bb homozygote has a frequency of 0.4 and the $c^e c^e$ homozygote a frequency of 0.2. Since both genes are assumed to be completely recessive the dominant homozygote and the heterozygote in each case have the same value and can be treated as one genotype, so that there are four genotypes whose interaction deviations are to be found. It will be useful for a later problem if the values of the four genotypes given in Example 7.7 are first converted to deviations from the population mean; this may also make the logic clearer. [Solution 86]

8 Variance

The genetics of a metric character centres round the study of its variation, for it is in terms of variation that the primary genetic questions are formulated. The basic idea in the study of variation is its partitioning into components attributable to different causes. The relative magnitude of these components determines the genetic properties of the population, in particular the degree of resemblance between relatives. In this chapter we shall consider the nature of these components and how the genetic components depend on the gene frequency. Then, in the next chapter, we shall show how the degree of resemblance between relatives is determined by the magnitudes of the components.

Components of variance

The amount of variation is measured and expressed as the variance: when values are expressed as deviations from the population mean the variance is simply the mean of the squared values. The components into which the variance is partitioned are the same as the components of value described in the last chapter; so that, for example, the genotypic variance is the variance of genotypic values, and the environmental variance is the variance of environmental deviations. The total variance is the phenotypic variance, or the variance of phenotypic values, and is the sum of the separate components. The components of variance and the values whose variance they measure are listed in Table 8.1.

The total variance is then, with certain qualifications, the sum of the components, thus:

$$V_P = V_G + V_E \quad \dots [8.1a]$$

$$= V_A + V_D + V_I + V_E \quad \dots [8.1b]$$

The qualifications are, first, that genotypic values and environmental deviations may be correlated, in which case V_P will be increased by twice the covariance of G with E ; and, second, there may be interaction between genotypes and environments, in which case there will be an additional component of variance attributable to the interaction. These two complications will be dealt with later in this chapter; meantime it will be assumed that they do not apply.

Components as proportions of the total

The partitioning of the variance into its components allows us to estimate the relative importance of the various determinants of the phenotype, in particular the role of heredity versus environment, or nature and nurture. The question of 'relative

Table 8.1 Components of variance.

Variance component	Symbol	Value whose variance is measured
Phenotypic	V_P	Phenotypic value
Genotypic	V_G	Genotypic value
Additive	V_A	Breeding value
Dominance	V_D	Dominance deviation
Interaction	V_I	Interaction deviation
Environmental	V_E	Environmental deviation

'importance' can be answered only if it is expressed in terms of the variance attributable to the different sources of variation. The relative importance of a source of variation is the variance due to that source, as a proportion of the total phenotypic variance. The relative importance of heredity in determining phenotypic values is called the *heritability* of the character. There are, however, two distinctly different meanings of 'heredity' and heritability, according to whether they refer to genotypic values or to breeding values. A character can be 'hereditary' in the sense of being determined by the genotype or in the sense of being transmitted from parents to offspring, and the extent to which it is hereditary in the two senses may not be the same. The ratio V_G/V_P expresses the extent to which individuals' phenotypes are determined by the genotypes. This is called the *heritability in the broad sense*, or the *degree of genetic determination*. The ratio V_A/V_P expresses the extent to which phenotypes are determined by the genes transmitted from the parents. This is called the *heritability in the narrow sense*, or simply the *heritability*. In all that follows, the term 'heritability' will be restricted to mean the narrow-sense heritability, V_A/V_P . The heritability V_A/V_P determines the degree of resemblance between relatives and is therefore of the greatest importance in breeding programmes. The degree of genetic determination V_G/V_P is of more theoretical interest than practical importance. It can be estimated in the following way.

Estimation of the degree of genetic determination, V_G/V_P

Estimation of the genotypic variance V_G is simple in theory though not so easy in practice. Neither the genotypic nor the environmental components of variance, V_G and V_E , can be estimated directly from observations on a single population, but in certain circumstances they can be estimated in experimental populations. If one or other component could be completely eliminated, the remaining phenotypic variance would provide an estimate of the remaining component. Environmental variance cannot be removed because it includes by definition all non-genetic variance, and much of this is beyond experimental control. Elimination of genotypic variance can, however, be achieved experimentally. Individuals with identical genotypes can be obtained from a highly inbred line or the F_1 of a cross between two such lines, or from a clone propagated from a single individual. (Identical twins in man and cattle also provide individuals of identical genotype, but their use in partitioning the variance is very limited for reasons to be discussed in Chapter 10.) If a group of such individuals is raised under the normal range of environmental circumstances, their phenotypic variance provides an estimate of the

environmental variance V_E . Subtraction of this from the phenotypic variance of a genetically mixed population then gives an estimate of the genotypic variance of this population. This estimation is illustrated in the following example.

Example 8.1

Partitioning of the phenotypic variance into its genotypic and environmental components has been done for several characters in *Drosophila melanogaster*. The results are given later, in Table 8.2, but here we may describe the results for one character in more detail in order to show how the partitioning is made. The character is the length of the thorax (in units of 1/100 mm), which may be regarded as a measure of body size. The phenotypic variance was measured in a genetically mixed, i.e., a random-bred population, and in a genetically uniform population, consisting of the F_1 generation of three crosses between highly inbred lines. The first estimates the genotypic and environmental variance together, and the second estimates the environmental variance alone, as shown in the table. So, by subtraction, an estimate of the genotypic variance is obtained. This shows that 49 per cent of the total variation of thorax length in the genetically mixed population is attributable to genetic differences between individuals and 51 per cent to non-genetic differences. (Data from F.W. Robertson, 1957b).

<i>Population</i>	<i>Components</i>	<i>Observed variance</i>
Mixed	$V_G + V_E$	0.366
Uniform	V_E	0.186
Difference	V_G	0.180
	$V_G/V_P =$	0.180/0.366 = 49%

The estimation of the genotypic variance in the manner described above is not quite as straightforward as it may seem. It rests on the assumption that the environmental variance is the same in all genotypes, and this is certainly not always true. The environmental variance measured in one inbred line or cross is that shown by this one particular genotype, and other genotypes may be more or less sensitive to environmental influences and may therefore show more or less environmental variance. The environmental variance of the mixed population may therefore not be the same as that measured in the genetically uniform group. Furthermore, some characters have been found to be more variable among inbred, homozygous, individuals than among crossbred, heterozygous, individuals, the homozygotes being more sensitive to environmental differences. Different sensitivities to the environment are an aspect of genotype-environment interaction which is discussed more fully later in this chapter. Because of possible differences of environmental sensitivity it is desirable to estimate the environmental variance from several different uniform groups, inbred lines and their crosses. For the ways of combining the separate estimates to get the most reliable mean estimate, see Wright (1968, p. 382).

The difficulties arising from the use of unrepresentative genotypes can be overcome with plants that can be propagated clonally. It is then possible to have a large number of genotypes each represented by many clonally produced individuals. If

the individuals are grown with genotypes randomized with respect to the environment, an analysis of variance provides an estimate of the component of variance between clones. The variance between clones is due mainly to differences of genotype, and can be regarded as an estimate of V_G . But there may be environmental effects included in it. That is to say, some part of the environmental differences between individuals may be transmitted to all their clonal descendants. For this reason the ratio V_G/V_P estimated in this way is liable to be an overestimate. Strictly speaking, it should be called the 'clonal repeatability'; the meaning of 'repeatability' is explained later in this chapter.

Genetic components of variance

The partition into genotypic and environmental variance does not take us far toward an understanding of the genetic properties of a population, and in particular it does not reveal the cause of resemblance between relatives. The genotypic variance must be further divided according to the division of genotypic value into breeding value, dominance deviation, and interaction deviation. Thus we have:

$$\begin{array}{lllllll} \text{Values} & G & = & A & + & D & + & I \\ \text{Variance components} & V_G & = & V_A & + & V_D & + & V_I \\ & (\text{genotypic}) & & (\text{additive}) & & (\text{dominance}) & & (\text{interaction}) \end{array} \dots [8.2]$$

The additive variance, which is the variance of breeding values, is the important component since, as already mentioned, it is the chief cause of resemblance between relatives and therefore the chief determinant of the observable genetic properties of the population and of the response of the population to selection. Moreover, it is the only component that can be readily estimated from observations made on the population. In practice, therefore, the important partition is into additive genetic variance versus all the rest, the rest being non-additive genetic and environmental variance. This partitioning yields the ratio V_A/V_P , which is the heritability of the character.

Estimation of the additive variance rests on observation of the degree of resemblance between relatives, and will be described later when we have discussed the causes of resemblance between relatives. Our immediate concern here is to show how the genetic components of variance are influenced by the gene frequency. To do this we have to express the variance in terms of the gene frequency and the assigned genotypic values a and d . We shall consider first a single locus with two alleles, thus excluding interaction variance for the moment.

Additive and dominance variance

The information needed to obtain expressions for the variance of breeding values and the variance of dominance deviations was given in the last chapter in Table 7.3. This table gives the breeding values and dominance deviations of the three genotypes, expressed as deviations from the population mean. It will be remembered that the means of both breeding values and dominance deviations are zero. Therefore no correction for an assumed mean is needed, and the variance is simply the mean of the squared values. The variances are thus obtained by squaring the values in the table, multiplying by the frequency of the genotype concerned, and

summing over the three genotypes. The additive variance, which is the variance of breeding values, is obtained as follows:

$$V_A = 4p^2q^2\alpha^2 + 2pq(q-p)^2\alpha^2 + 4p^2q^2\alpha^2 \\ = 2pq\alpha^2(2pq + q^2 - 2pq + p^2 + 2pq) \\ = 2pq\alpha^2(p^2 + 2pq + q^2)$$

$$= 2pq\alpha^2 \\ = 2pq[\alpha + d(q-p)]^2 \quad \dots [8.3a]$$

$$\dots [8.3b]$$

As in Table 7.3, q is here the frequency of the allele that reduces value.

Similarly, the variance of dominance deviations is

$$V_D = d^2(4q^4p^2 + 8p^3q^3 + 4p^4q^2) \\ = 4p^2q^2d^2(q^2 + 2pq + p^2) \\ = (2pqd)^2 \quad \dots [8.4]$$

If there is no dominance at the locus under consideration ($d = 0$), the expression for the additive variance simplifies to

$$V_A = 2pq\alpha^2 \quad \dots [8.5]$$

If there is complete dominance ($d = a$), the additive variance becomes

$$V_A = 8pq^3a^2 \quad \dots [8.6]$$

where q is the frequency of the recessive allele.

With any degree of dominance, the expressions for both the additive and the dominance variances become much simpler if the frequencies of all segregating genes are one-half ($p = q = 0.5$), as they are in populations derived from a cross of two highly inbred lines. Equations [8.3b] and [8.4] then reduce to

$$\left. \begin{aligned} V_A &= \frac{1}{2}a^2 \\ V_D &= \frac{1}{4}a^2 \end{aligned} \right\} \quad \dots [8.7]$$

For a full account of the analysis of such populations, see Mather and Jinks (1977, 1982).

Total genetic variance

The total genetic variance, V_G , arising from one locus can be calculated directly from Table 7.3 in the same way as was done above for V_A and V_D . But to do so requires a lengthy algebraic reduction, and it is simpler to get V_G from the values of V_A and V_D calculated above. Since $G = A + D$, the variance of G is given by $V_G = V_A + V_D + 2\text{cov}_{AD}$, where cov_{AD} is the covariance of breeding values with dominance deviations. This covariance can be shown to be zero as follows. The breeding values, dominance deviations, and frequencies of the three genotypes were given in Table 7.3. Multiplying breeding value by dominance deviation by frequency, and summing over the three genotypes, gives the covariance as

$$-4p^2q^3\alpha d + 4p^2q^2(q-p)\alpha d + 4p^3q^2\alpha d = 4p^2q^2\alpha d(-q + q - p + p) = 0$$

Thus

$$\begin{aligned} V_G &= V_A + V_D \\ &= 2pq[a + d(q - p)]^2 + [2pqd]^2 \end{aligned} \quad \dots [8.8]$$

Example 8.2

To illustrate the genetic components of variance arising from a single locus, let us return to the pygmy gene in mice, used for several examples in the last chapter. From the values tabulated in Example 7.6, we may compute the components of variance directly. Since the values are expressed as deviations from the population mean, the variance is obtained by multiplying the frequency of each genotype by the square of its value, and summing over the three genotypes. For example, the genotypic variance when $q = 0.1$ is $0.81(0.44)^2 + 0.18(-1.56)^2 + 0.01(-7.56)^2 = 1.1664$. The additive variance is obtained in the same way from the variance of breeding values, and the dominance variance from the variance of dominance deviations. The variances obtained are as follows:

	$q = 0.1$	$q = 0.4$
Genotypic, V_G	1.1664	7.1424
Additive, V_A	1.0368	6.2208
Dominance, V_D	0.1296	0.9216

The variances may be obtained also, and with less trouble, by use of the formulae given above in equations [8.3], [8.4], and [8.8]. The values to be substituted were given in Example 7.1; namely, $a = 4$ and $d = 2$. Notice that the dominance variance is quite small in comparison with the additive.

The ways in which the gene frequency and the degree of dominance influence the magnitude of the genetic components of variance can best be appreciated from graphical representations of the relationships derived above in equations [8.3], [8.4], and [8.8]. The graphs in Fig. 8.1 show the amounts of genotypic, additive, and dominance variance arising from a single locus with two alleles, plotted against the gene frequency. Three cases are shown to illustrate the effect of different degrees of dominance: in graph (a) there is no dominance ($d = 0$); in graph (b) there is complete dominance ($d = a$); and in graph (c) there is 'pure' overdominance ($a = 0$). In the first case the genotypic variance is all additive, and it is greatest when $p = q = 0.5$. In the second case the dominance variance is maximal when $p = q = 0.5$, the additive variance is maximal when the frequency of the recessive allele is $p = 0.75$, and the genotypic variance is maximal when $q^2 = 0.5$, i.e., $q = 0.71$. In the third case the dominance variance is the same as in the second and is maximal when $p = q = 0.5$. The additive variance, however, is zero when $p = q = 0.5$, and has two maxima, one at $q = 0.15$ and the other at $q = 0.85$. The genotypic variance, in this case, remains practically constant over a wide range of gene frequency, though its composition changes profoundly. The general conclusion to be drawn from these graphs is that genes contribute much more variance when at intermediate frequencies than when at high or low frequencies: recessives at low frequency, in particular, contribute very little variance.

The foregoing account of the genetic variance is mainly theoretical. In practice we are not concerned with gene frequencies or gene effects because these are not known

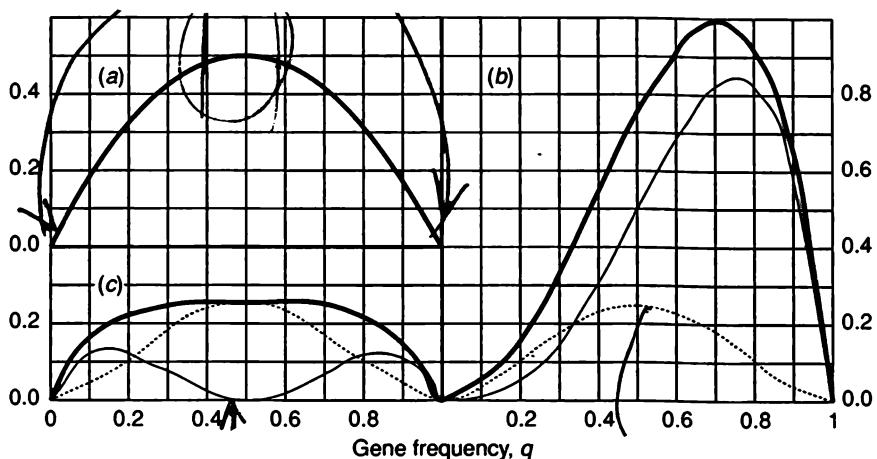


Fig. 8.1. Magnitude of the genetic components of variance arising from a single locus with two alleles, in relation to the gene frequency. Genotypic variance – thick lines; additive variance – thin lines; dominance variance – broken lines. The gene frequency, q , is that of the recessive allele. The degrees of dominance are: in (a) no dominance ($d = 0$); in (b) complete dominance ($d = a$); and in (c) 'pure' overdominance ($a = 0$). The figures on the vertical scale, showing the amount of variance, are to be multiplied by a^2 in graphs (a) and (b), and by d^2 in graph (c).

except in specially constructed populations. In practice, therefore, we are concerned only with the estimation of the components. It should be noted, however, that all the components of genetic variance are dependent on the gene frequencies, so any estimates of them are valid only for the population from which they are estimated. When observations on the resemblance between relatives are available, the additive genetic variance can be estimated. (The way in which this is done is the subject of the next two chapters.) The total phenotypic variance can then be partitioned into $V_A:(V_D + V_I + V_E)$, the non-additive genetic variance being included with the environmental variance. If inbred lines are available the environmental variance can be estimated and so the phenotypic variance can be partitioned into $V_G:V_E$.

If both these partitions are made, we can separate the additive genetic from the rest of the genetic variance, and so make the three-fold partition into additive genetic, non-additive genetic, and environmental variance, $V_A:(V_D + V_I):V_E$, the dominance and interaction components being lumped together as non-additive genetic variance. Examples of this partitioning are given in Table 8.2.

A possible misunderstanding about the concept of additive genetic variance, to which the terminology may give rise, should be mentioned here. The concept of additive variance does not carry with it the assumption of additive gene action; and the existence of additive variance is not an indication that any of the genes act additively (i.e., show neither dominance nor epistasis). No assumption is made about the mode of action of the genes concerned. Additive variance can arise from genes with any degree of dominance or epistasis, and only if we find that all the genotypic variance is additive can we conclude that the genes show neither dominance nor epistasis.

The existence of more than two alleles at a locus introduces no new principle, though it complicates the theoretical description of the effect of the locus.

Expressions for the additive and dominance variances are given by Kempthorne (1955a). The locus contributes additive variance arising from the average effects of its several alleles, and dominance variance arising from the several dominance deviations.

Table 8.2 Partitioning of the variance of four characters in *Drosophila melanogaster*. Components as percentages of the total phenotypic variance.

	<i>Character</i>			
	(1) <i>Bristles</i>	(2) <i>Thorax</i>	(3) <i>Ovary</i>	(4) <i>Eggs</i>
Phenotypic	V_P	100	100	100
Additive genetic	V_A	52	43	30
Non-additive genetic	$V_D + V_I$	9	6	35
Environmental	V_E	39	51	38

Characters and sources of data:

- (1) Number of bristles on 4th + 5th abdominal segments (Clayton, Morris, and Robertson, 1957; Reeve and Robertson, 1954).
- (2) Length of thorax (Robertson, 1957b).
- (3) Size of ovaries, i.e., number of ovarioles in both ovaries. (Robertson, 1957a).
- (4) Number of eggs laid in 4 days (4th to 8th after emergence) (Robertson, 1957b).

To arrive at the variance components expressed in the population, the separate effects of all loci that contribute variance have to be combined. When a random-mating population is in equilibrium, the additive variance arising from all loci together is the sum of the additive variances attributable to each locus separately; and the dominance variance is similarly the sum of the separate contributions. But when more than one locus is under consideration then the interaction deviations, if present, give rise to another component of variance, the interaction variance, which is the variance of the interaction deviations.

Interaction variance

If the genotypes at different loci show epistatic interaction, in the manner described in the previous chapter, then the interactions give rise to a component of variance V_I , which is the variance of the interaction deviations. Theoretical description of the properties of interaction variances rests on its further subdivision into components. It is first subdivided according to the number of loci involved: two-factor interaction arises from the interaction of two loci, three-factor from three loci, etc. Interactions involving larger numbers of loci contribute so little variance that they can be ignored, and we shall confine our attention to two-factor interactions since these suffice to illustrate the principles involved. The next subdivision of the interaction variance is according to whether the interaction involves breeding values or dominance deviations. There are thus three sorts of two-factor interactions. Interaction between the two breeding values gives rise to additive \times additive variance, V_{AA} ; interaction between the breeding value of one locus and the dominance deviation of the other gives rise to additive \times dominance variance, V_{AD} ; and interaction between the two dominance deviations gives rise to dominance \times dominance variance, V_{DD} . So the interaction variance is broken down into components thus:

$$V_I = V_{AA} + V_{AD} + V_{DD} + \text{etc.} \quad \dots [8.9]$$

the terms designated 'etc.' being similar components arising from interactions between more than two loci.

There is no doubt that interaction between loci controlling quantitative characters is a frequent occurrence: it has been demonstrated in many studies of *Drosophila*, for example (see Kearsey and Kojima, 1967). It is not easy, however, to estimate the amount of variance that it generates, and little is known about its relative importance as a source of variation. The experimental evidence is reviewed by Barker (1979). For further details of epistatic interaction, see Cockerham (1954, 1963), Kempthorne (1957), Crow and Kimura (1970).

In the partitioning of the variance by relatively simple experiments, such as are considered here, most of the interaction variance is included with the dominance component, which is then referred to as *non-additive genetic* variance. This is as far as we can go here in the description of the interaction variance, but we shall see in the next chapter how it contributes to the resemblance between relatives.

Variance due to disequilibrium

There is one additional source of genetic variance that must be mentioned at this point, although it will concern us only at a few places in later chapters. It arises when a population is not in equilibrium under random mating. Disequilibrium exists when the genotype frequencies at two or more loci considered jointly are not what would be expected from the gene frequencies. The disequilibrium introduces an additional source of genetic variance for the following reason. For simplicity, consider just two loci which do not interact in the manner described above. Let G' and G'' be genotypic values of individuals with respect to each locus separately, and let G be the genotypic value with respect to both jointly, i.e., $G = G' + G''$. The total genotypic variance caused by the two loci together is then

$$V_G = V_{G'} + V_{G''} + 2\text{cov}_{G'G''} \quad \dots [8.10]$$

The covariance term represents correlation between the genotypic values at the two loci in different individuals. The correlation can be positive or negative, so disequilibrium can either increase or decrease the variance. When more than two loci are to be considered, there will be a covariance term for each pair of loci. When there is no disequilibrium, all the covariance terms are zero and the variance is as described in the previous sections.

There are two forms of non-random mating that generate disequilibrium, and they differ in the way they produce the covariance in equation [8.10]. The first occurs when parents are not a random sample of the individuals in their generation. Selection of parents, which is the subject of later chapters, constitutes non-random mating of this sort. The second form of non-random mating is assortative mating, as described in Chapter 1. The two sorts of covariance produced represent different correlations of gene effects. First, there is a correlation between genes at different loci in the same gamete. This is gametic phase, or linkage, disequilibrium, which was explained in Chapter 1. The second sort of covariance represents correlation between the genes in uniting pairs of gametes, i.e., between the genes an individual receives from its two parents. The first form of non-random mating alone, i.e., selection of

parents, which are then random-mated, generates the first sort of covariance, that due to gametic phase disequilibrium. The second form of non-random mating, i.e., assortative mating, generates both sorts of covariance. If the source of the disequilibrium ceases to operate, the covariance that is not due to gametic phase disequilibrium disappears immediately. The gametic phase disequilibrium of unlinked loci is halved in each subsequent generation, but with linked loci it persists for longer.

Correlation and interaction between genotype and environment

Two complications arise in connection with the partitioning of the variance into genotypic and environmental components as expressed in equation [8.1]. These can both normally be neglected without seriously affecting the conclusions drawn from partitioning the variance, but it is important to know what the consequences of neglecting them are.

Correlation

In the foregoing account of the variance components it has been assumed that environmental deviations and genotypic values are independent of each other; in other words, that there is no correlation between genotypic value and environmental deviation, such as would arise if the better genotypes were given better environments. Correlation between genotype and environment is seldom an important complication, and can usually be neglected in experimental populations, where randomization of environment is one of the chief objects of experimental design. There are some situations, however, in which the correlation exists. Milk-yield in dairy cattle provides an example. The normal practice of dairy husbandry is to feed cows according to their yield, the better phenotypes being given more food. This introduces a correlation between phenotypic value and environmental deviation; and, since genotypic and phenotypic values are correlated, there is also a correlation between genotypic value and environmental deviation. Another example is human intelligence. The phenotypic values of the parents affect the environment in which the children grow up; so, to the extent that intelligence is inherited, this introduces a correlation between the genotype and the environment of the children. Equation [8.1a] is true only if environmental deviations and genotypic values are uncorrelated. When a correlation is present the phenotypic variance is increased by twice the covariance of genotypic values and environmental deviations, and equation [8.1a] becomes

$$V_P = V_G + V_E + 2\text{cov}_{GE} \quad \dots [8.11]$$

The only way by which cov_{GE} could be measured is if we estimated V_E directly as in Example 8.1, and also estimated V_G directly by the variance of varying genotypes in a constant environment. Then subtraction of the directly estimated V_G and V_E from V_P in equation [8.11] would yield an estimate of 2cov_{GE} . This, however, could only be done if inbred lines were available and if the non-random aspects of the environment, such as feeding levels, could be identified. The covariance, being in practice unknown, is best regarded as part of the genetic variance because the non-random aspects of the environment are a consequence of the genotypic value

and so an individual's environment can be thought of as part of its genotype. This is not unreasonable with cows' milk-yield. It is less satisfactory with human intelligence, because the environmental effects on the children are not a consequence of their own genotypes but of their parents' genotypes.

Interaction

Another assumption that has been made, which is not always justifiable, is that a specific difference of environment has the same effect on different genotypes; or, in other words, that we can associate a certain environmental deviation with a specific difference of environment, irrespective of the genotype on which it acts. When this is not so there is an interaction, in the statistical sense, between genotypes and environments. There are several forms which this interaction may take. For example, a specific difference of environment may have a greater effect on some genotypes than on others; or there may be a change in the order of merit of a series of genotypes when measured under different environments. That is to say, genotype A may be superior to genotype B in environment X, but inferior in environment Y.

When interaction between genotypes and environments is present, the phenotypic value of an individual is not simply $P = G + E$, as in equation [7.1], but includes also an interaction component: $P = G + E + I_{GE}$. The interaction component gives rise to an additional source of variation and equation [8.11] becomes $V_P = V_G + V_E + 2\text{cov}_{GE} + V_{GE}$.

In an experiment of the sort illustrated in Example 8.1 the genetically uniform group is a single genotype. Its variance is due entirely to environmental differences among individuals, and depends on the way in which the particular genotype responds to the environmental differences. Therefore the variance due to interaction is included with the environmental variance estimated from the phenotypic variance of that genotype. Some genotypes, as already noted, may be more sensitive than others to environmental differences. So, to some extent, the environmental variance is a property of the genotype. But the source of the variation is environmental and not genetic. It is therefore logical, as well as experimentally necessary, to regard any variance due to genotype-environment interaction as being part of the environmental variance included in any estimate of V_E .

Genotype-environment interaction becomes very important if individuals of a particular population are to be reared under different conditions. For example, a breed of livestock may be used by different farmers who treat it differently; and varieties of plants are grown in different seasons, at different places, and under different conditions. This situation is different in one respect from what we have been considering hitherto. The different farms, seasons, or locations are 'specific environments', shared by all the individuals in them, and are more in the nature of 'treatments'. In the situation considered hitherto, each individual has its own particular environment, and individuals cannot be grouped according to any particular aspect of their environments, such as nutrition, temperature, or crowding. When individuals are reared in specific environments the genotype-environment interaction can be studied in more detail. If genotypes can be replicated, and more than one individual of each of several genotypes is reared in different specific environments, then an analysis of variance in a two-way classification of genotypes \times

environments will yield estimates of the variance between genotypes, the variance between the specific environments, and the variance attributable to interaction of genotypes with environments. If there is no interaction, then the best genotype in one environment will be the best in all. But if there is much interaction then particular genotypes must be sought for particular environments. The specialization of breeds or varieties for specific environments will be taken up again later, in Chapter 19, because it can be discussed more usefully from a different viewpoint. We shall next consider the idea of environmental sensitivity and how it can be measured.

Environmental sensitivity Some of the genotype-environment interaction can be ascribed to differences of sensitivity of different genotypes. In other words, a given environmental difference has more effect on some genotypes than it has on others. (The environmental sensitivity of a genotype is also known as its 'reaction norm'.) To measure environmental sensitivities, and to see how much of the interaction variance is ascribable to differences of sensitivity, different genotypes are reared or grown in a range of specific environments. The specific environments have to be quantified as more or less favourable for expression of the character under study. The only way in which environments can be quantified is by the mean performance of all the genotypes. In other words, the measure of an environment is the mean of all genotypes in that environment. This will be called the *environmental value*. Each genotype has its own mean value in each of the specific environments. The genotype's environmental sensitivity is then the regression of its own value on the environmental value. The procedure will be made clearer by Example 8.3 below. The variance due to interaction of genotypes with the specific environments is estimated from an analysis of variance, and the amount attributable to differences of sensitivity is obtained from the heterogeneity of regression slopes. For details, see Perkins and Jinks (1968); and for another example, see Zuberi and Gale (1976).

Example 8.3

(*From data kindly supplied by Professor J.L. Jinks*) Ten inbred lines of the tobacco plant *Nicotiana rustica* were grown in each of eight specific environments created by different dates of sowing and different densities of planting. The final heights of 8 plants of each line in each environment were measured. An analysis of variance showed that the differences between the genotypes (lines) and between the environments were significant and that there was a significant genotype \times environment interaction. The environmental sensitivities of four of the genotypes are depicted in Fig. 8.2. To estimate the environmental sensitivity of a genotype, the general effect of each environment is first evaluated as the mean of all 10 genotypes in that environment. Then the value of each genotype is plotted against the environmental mean. The slope of the regression line measures the environmental sensitivity of the genotype. A regression coefficient of 1.0 represents the average sensitivity of all genotypes. The sensitivities of the four genotypes in the graphs are shown at the right-hand margin. Of particular interest are the two genotypes in the middle, which had the highest and lowest sensitivities of the 10 lines. They had nearly equal means over all environments, but in consequence of their different sensitivities one was taller in good environments and the other was taller in poor environments, a reversal of the order of merit. (For further details see Mather and Jinks, 1982, p. 118.)

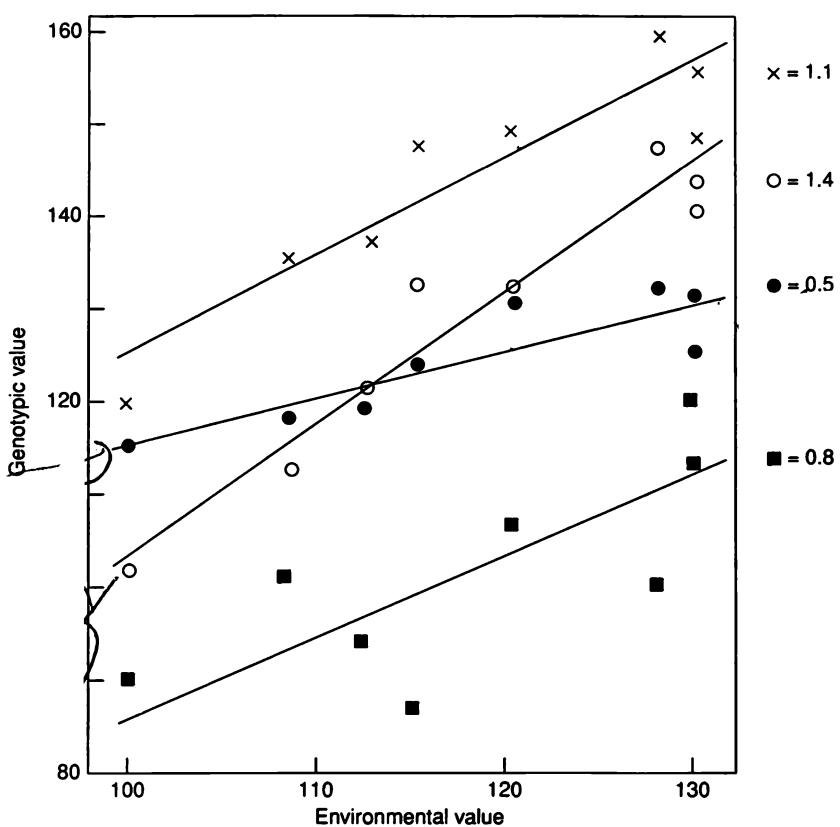


Fig. 8.2. Plant height (cm) of *Nicotiana rustica* genotypes grown in eight specific environments as explained in Example 8.3. (These are genotypes numbered 3, 6, 7, 10 in Tables 42 and 44 of Mather and Jinks, 1982.)

Environmental variance

Environmental variance, which by definition embraces all variation of non-genetic origin, can have a great variety of causes and its nature depends very much on the character and the organism studied. Generally speaking, environmental variance is a source of error that reduces precision in genetic studies and the aim of the experimenter or breeder is therefore to reduce it as much as possible by careful management or proper design of experiments. Nutritional and climatic factors are the commonest external causes of environmental variation, and they are at least partly under experimental control. Maternal effects form another source of environmental variation that is sometimes important, particularly in mammals, but is less susceptible to control. Maternal effects are prenatal and postnatal influences, mainly nutritional, of the mother on her young: we shall have more to say about them in the next chapter in connection with resemblance between relatives. Error of measurement is another source of variation, though it is usually quite trivial. When a character can be measured in units of length or weight it is usually measured so

accurately that the variance attributable to measurement is negligible in comparison with the rest of the variance. Some characters, however, cannot strictly speaking be measured, but have to be graded by judgement into classes. Carcass qualities of livestock are an example. With such characters the variance due to measurement may be considerable.

In addition to the variation arising from recognizable causes, such as those mentioned, there is usually also a substantial amount of non-genetic variation whose cause is unknown, and which therefore cannot be eliminated by experimental design. This is generally referred to as 'intangible' variation. Some of the intangible variation may be caused by 'environmental' circumstances, in the common meaning of the word – that is, by circumstances external to the individual – even though their nature is not known. Some, however, may arise from 'developmental' variation: variation, that is, which cannot be attributed to external circumstances, but is attributed, in ignorance of its exact nature, to 'accidents' or 'errors' of development as a general cause. Characters whose intangible variation is predominantly developmental are those connected with anatomical structure, which do not change after development is complete, such as skeletal form, pigmentation, or bristle number in *Drosophila*. Characters more susceptible to the influences of the external environment, in contrast, are those connected with metabolic processes, such as growth, fertility, and lactation.

Example 8.4

Human birth weight provides an example of a character subject to much environmental variation whose nature has been analysed in detail (Penrose, 1954; Robson, 1955). The partitioning of the phenotypic variance given in the table shows the relative importance of all the identified sources of variation, birth weight being regarded as a character of the child. All the environmental variation is 'maternal' in the sense that it is connected with the prenatal environment, but several distinct components of the maternal environment are distinguished. 'Maternal genotype', which accounts for 20 per cent of the total phenotypic variance, reflects genetic variation (chiefly additive) between mothers in the birth weight of their children; i.e., birth weight regarded as a character of the mother. 'Maternal environment, general', which accounts for another 18 per cent, reflects non-genetic variation between mothers in the same way. These two components, totalling 38 per cent, are maternal causes of variation in birth weight that affect all children of the same mother alike. 'Maternal environment, immediate' means causes attributable to the mother but differing in successive pregnancies. Two causes of the same nature – 'Age of mother' and 'Parity' (i.e., whether the child is the first, second, etc.) – are separately identifiable. Finally, the 'Intangible' variation is all the remainder, of which the causes cannot be identified. To explain how these various components were estimated would take too much space, and could not properly be done until the end of Chapter 10. It must suffice to say that the estimates all come from comparisons of the degree of resemblance between identical twins, fraternal twins, full sibs, children of sisters, and other sorts of cousins. It should be noted that the estimates are not very precise and must not be taken as definitive parameters of human populations. In another study (Morton, 1955) with different data, no effect of genetic factors in the foetus was found, all the variation of birth weight being environmental.

Continued

Example 8.4 *continued*

Partitioning of variance of human birth weight. Components as percentages of total phenotypic variance.

<i>Cause of variation</i>	<i>% of total</i>
<i>Genetic</i>	
Additive	15
Non-additive (approx)	1
Sex	2
Total genotypic	18
<i>Environmental</i>	
Maternal genotype	20
Maternal environment, general	18
Maternal environment, immediate	6
Age of mother	1
Parity	7
Intangible	30
Total environmental	82

Multiple measurements: repeatability

When more than one measurement of the character can be made on each individual, the phenotypic variance can be partitioned into variance within individuals and variance between individuals. This partitioning leads to a ratio of variance components called the repeatability, which has three main uses: to show how much is to be gained by the repetition of measurements, to set upper limits to the ratios V_G/V_P or V_A/V_P , and to predict future performance from past records. It may also throw light on the nature of the environmental variance. The partitioning of the variance corresponding to the repeatability is not a part of genetic theory, because it is the environmental, not the genetic, variance that is partitioned. It does, however, have some practical implications for genetical analysis and breeding programmes, as we shall see.

There are two ways by which the repetition of a character may provide multiple measurements: by temporal repetition and by spatial repetition. Milk-yield and litter size are examples of characters repeated in time. Milk-yield can be measured in successive lactations, and litter size in successive pregnancies. Several measurements of each individual can thus be obtained. The variance of yield per lactation, or of the number of young per litter, can then be analysed into a component within individuals, measuring the differences between the performance of the same individual, and a component between individuals, measuring the permanent differences between individuals. The within-individual component is entirely environmental in origin, caused by temporary differences of environment between successive performances. The between-individual component is partly environmental and partly genetic, the environmental part being caused by circumstances that affect the

individuals permanently. By this analysis, therefore, the variance due to temporary environmental circumstances is separated from the rest, and can be measured.

Characters repeated in space are chiefly structural or anatomical, and are found more often in plants than in animals. For example, plants that bear more than one fruit yield more than one measurement of any character of the fruit, such as its shape or seed content. Spatial repetition in animals is chiefly found in characters that can be measured on the two sides of the body or on serially repeated parts, such as the number of bristles on the abdominal segments of *Drosophila*. With spatially repeated characters the within-individual variance is again entirely environmental in origin but, unlike that of temporally repeated characters, it represents the 'developmental' variation arising from localized circumstances operating during development.

In order that we may discuss both temporal and spatial repetition together, we shall use the terms *special environmental variance*, V_{Es} , to refer to the within-individual variance arising from temporary or localized circumstances; and *general environmental variance*, V_{Eg} , to refer to the environmental variance contributing to the between-individual component and arising from permanent or non-localized circumstances. The ratio of the between-individual component to the total phenotypic variance is the intraclass correlation r . It is the correlation between repeated measurements of the same individual, and is known as the *repeatability* of the character. The partitioning of the phenotypic variance expressed by the repeatability is thus into two components, V_{Es} versus $(V_G + V_{Eg})$, so that the repeatability is

$$r = \frac{V_G + V_{Eg}}{V_P} \quad \dots [8.12]$$

The repeatability therefore expresses the proportion of the variance of single measurements that is due to permanent, or non-localized, differences between individuals, both genetic and environmental. It allows the separate estimation of the component V_{Es} due to the special environment which, as a proportion of the total, is given by

$$\frac{V_{Es}}{V_P} = 1 - r \quad \dots [8.13]$$

From equation [8.12] it can be seen that the repeatability sets an upper limit to the degree of genetic determination V_G/V_P , and to the heritability V_A/V_P . The repeatability is usually much easier to determine than either of these two ratios and it may often be known when they are not. The heritability, which is the ratio of practical importance, may of course be much less than the repeatability, but it cannot be greater, and this knowledge is better than no knowledge at all of the heritability. The repeatability differs very much according to the nature of the character, and also, of course, according to the genetic properties of the population and the environmental conditions under which the individuals are kept. The estimates in Table 8.3 give some idea of the sort of values that may be found with various characters, and two cases are described in more detail in Example 8.5.

Table 8.3 Some examples of repeatability.

	<i>Repeatability</i>
<i>Drosophila melanogaster</i> :	
Abdominal bristle number (see Example 8.5)	0.42
Ovary size (see Table 8.4)	0.54
<i>Mouse</i> : (original data)	
Weight at 6 weeks	0.96
Litter size in 1st and 2nd litters	0.45
<i>Sheep</i> : (Morley, 1951)	
Weight of fleece in different years	0.74
<i>Cattle</i> (British Friesians): (Barker and Robertson, 1966)	
Milk yield in 1st and 2nd lactations	0.40
Percent fat in 1st and 2nd lactations	0.67

There are two assumptions implicit in the idea of repeatability. The first is that the variances of the different measurements are equal, and have their components in the same proportions. The second is that the different measurements reflect what is genetically the same character – a point that will be explained in Chapter 19. If these assumptions are not valid, the repeatability becomes a somewhat vague concept, without precise meaning in relation to the components of variance. Some of the characters in Table 8.3 do not conform strictly with the assumptions.

Example 8.5

The number of bristles on the ventral surfaces of the abdominal segments is a character that has been much studied in *Drosophila melanogaster*, because it is technically convenient and its genetic properties are relatively simple. We have already mentioned it several times but have not yet used it as an example. There are about 20 bristles on each of 3 segments in males and each of 4 segments in females. The number of bristles per segment can therefore be treated as a spatially repeated character. The sources of variation in this character have been studied in detail by Reeve and Robertson (1954), and the components of variance found are given in the table.

		$\delta \delta$	$\varnothing \varnothing$
Total phenotypic	V_P	4.24	5.44
Between flies	$V_G + V_{Eg}$	1.82	2.19
Within flies	V_{Es}	2.42	3.25
Repeatability	.	0.429	0.403

Estimation of the repeatability of a character separates off the component of variance due to special environment, V_{Es} , but it leaves the other component of environmental variance – that due to general environment, V_{Eg} – confounded with the genotypic variance, as shown in the above example. To complete the partitioning we need to separate V_{Eg} from V_G . This can be done in two ways: either by estimating the genotypic variance V_G , in the manner of Example 8.1, or by calculating the repeatability in a genetically uniform group such as an inbred line or F_1 cross. Where there is no genetic variation, the between-individual component of variance consists

only of the general environment component V_{Eg} , and the repeatability measures the ratio $V_{Eg}/(V_{Eg} + V_{Es})$. The environmental variance has been partitioned in this way for two characters in *Drosophila* and the full partitioning that this leads to is shown in Table 8.4. The main point of interest is the very small amount of variation arising from the general environment. These characters are therefore very little influenced by the external environment; or perhaps it would be more accurate to say that the technique of rearing the flies has been very successful in eliminating unwanted sources of environmental variation. Under the conditions of the experiment, virtually all the non-genetic variation is due to strictly localized causes that influence the segments or the ovaries independently. Because the V_{Eg} component is so small, the repeatability gives a good estimate of the degree of genetic determination, V_G/V_P . Furthermore, the non-additive genetic variance of bristle number is small, so the repeatability is not very different from the heritability, V_A/V_P .

Table 8.4 Partitioning of the phenotypic variance of two characters in *Drosophila melanogaster*. Each component is given as a percentage of the total variance of single measurements.

Component		(1) Bristle number	(2) Ovary size
Additive genetic,	V_A	33	23
Non-additive genetic,	V_{NA}	6	27
General environment,	V_{Eg}	3	4
Special environment,	V_{Es}	58	46
Total, phenotypic,	V_P	100	100

Characters and sources of data:

- (1) Counts on one abdominal segment (Reeve and Robertson, 1954). The results for males and females were calculated separately and then averaged.
- (2) Number of ovarioles in one ovary (Robertson, 1957a).

The proportions of the genetic components here are lower than those in Table 8.2 because Table 8.2 refers to the variance of the sum of two measurements; see Example 8.6.

Gain from multiple measurements One way in which knowledge of the repeatability is useful is to indicate the gain in accuracy expected from multiple measurements. If the repeatability is high, little will be gained; if it is low, more will be gained. The question is: how is the gain in accuracy related to the repeatability? The only component of variance that is reduced by repeated measurements is that due to the special environment, V_{Es} , and the amount by which it is reduced depends on the number of measurements made. Suppose that each individual is measured n times, and that the mean of these n measurements is taken to be the phenotypic value of the individual, say $P_{(n)}$. Then the phenotypic variance is made up of the genotypic variance, the general environmental variance, and one n th of the special environmental variance:

$$V_{P(n)} = V_G + V_{Eg} + \frac{1}{n} V_{Es} \quad \dots [8.14]$$

Thus, increasing the number of measurements reduces the amount of variance due to special environment that appears in the phenotypic variance, and this reduction

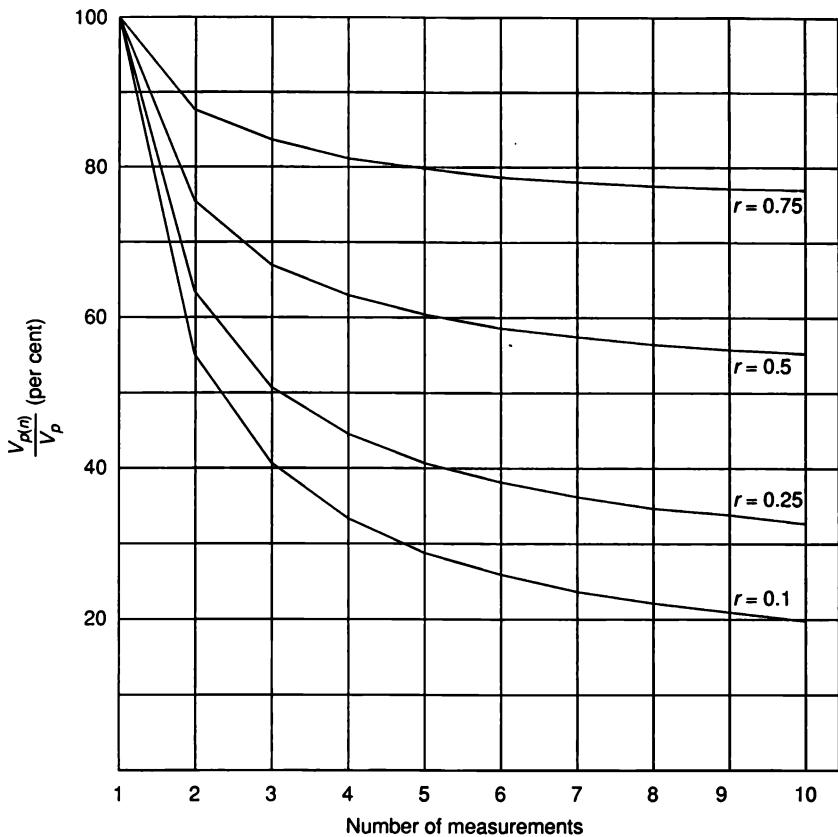


Fig. 8.3. Gain in accuracy from multiple measurements of each individual. The vertical scale gives the variance of the mean of n measurements as a percentage of the variance of one measurement. The horizontal scale gives the number of measurements, up to 10. The four graphs refer to characters of different repeatability as indicated.

of the phenotypic variance represents the gain in accuracy. The variance of the mean of n measurements as a proportion of the variance of one measurement can be expressed in terms of the repeatability, as follows. Writing the components in terms of r and $1 - r$, from equations [8.12] and [8.13], and substituting into equation [8.14], gives

$$V_{P(n)} = \left(r + \frac{1-r}{n} \right) V_P$$

and rearrangement leads to

$$\frac{V_{P(n)}}{V_P} = \frac{1 + r(n-1)}{n} \quad \dots [8.15]$$

This ratio is plotted in Fig. 8.3 to show how the phenotypic variance is reduced by multiple measurements, with characters of different repeatabilities. When the repeatability is high, and there is therefore little special environmental variance,

multiple measurements give little gain in accuracy. When the repeatability is low, multiple measurements may lead to a worthwhile gain in accuracy. The gain in accuracy, however, falls off rapidly as the number of measurements increases, and it is seldom worth while to make more than two or three measurements. In practice it does not make any difference whether one works with the mean or with the sum of the measurements: though the actual variance will be different, the relative magnitudes of the components are not affected.

Example 8.6

Most of the studies of abdominal bristle number in *Drosophila* have been based on counts of the bristles on two segments. The table shows how the percentage composition of the variance is affected by counting two segments instead of one. Column (1) gives the percentage composition of the phenotypic variance when only one segment is counted, as in Table 8.4. If two segments are counted and the mean of the two counts is taken as the phenotype of the individual, V_{Es} is halved but the other components are unaltered, giving the figures in column (2). The total variance V_p is now reduced to 71. Dividing each component by 71 and multiplying by 100 gives, in column (3), the percentage composition of the variance when phenotypic values are based on counts of two segments. The point of practical importance is that the additive genetic variance has been increased from 33 to 46 per cent. (The reason why V_A is 46 per cent and not 52 per cent as in Table 8.2 is that the two estimates are derived from different strains.)

	<i>One segment</i>	<i>Two segments</i>	
	(1)	(2)	(3)
V_A	33	33	46.4
V_{NA}	6	6	8.2
V_{Eg}	3	3	4.1
V_{Es}	58	29	41.3
V_p	100	71	100.0

The advantage for breeding programmes from the gain in accuracy is the increased proportion of additive genetic variance. That is to say, the mean of two or more measurements has a higher heritability than does a single measurement and is therefore a better guide to an individual's breeding value. This increase of heritability, however, cannot be relied on unless the two assumptions mentioned earlier are valid, namely that the different measurements have equal variances and represent the same character genetically. These conditions are met by the number of bristles on the abdominal segments of *Drosophila*, and the conclusions reached in Example 8.6 are valid. A character for which the assumptions do not hold is milk-yield of cows in successive lactations (Rendel *et al.*, 1957). In this case the proportion of additive genetic variance is actually less for the mean of several lactations than it is for first lactations only.

Prediction of future performance The prediction of future performance is a problem that occurs in many contexts. It has no general connotation but rests on the partitioning of the variance into components due to permanent and temporary effects, i.e., the partitioning made by the repeatability. Performances, both past and future, must be thought of in terms of deviations from the population means, past and future. A good past performance is partly due to the temporary environmental effects on the individual and these are not carried through to the subsequent performance, so the future performance tends to 'regress' toward the population mean. No prediction can be made without a knowledge of the characteristics of the population with respect to the two performances, for example milk-yield in first and second lactations. The repeatability, which is the correlation between the two performances, tells us how accurately we can predict the second from a knowledge of the first. The prediction itself is made from the regression coefficient of second on first performance. If x and y are first and second performances respectively, \bar{x} and \bar{y} are the population means, and b is the regression coefficient of y on x , then the prediction is given by $(y - \bar{y}) = b(x - \bar{x})$. The relationship between the regression and correlation coefficients is $b = r\sigma_y/\sigma_x$, where σ_x and σ_y are the standard deviations.

Example 8.7

The prediction of future performance can be illustrated from the data of Barker and Robertson (1966) on the milk-yield of British Friesian cows. The data refer to 3,764 cows with records of yields in first, second, and third lactations. The means and standard deviations are given in the table, yields being here converted to kilograms. Both mean and standard deviation increased in successive lactations. Let us predict the mean yield in second and third lactations of a heifer with a yield of 5,000 kg in her first lactation. The repeatabilities required are the correlations of second with first and of third with first; both were 0.40. The regression, for example of second on first, is then calculated as $b = r\sigma_2/\sigma_1$. The predicted yield in the second lactation is obtained from $y - \bar{y} = b(x - \bar{x})$ where y is the prediction, \bar{y} is the mean yield in second lactations, x is observed yield of 5,000 kg and \bar{x} is the mean yield in first lactations. The calculations for second and third lactations and the predicted mean are set out in the table.

	<i>Lactation</i>		
	1st	2nd	3rd
Mean, kg	4,096	4,232	4,731
Standard deviation (σ)	696	934	960
Correlation with 1st (r)	—	0.40	0.40
Regression on 1st (b)	—	0.536	0.552

Observed yield in 1st lactation = 5,000

Deviation from mean = +904

Predicted yield in 2nd = 4,232 + (0.536 × 904) = 4,716.5

Predicted yield in 3rd = 4,731 + (0.552 × 904) = 5,230.0

Predicted mean in 2nd and 3rd	4,973
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Summary of variance partitioning

This chapter has shown how the phenotypic variance of a genetically variable population can be partitioned into four components, two genetic and two environmental. The data needed to do this are of three different kinds, each making a partition into two parts, but in different ways. Table 8.5 summarizes the different partitions that can be made.

Table 8.5 Summary of variance partitioning.

<i>Data needed</i>	<i>Partition made</i>	<i>Ratio estimated</i>
Resemblance between relatives	$(V_A) \cdot (V_{NA} + V_{Eg} + V_{Es})$	heritability, V_A/V_P
Genetically uniform group	$(V_A + V_{NA}) \cdot (V_{Eg} + V_{Es})$ $= (V_G) \cdot (V_E)$	degree of genetic determination, V_G/V_P
Multiple measurements	$(V_G + V_{Eg}) \cdot V_{Es}$	repeatability $(V_G + V_{Eg})/V_P$
All three	$V_A \cdot V_{NA} \cdot V_{Eg} \cdot V_{Es}$	

Problems

8.1 The variances of leaf number in the F_1 and F_2 generations of a cross of tobacco varieties were calculated in Problem 6.1. The variances were 1.46 in the F_1 and 5.97 in the F_2 . Estimate the degree of genetic determination in the F_2 generation. What assumptions have to be made to do this? [Solution 7]

8.2 Calculate the amounts of additive genetic and dominance variance arising from the genes referred to in the population specified in (1) Problems 7.2 and 7.5 (all three populations), (2) Problems 7.3 and 7.7, (3) Problems 7.4 and 7.8. [Solution 17]

8.3 Work out the proportion of the total genetic variance that is due to dominance, i.e., V_D/V_G , when the variance is caused by a single locus with the following degrees of dominance. (1) $d = \frac{1}{2}a$, i.e., incomplete dominance, (2) $d = a$, i.e., complete dominance, and (3) $d = 2a$, i.e., overdominance. The ratio V_D/V_G depends on the gene frequency. Plot graphs to show this relationship in each case and find from the graphs the approximate maximum value of the ratio and the gene frequency at which this occurs. [Solution 27]

8.4 Refer to Problem 7.9 and its solution. Work out the three components of genetic variance, i.e., V_A , V_D and V_I , attributable to the two genes in the population specified. Express each component as a percentage of the total genetic variance, V_G . [Solution 37]

8.5 A sample of 10 female mice from a random-bred strain had the following numbers of live young born in their first and second litters.

<i>Mouse</i>	1	2	3	4	5	6	7	8	9	10
1st litter	11	9	13	10	9	8	10	11	10	13
2nd litter	10	12	12	10	8	6	12	9	12	12

- (1) From this sample calculate the repeatability of litter size.
- (2) What would you predict as being the expected size of the second litters of other mice from the same strain which had first litters of (a) 14 and (b) 5?

[Solution 47]

- 8.6** In a study of the fertility of pigs the litter sizes of 156 sows each of which had 10 litters were subjected to an analysis of variance with the following result. (The item 'Litter order' refers to differences between means of litters of the same order, first, second, third, etc.)

<i>Source</i>	<i>d.f.</i>	<i>Mean square</i>
Between sows	155	25.56
Litter order	9	93.95
Within sows	1.395	3.23

- (1) Calculate the repeatability of litter size.
- (2) Suppose that you are planning a breeding programme for which a high heritability (V_A/V_P) is desirable. The fertility of individual sows can be measured by one litter, or with greater precision by the mean of several litters. By how much would the heritability be increased if fertility were measured as the mean of the first 2 litters, the first 3, and the first 4 litters? Assume that the repeatability is the same as that estimated from 10 litters.

Data from Olbrycht, T.M. (1943) *J. Agric. Sci.*, **33**, 28–84.

[Solution 57]

9 Resemblance between Relatives

The resemblance between relatives is one of the basic genetic phenomena displayed by metric characters, and the degree of resemblance is a property of the character that can be determined by relatively simple measurements made on the population without special experimental techniques. The degree of resemblance provides the means of estimating the amount of additive genetic variance, and it is the proportionate amount of additive variance (i.e., the heritability) that chiefly determines the best breeding method to be used for improvement. An understanding of the causes of resemblance between relatives is therefore fundamental to the practical study of metric characters and to its application in animal and plant improvement. In this chapter, therefore, we shall examine the causes of resemblance between relatives, and show in principle how the amount of additive variance can be estimated from the observed degree of resemblance, leaving the more practical aspects of the estimation of the heritability for consideration in the next chapter.

In the last chapter we saw how the phenotypic variance can be partitioned into components attributable to different causes. These components we shall call *causal components* of variance, and denote them as before by the symbol V . The measurement of the degree of resemblance between relatives rests on the partitioning of the phenotypic variance in a different way, into components corresponding to the grouping of the individuals into families. These components can be estimated directly from the phenotypic values and for this reason we shall call them *observational components* of phenotypic variance, and denote them by the symbol σ^2 in order to keep the distinction clear. Consider, for example, the grouping of individuals into families of full sibs. By the analysis of variance we can partition the total observed variance into two components, between (or among) groups and within groups. The between-group component is the variance of the 'true' means of the groups about the population mean, and the within-group component is the variance of individuals about the true mean of their group. The true mean of a group is the mean that would be found if it were estimated without error from a very large number of individuals. An explanation of the estimation of these two components will be given, with examples, in the next chapter. Now, the resemblance between related individuals, i.e., between full sibs in the case under discussion, can be looked at either as similarity of individuals in the same group, or as difference between individuals in different groups. The greater the similarity within the groups, the greater will be the difference between the groups. The degree of resemblance can therefore be expressed as the between-group component as a proportion of the total variance. This is the intraclass correlation coefficient and is given by

$$t = \frac{\sigma_B^2}{\sigma_B^2 + \sigma_W^2}$$

where σ_B^2 is the between-group component and σ_W^2 the within-group component. (It is customary to use the symbol t for the intraclass correlation of phenotypic values in order to avoid confusion with other correlations, for which the symbol r is used.)

The between-group component expresses the amount of variation that is common to members of the same group and it can equally well be referred to as the covariance of members of the groups. In the case of the resemblance between offspring and parents, the grouping of the observations is into pairs rather than groups; one parent, or the mean of two parents, paired with one offspring or the mean of several offspring. The between-pair component of variance is then meaningful only if the parental values and the offspring values have the same variance, which they often do not. The covariance of offspring with parents is therefore calculated from the sum of cross-products, and the degree of resemblance is expressed as the regression of offspring on parents. The reason why the correlation is often inappropriate will become apparent later. The regression is given by

$$b_{OP} = \frac{\text{cov}_{OP}}{\sigma_P^2}$$

where cov_{OP} is the covariance of offspring and parents, and σ_P^2 is the variance of parents.

Thus, the covariance of related individuals is the new property of the population that we have to deduce in seeking the cause of resemblance between relatives, whether sibs or offspring with parents. The covariance, being simply a portion of the total phenotypic variance, is composed of the causal components described in the last chapter, but in amounts and proportions differing according to the sort of relationship. By finding out how the causal components contribute to the covariance, we shall see how an observed covariance can be used to estimate the causal components of which it is composed.

The commonest and most useful relationships are offspring with parents, half sibs, full sibs, and (in human studies) twins. The covariances in these relationships will be explained fully, and those of other relationships summarized afterwards. Twins have their special problems which will be dealt with in the next chapter.

Both genetic and environmental sources of variance contribute to the covariance of relatives, the covariance of phenotypic values being the sum of the genetic and environmental covariances. The genetic covariances will be described first, with the regressions or correlations that they give rise to, and the environmental causes of resemblance will be commented on later.

Genetic covariance

Our object now is to deduce from theoretical considerations the covariance of relatives arising from genetic causes, neglecting for the time being any non-genetic causes of resemblance that there may be. This means that we have to deduce the covariance of the genotypic values of the related individuals. The population will

be assumed to be in Hardy-Weinberg equilibrium, all parents mating at random with respect to the character under consideration. The effects of assortative mating will be considered in the next chapter. Any variance arising from epistatic interaction between loci will at first be neglected, its effects being described briefly later. For each relationship, two ways of deducing the covariance will be described, the first being more concise and the second more explicit.

Offspring and one parent

The covariance to be deduced is that of the genotypic values of individuals with the mean genotypic values of their offspring produced by mating at random in the population. If values are expressed as deviations from the population mean, then the mean value of the offspring is by definition half the breeding value of the parent, as explained in Chapter 7. Therefore the covariance to be computed is that of an individual's genotypic value with half its breeding value, i.e., the covariance of G with $\frac{1}{2}A$. Since $G = A + D$ (D being the dominance deviation), the covariance is that of $(A + D)$ with $\frac{1}{2}A$. Multiplying these terms together and summing over all parents gives

$$\begin{aligned}\text{Sum of cross-products} &= \sum \frac{1}{2}A(A + D) \\ &= \frac{1}{2}\sum A^2 + \frac{1}{2}\sum AD\end{aligned}$$

Dividing both sides by the number of parents gives the covariance as $\frac{1}{2}V_A + \frac{1}{2}\text{cov}_{AD}$. It was shown in the previous chapter that cov_{AD} is zero, so

$$\text{cov}_{OP} = \frac{1}{2}V_A \quad \dots [9.1]$$

The genetic covariance of offspring and one parent is therefore half the additive genetic variance of the parents.

The second, more explicit, way of deriving the covariance is by consideration of the effects of single loci. This will be done by reference to a locus with two alleles but the conclusions are equally valid for loci with any number of alleles. Table 9.1 gives the genotypes of the parents, their frequencies in the population, and their genotypic values expressed as deviations from the population mean (from Table 7.3). The right-hand column gives the mean genotypic values of the offspring, which are half the breeding values of the parents as given in Table 7.3. The covariance of offspring and parent is then the mean cross-product, and is obtained by multiplying together the three columns – frequency \times genotypic value of parent \times genotypic value of offspring – and summing over the three genotypes of the parents. After collecting together the terms in α^2 and the terms in αd we obtain

Table 9.1

Parents		Offspring	
Genotype	Frequency	Genotypic value	Mean genotypic value
A_1A_1	p^2	$2q(\alpha - qd)$	$q\alpha$
A_1A_2	$2pq$	$(q - p)\alpha + 2pqd$	$\frac{1}{2}(q - p)\alpha$
A_2A_2	q^2	$-2p(\alpha + pd)$	$-p\alpha$

$$\begin{aligned}\text{cov}_{OP} &= pq\alpha^2(p^2 + 2pq + q^2) + 2p^2q^2\alpha d(-q + q - p + p) \\ &= pq\alpha^2 \\ &= \frac{1}{2} V_A\end{aligned}$$

since, from equation [8.3a], $V_A = 2pq\alpha^2$. Summing over all loci we again reach the conclusion that the covariance of offspring and one parent is equal to half the additive variance.

The regression of offspring on one parent is got by dividing the covariance by the variance of the parents, which is the phenotypic variance of the population. Thus the regression is

$$b_{OP} = \frac{1}{2} \frac{V_A}{V_P} \quad \dots [9.2]$$

The covariance was deduced above by considering the mean value of the offspring of each parent, without specifying the number of offspring on which the mean is based. In fact, the covariance is the same whatever the number of offspring, even if only one is used, for the following reasons. The mean of n offspring is $(1/n)\Sigma O$, where ΣO is the sum of the values of the offspring. The covariance of one parent with the mean of n offspring is $\text{cov}(P, (1/n)\Sigma O) = (1/n)\Sigma \text{cov}(P, O) = \text{cov}(P, O)$, which is the covariance of parents with any one offspring. This conclusion is applicable to relatives of any kind. In general, therefore, the covariance of any individual with the mean value of a number of relatives is equal to its covariance with any one of those relatives. The regression of offspring on parents is also unaffected by the number of offspring used, because the variance of offspring does not enter into the calculation of the regression.

Offspring and mid-parent

The covariance of the mean of the offspring and the mean of both parents (commonly called the 'mid-parent') may be deduced in the following way. Let O be the mean of the offspring, and P and P' be the values of the two parents. The mid-parent value is $\bar{P} = \frac{1}{2}(P + P')$. The sum of cross-products is $\Sigma OP = \frac{1}{2}(\Sigma OP + \Sigma O'P)$, and the covariance is $\text{cov}_{OP} = \frac{1}{2}(\text{cov}_{OP} + \text{cov}_{O'P})$. If P and P' have the same variance, then $\text{cov}_{OP} = \text{cov}_{O'P}$ and consequently

$$\text{cov}_{OP} = \text{cov}_{O'P} = \frac{1}{2} V_A \quad \dots [9.3]$$

Thus, provided the two sexes have equal variances, the covariance of offspring and mid-parent is the same as that of offspring with one parent, which we have seen is equal to half the additive variance.

The longer method of demonstrating the covariance of offspring with mid-parent is rather laborious, but it must be given since it will be needed for arriving at the covariance of full sibs. We shall, however, omit some of the steps of algebraic reduction. A table (Table 9.2) is made in the same manner as for offspring and one parent, but now we have to tabulate types of mating and their frequencies, instead of single parents. Against each type of mating we put the mean genotypic value of the two parents, i.e., the mid-parent value; then the proportions of the three genotypes among the progeny, and the mean genotypic value of the progeny. The working is

Table 9.2

Genotype of parents		Frequencies of matings	Mid-parent value	Progeny			Mean value of progeny	Progeny mean \times mid-parent	Square of progeny mean
				A ₁ A ₁ a	A ₁ A ₂ d	A ₂ A ₂ -a			
A ₁ A ₁	A ₁ A ₁	p^4	a	1	—	—	a	a^2	a^2
A ₁ A ₁	A ₁ A ₂	$4p^3q$	$\frac{1}{2}(a+d)$	$\frac{1}{2}$	$\frac{1}{2}$	—	$\frac{1}{2}(a+d)$	$\frac{1}{2}(a^2 + 2ad + d^2)$	$\frac{1}{4}(a^2 + 2ad + d^2)$
A ₁ A ₁	A ₂ A ₂	$2p^2q^2$	0	—	1	—	d	0	d^2
A ₁ A ₂	A ₁ A ₂	$4p^2q^2$	d	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}d$	$\frac{1}{4}d^2$	$\frac{1}{4}d^2$
A ₁ A ₂	A ₂ A ₂	$4pq^3$	$\frac{1}{2}(-a+d)$	—	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}(-a+d)$	$\frac{1}{2}(a^2 - 2ad + d^2)$	$\frac{1}{4}(a^2 - 2ad + d^2)$
A ₂ A ₂	A ₂ A ₂	q^4	-a	—	—	1	-a	a^2	a^2

made easier by writing the genotypic values in terms of a and d instead of as deviations from the population mean. The last two columns of the table give the product of progeny mean \times mid-parent, and the square of the progeny for later use. To get the covariance of progeny mean and mid-parent value, we take the product of progeny mean \times mid-parent and multiply it by the frequency of the mating type, and then sum over mating types. This gives the mean product (MP), from which we have to deduct a correction for the population mean, since values are not here expressed as deviations from the mean. The correction is simply the square of the population mean (M^2) since the means of parents and of progeny are equal. Both MP and M^2 contain terms in a^2 , in ad , and in d^2 . By collecting together these terms and simplifying a little we obtain

$$\begin{aligned} MP &= a^2[p^3(p+q) + q^3(p+q)] + 2adpq(p^2 - q^2) + d^2pq(p^2 + 2pq + q^2) \\ M^2 &= a^2(p^2 - 2pq + q^2) \quad + 4adpq(p-q) \quad + 4d^2p^2q^2 \end{aligned}$$

Then,

$$\begin{aligned} \text{cov}_{OP} &= MP - M^2 \\ &= a^2pq - 2adpq(p-q) + d^2pq(p-q)^2 \\ &= pq[a + d(q-p)]^2 \\ &= pq\alpha^2 \\ &= \frac{1}{2}V_A \end{aligned}$$

when summed over all loci.

Though the covariance of offspring with the mean of both parents is the same as the covariance with a single parent, the degree of resemblance is not the same. The regression of offspring on mid-parent values is $b = \text{cov}_{OP}/\sigma_{\bar{P}}^2$, where $\sigma_{\bar{P}}^2$ is the variance of mid-parent values. If the variances of the two sexes are equal, then $\sigma_{\bar{P}}^2 = \frac{1}{2}V_P$ because, in general, the variance of the mean of n individuals is one n th of the variance of single individuals. The regression of offspring on mid-parent values is therefore

$$b_{OP} = \frac{\frac{1}{2}V_A}{\frac{1}{2}V_P} = \frac{V_A}{V_P} \quad \dots [9.4]$$

which is twice the regression on single parents. As with single parents, the number of offspring used does not affect the covariance or the regression.

The regression of offspring on parents is a useful measure of the degree of resemblance because it is simply related to the causal components of variance. The correlation between offspring and parents, however, does not have this useful feature. The correlation is calculated as $\text{cov}_{OP}/\sigma_O\sigma_P$, where σ_O and σ_P are the square roots of the variances of offspring and parents respectively, whether single or the mean of more than one. So the correlation is affected by the number of offspring as well as by the number of parents. If there is only one offspring, the correlation with a single parent is the same as the regression, but under all other circumstances it is different. The correlation of one offspring with mid-parent values is $(\frac{1}{2})V_A/V_P$. When there is more than one offspring, the correlation depends on the variance of the observed means of the offspring and has no simple relationship with the causal components of variance.

Half sibs

Half sibs are individuals that have one parent in common and the other parent different. A group of half sibs is therefore the progeny of one individual mated to a random group of the other sex and having one offspring by each mate. Thus the mean genotypic value of the group of half sibs is by definition half the breeding value of the common parent. The covariance is the variance of the true means of the half-sib groups, and is therefore the variance of half the breeding values of the common parents, which is a quarter of the additive variance:

$$\text{cov}_{(\text{HS})} = V_{\frac{1}{2}A} = \frac{1}{4}V_A \quad \dots [9.5]$$

This covariance also can be demonstrated by the longer method, from the values already given in Table 9.1. The covariance is the variance of the means of the groups of offspring listed in the right-hand column. Squaring the offspring values and multiplying by their frequencies gives:

Variance of means of half-sib families

$$\begin{aligned} &= p^2q^2\alpha^2 + 2pq\cdot\frac{1}{4}(q-p)^2\alpha^2 + q^2p^2\alpha^2 \\ &= pq\alpha^2[pq + \frac{1}{2}(q-p)^2 + pq] \\ &= pq\alpha^2[\frac{1}{2}(p+q)^2] \\ &= \frac{1}{2}pq\alpha^2 \end{aligned}$$

Therefore, since $2pq\alpha^2 = V_A$ (from equation [8.3a]),

$$\text{cov}_{(\text{HS})} = \frac{1}{4}V_A$$

summation being made over all loci.

The degree of resemblance between sibs is expressed as the intraclass correlation, which is the between-group variance, i.e., the covariance as a proportion of the total variance. So the correlation of half sibs is

$$r = \frac{1}{4} \frac{V_A}{V_P} \quad \dots [9.6]$$

Full sibs

The covariance of full sibs is less simple than those of the relationships so far considered, because the dominance variance contributes to it. Consider first the covariance due to the additive variance alone. Full sibs have both parents in common and the mean genotypic value of a group of full sibs is then equal to the mean breeding value of the two parents. Let A and A' be the breeding values of the two parents. Then the covariance is the variance of $\frac{1}{2}(A + A')$ which is $\frac{1}{4}(V_A + V_{A'}) = \frac{1}{2}V_A$ if the additive variance is the same in the two sexes. Now consider the contribution of dominance. It is easier to think of the covariance being calculated from the sum of cross-products in pairs of sibs taken at random. Let the parents have genotypes A_1A_2 and A_3A_4 . There are then four genotypes among the progeny, A_1A_3 , A_1A_4 , A_2A_3 , and A_2A_4 , each with a frequency of $\frac{1}{4}$. Let the first sib chosen have any one of these genotypes. Then the probability that the second sib has the same genotype is $\frac{1}{4}$. Thus, one-quarter of all sib-pairs have the same genotype and consequently the same dominance deviation, D . For these pairs having the same dominance deviation, the cross-product of the dominance deviations is D^2 ; other

pairs, with different dominance deviations, have a mean cross-product of zero. Over all pairs, therefore, the sum of the cross-product is $\frac{1}{4} \Sigma D^2$, and so the mean cross-product is $\frac{1}{4} V_D$. This is the covariance due to dominance deviations, and it adds to the covariance due to breeding values. The genetic covariance of full sibs is therefore

$$\text{cov}_{(\text{FS})} = \frac{1}{2} V_A + \frac{1}{4} V_D \quad \dots [9.7]$$

The second way of deriving the covariance of full sibs comes from Table 9.2 with little additional work. The covariance is the variance of the means of families. The right-hand column shows the squares of the progeny means, and it will be seen that these are all exactly the same as the products of progeny mean \times mid-parent, except for the two entries in the middle involving terms in d^2 . The mean square (MS) can therefore be got from the mean product (MP) already calculated; thus

$$\begin{aligned} MS &= MP + d^2 2p^2q^2 - \frac{1}{4} d^2 4p^2q^2 \\ &= MP + d^2 p^2 q^2 \end{aligned}$$

The correction for the mean is the same as before, so we have

$$\begin{aligned} \text{cov}_{(\text{FS})} &= \text{cov}_{\text{QP}} + d^2 p^2 q^2 \\ &= pq\alpha^2 + d^2 p^2 q^2 \end{aligned}$$

Since $2pq\alpha^2 = V_A$ (from equation [8.3a]) and $4d^2 p^2 q^2 = V_D$ (from equation [8.4]) the covariance of full sibs is

$$\text{cov}_{(\text{FS})} = \frac{1}{2} V_A + \frac{1}{4} V_D$$

summing over all loci.

The correlation of full sibs is

$$t = \frac{\frac{1}{2} V_A + \frac{1}{4} V_D}{V_P} \quad \dots [9.8]$$

In principle the difference between the covariances of full sibs and of half sibs provides a way of estimating the dominance variance, since $\text{cov}_{(\text{FS})} - 2\text{cov}_{(\text{HS})} = \frac{1}{4} V_D$. In practice, however, this can be done only if there are no environmental contributions to the phenotypic covariances.

Twins

The genetic covariances of twins are very simple. Dizygotic (fraternal) twins are related as full sibs and their genetic covariance is that of full sibs. Monozygotic (identical) twins have identical genotypes, so there is no genetic variance within pairs and the whole of the genetic variance appears in the between-pair component. The genetic covariance is therefore

$$\text{cov}_{(\text{MZ})} = V_G \quad \dots [9.9]$$

General

From the relationships explained above, it will have been seen that the covariance is made up of simple fractions of the causal components of variance, V_A and V_D , the fractions in the cases dealt with being $\frac{1}{2}$ or $\frac{1}{4}$. These fractions, or coefficients, are

related in a simple manner to the coancestries of the relatives and their parents, so that the covariance of any sort of relatives can be easily deduced from a consideration of the appropriate pedigree. Let r be the fraction of the additive genetic variance, and u that of the dominance variance, appearing in the covariance. Then the generalized covariance for any sort of relationship is

$$\text{cov} = rV_A + uV_D \quad \dots [9.10]$$

Let P and Q be two individuals representing the relationship whose covariance is required, and let A, B and C, D be their parents respectively, as shown in Fig. 5.4. Then, letting f stand for the coancestry as explained in Chapter 5, the values of r and u are obtained as

$$r = 2f_{PQ} \quad \dots [9.11]$$

$$u = f_{AC}f_{BD} + f_{AD}f_{BC} \quad \dots [9.12]$$

(see Crow and Kimura, 1970, p. 134). Table 9.3 gives the values of r and u , summarizing the relationships already described and adding some other, more distant, relationships. Equations [9.11] and [9.12] apply to a random-breeding population. Inbreeding of the parents, however, does not affect them, but if the relatives themselves are inbred then

$$r = 2f_{PQ}/\sqrt{(1 + F_P)(1 + F_Q)}$$

(Crow and Kimura, 1970, p. 138).

The coefficient r of the additive variance is sometimes called the *coefficient of relationship*, or the *theoretical correlation*, between the relatives in question. It is the correlation between their breeding values, and it represents the correlation that would be found if all the phenotypic variance were additive genetic. We shall return to this point when considering the estimation of the heritability in the next chapter. The coefficient u of the dominance variance represents the probability of the relatives having the same genotype through identity by descent. It is zero unless the related individuals have paths of coancestry through both of their respective parents, as have full sibs and double first cousins.

Table 9.3 Coefficients of the variance components in the covariances of relatives.

<i>Relationship</i>	<i>Coefficient</i>	
	r (of V_A)	u (of V_D)
<i>MZ twins</i>	1	1
<i>First-degree</i>	Offspring: parent	$\frac{1}{2}$
	Full sib	$\frac{1}{2}$
<i>Second-degree</i>	Half sib	$\frac{1}{4}$
	Offspring: grandparent	$\frac{1}{4}$
	Uncle (aunt): nephew (niece)	0
<i>Third-degree</i>	Double first cousin	$\frac{1}{8}$
	Offspring: great-grandparent	$\frac{1}{8}$
	Single first cousin	0

Epistatic interaction

The variance arising from epistatic interaction between loci contributes small fractions to the covariances of relatives. In Chapter 8 it was noted that the interaction variance V_I is subdivided into components according to the number of interacting loci, and according to whether the interaction is between breeding values or dominance deviations. The generalized covariance of any sort of relatives is as follows when the interaction components are included (for details, see Kempthorne, 1955*a*, *b*):

$$\text{cov} = rV_A + uV_D + r^2V_{AA} + ruV_{AD} + u^2V_{DD} + \dots [9.13]$$

etc.

Table 9.4 gives the coefficients of the variance components in the covariances with two-factor interactions included. The offspring-parent covariance refers equally to one parent and to mid-parent values. The conclusions that come from consideration of the interaction components are the following. First, only small fractions of the interaction components contribute to any covariance, the most being $\frac{1}{4}$, the contributions of interactions between more than two loci are even smaller. Second, interaction components involving dominance variance do not contribute unless the dominance variance itself contributes. Third, the interactions of breeding values, V_{AA} , V_{AAA} , etc., contribute to all covariances of relatives. It was noted in Chapter 7 that the two definitions of breeding value given there are not equivalent if there is interaction between loci. We can now see how this comes about. One definition, the theoretical, is in terms of the average effects of the genes at each locus separately, and it excludes interaction deviations. The other, the practical definition, is in terms of the measured values of progeny, and it includes fractions of the interaction deviations of breeding values. There are similarly two definitions of additive variance, which is the variance of breeding values. The theoretical one, described in the previous chapter, is derived by summation over loci considered separately, and it excludes interaction variance. The practical one is that which determines, and is estimated from, covariances of relatives, and it contains fractions of the additive \times additive interaction variances; for example, twice the offspring-parent covariance estimates $V_A + \frac{1}{2}V_{AA}$ + smaller fractions of the higher order interactions, where V_A is the theoretically defined additive variance. The only way of estimating the additive variance is from covariances of relatives, and it is this that is needed for predictions, such as responses to selection. So when we speak of 'additive variance' and write ' V_A ' it is best to regard these as referring to the practical definition with its included fractions of interaction variances. In reality, however, the difference between the two definitions is probably seldom more than trivial compared with the errors of estimation.

From the coefficients in Table 9.4 one can see how in principle the interaction components can be estimated. For example, $\text{cov}_{OP} - 2\text{cov}_{(HS)} = \frac{1}{8}V_{AA}$. To estimate the interaction components, however, requires complex experiments of great precision, providing comparisons of the covariances of many different sorts of relatives free of environmental covariance. This is hardly practicable with animals but it can be done with plants: see, for example, Pooni *et al.* (1978), and Chi *et al.* (1969), who found negligible interaction variances in seven characters of maize.

Table 9.4 Covariances of relatives including the contributions of two-factor interactions.

<i>Relatives</i>	<i>Variance components and the coefficients of their contributions</i>				
	V_A	V_D	V_{AA}	V_{AD}	V_{DD}
Offspring-parent:	$\text{cov}_{OP} = \frac{1}{2}$	—	$\frac{1}{4}$	—	—
Half sibs:	$\text{cov}_{(HS)} = \frac{1}{4}$	—	$\frac{1}{16}$	—	—
Full sibs:	$\text{cov}_{(FS)} = \frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{8}$	$\frac{1}{16}$
General:	$\text{cov} = r$	u	r^2	ru	u^2

Effects of linkage In the derivations of all the covariances given above, the effects of linkage have been ignored, the summation over loci carrying the implicit assumption that all the loci segregate independently. Linkage does not affect the covariances if the population is in linkage equilibrium, unless there is epistatic interaction between the loci; the full- and half-sib covariances are then increased by linkage between the interacting loci. For details see Cockerham (1956) and Weir, Cockerham, and Reynolds (1980).

Environmental covariance

Genetic causes are not the only reasons for resemblance between relatives; there are also environmental circumstances that tend to make relatives resemble each other; some sorts of relatives more than others. If members of a family are reared together, as with human families or litters of pigs or mice, they share a common environment. This means that some environmental circumstances that cause differences between unrelated individuals are not a cause of difference between members of the same family. In other words, there is a component of environmental variance that contributes to the variance between means of families but not to the variance within the families, and it therefore contributes to the covariance of the related individuals. This between-group environmental component, for which we shall use the symbol V_{Ec} , is usually called the *common environment*, a term that seems more appropriate when we think of the component as a cause of similarity between members of a group than when we think of it as a cause of difference between members of different groups. The remainder of the environmental variance, which we shall denote by V_{Ew} , arises from causes of difference that are unconnected with whether the individuals are related or not. It therefore appears in the within-group component of variance, but does not contribute to the between-group component, which is the variance of the true means of the groups. In considerations of the resemblance between relatives, therefore, the environmental variance must be divided into two components:

$$V_E = V_{Ec} + V_{Ew} \quad \dots [9.14]$$

one of the components, V_{Ec} , contributing to the covariance of the related individuals.

The sources of the common environmental variance are many and varied, and arise from environmental factors such as nutrition, climatic conditions or, in man, cultural influences. Whenever families differ in respect of these factors there will

be, or may be, environmentally caused differences between the means of families, which appear in the covariance as the V_{Ec} component. What we designate as the V_{Ec} component depends on the way in which individuals are grouped when we estimate the observational components of phenotypic variance. Whatever the form of the analysis, the part of the variance between the means of groups that can be ascribed to environmental causes is called the V_{Ec} component. The nature of this component thus depends on the form of the analysis applied. If the groups in the analysis are full-sib families then the V_{Ec} component represents environmental causes of similarity between full sibs; if the groups are half sibs it represents causes of similarity between half sibs. And in parent-offspring relationships a comparable covariance term represents environmental causes of resemblance between offspring and parent. Thus, whenever we measure a phenotypic covariance with the object of using it to estimate a causal component of variance, we have to decide whether it includes an appreciable component due to common environment, and this is often a matter of judgement based on a biological understanding of the organism and the character. In experiments, much of the V_{Ec} component can often be eliminated by suitable design. For example, members of the same family need not always be reared in the same vial, cage, or plot: they can be randomized over the rearing environments. Or, by dividing families into two or more groups, the V_{Ec} component can be measured and deducted from the covariance.

Maternal effects are a frequent, and often troublesome, source of environmental resemblance, particularly with mammals. The young are subject to a maternal environment during the first stages of their life, and this influences the phenotypic values of many metric characters even when measured on the adult, causing offspring of the same mother to resemble each other. Two sorts of maternal effect need to be distinguished. First, the phenotypic value of the mother for the character in question may influence the value of the offspring for the same character. For example, large mice give more milk than small mice and consequently their young grow better. This leads to an environmentally caused resemblance between the weight of the offspring and the weight of their mother. Furthermore, offspring of the same mother resemble each other in weight because they have shared the same milk supply. This sort of maternal effect therefore contributes an environmental component to the covariance of offspring with mothers, and to the covariance of full sibs or maternal half sibs. A way of evaluating the effect that the phenotypes of mothers have on the same character in their offspring is described by Falconer (1965b). The second sort of maternal effect causes resemblance between offspring of the same mother, but not between the offspring and their mother. This arises when the character in the mother that gives rise to the maternal effect is not the character whose covariance is being studied. For example, the growth of the tails of young mice is influenced by the temperature in the nest. Mothers differ in the assiduity with which they nurse their young, and consequently there are differences in nest temperature between families. This produces an environmental component in the covariance of sibs in respect of tail length. But the nest temperature is not related to the mother's tail length, so there is no environmental covariance of offspring and mothers in respect of tail length. The variation among offspring due to a

maternal effect results from variation among the mothers in the character that gives rise to the maternal effect, such as milk-yield. The maternal character is, to a greater or lesser degree, determined by the mother's genotype. Therefore the environmental variance V_{Ec} seen in the offspring is to some extent the consequence of genetic variation of some other character in the mothers. The resemblance between relatives becomes very complicated when the genetic basis of a maternal effect is taken into account. For details, see Willham (1963, 1972), Thompson (1976).

Relatives of all sorts may be subject to an environmental source of resemblance. In what follows, however, we shall make the simplification of disregarding the V_{Ec} component for all relatives except full sibs. The common maternal environment of full sibs is often the most troublesome source of environmental resemblance to overcome by experimental design. Consequently, a V_{Ec} component contributes more often and in greater amount to the covariance of full sibs than to that of any other sort of relative.

Competition Brief mention must be made of a way by which resemblance between relatives can be reduced, instead of increased, for environmental reasons. This occurs when members of the same family compete for limited resources. Suppose, for example, that sib-families of animals are reared with each family in a separate pen, and that all pens are given the same fixed amount of food, growth rate being the character of interest. There would then be little or no variation in growth rate between families, and the covariance would consequently be reduced. There would, however, still be variation within families; indeed, there might be more variation than with unrestricted feeding because the competition is an additional source of variation. The intraclass correlation would therefore be reduced by the competition for fixed resources. The correlation could even be negative, because if one individual gets more to eat, another must of necessity get less. Competition is an important factor in plants, often making sib-correlations largely meaningless, particularly with characters related to yield.

Phenotypic resemblance

The covariance of phenotypic values is the sum of the covariances arising from genetic and from environmental causes. Thus by putting together the conclusions of the two preceding sections we arrive at the phenotypic covariances summarized in Table 9.5. (It will be remembered that some possible sources of environmental covariance are being neglected, particularly in offspring-parent relationships involving the mother.) In all these relationships except that of full sibs, the covariance is either a half or a quarter of the additive genetic variance. By observing the phenotypic covariance of relatives, we can thus estimate the amount of additive genetic variance. Similarly, the regression or correlation provides a means of estimating the proportionate amount of additive genetic variance, V_A/V_P , which is the heritability, and this is the chief use of measurements of the degree of resemblance between relatives. The method of estimating the heritability will be considered more fully in the next chapter.

Table 9.5 Phenotypic resemblance between relatives.

<i>Relatives</i>	<i>Covariance</i>	<i>Regression (b) or correlation (t)</i>
Offspring and one parent	$\frac{1}{2}V_A$	$b = \frac{1}{2} \frac{V_A}{V_P}$
Offspring and mid-parent	$\frac{1}{2}V_A$	$b = \frac{V_A}{V_P}$
Half sibs	$\frac{1}{4}V_A$	$t = \frac{1}{4} \frac{V_A}{V_P}$
Full sibs	$\frac{1}{2}V_A + \frac{1}{4}V_D + V_{Ec}$	$t = \frac{\frac{1}{2}V_A + \frac{1}{4}V_D + V_{Ec}}{V_P}$

Problems

9.1 What is the coefficient of relationship, r , between the children of a pair of MZ twins married to unrelated spouses? [Solution 8]

9.2 Problems 7.4, 7.8 and 8.2(3) dealt with the effects of two genes on the pigmentation of mouse hairs in a specified population. Suppose that the measurements of individuals were subject to environmental variance amounting to one-third of the total genetic variance, but that there were no environmental differences between family means. What would then be the phenotypic resemblance between the following relatives in this population: (1) offspring and mid-parent, (2) offspring and one parent, (3) full sibs, (4) half sibs, (5) double first cousins? [Solution 18]

9.3 The following correlations of total finger-ridge counts have been reported. Are they consistent with each other? What assumptions have to be made in comparing the correlations?

Midparent-child:	$r = 0.69 \pm 0.03$
Father-child:	$r = 0.50 \pm 0.04$
Mother-child:	$r = 0.49 \pm 0.04$

Data from Holt, S. B. (1956/57) *Acta Genet.*, **6**, 473–6.

[Solution 28]

9.4 The estimates below refer to the litter size of mice under different experimental procedures. Litter size is the number of young born and is a character of the mother. In one case the litters by which the litter size of the mother was measured were all standardized at birth to 8 young by removing young in excess of 8 or fostering young from other litters to make up to 8. In the other case the litters were not manipulated and most of the young born were reared to weaning. Suggest reasons, other than sampling error and strain differences, that might account for the differences between the estimates. In both cases the full sibs were mothers born in the same litter.

	<i>Litters standardized</i>	<i>Litters not standardized</i>
Full-sib correlation	0.055	0.107
Daughter-dam regression	0.045	-0.028

Data from Eisen, E. J. (1978) *Genetics*, **88**, 781–811; Falconer, D. S. (1965) pp. 763–74 in Geerts, S. J. (ed.), *Genetics Today*. Proc. XI Internat. Congr. Genetics, Vol. 3. Pergamon, Oxford.

[Solution 38]

10 Heritability

The heritability of a metric character is one of its most important properties. It expresses, as we have seen, the proportion of the total variance that is attributable to differences of breeding values, and this is what determines the degree of resemblance between relatives. But the most important function of the heritability in the genetic study of metric characters is its predictive role, expressing the reliability of the phenotypic value as a guide to the breeding value. Only the phenotypic values of individuals can be directly measured, but it is the breeding value that determines their influence on the next generation. Therefore if the breeder or experimenter chooses individuals to be parents according to their phenotypic values, his success in changing the characteristics of the population can be predicted only from a knowledge of the degree of correspondence between phenotypic values and breeding values. This degree of correspondence is measured by the heritability, as the following considerations will show.

The heritability is defined as the ratio of additive genetic variance to phenotypic variance:

$$h^2 = \frac{V_A}{V_P} \quad \dots [10.1]$$

(The customary symbol h^2 stands for the heritability itself and not for its square. The symbol derives from Wright's (1921) terminology, where h stands for the corresponding ratio of standard deviations.) An equivalent meaning of the heritability is the regression of breeding value on phenotypic value:

$$h^2 = b_{AP} = \frac{\text{regression}}{\text{of } A \text{ on } P} \quad \dots [10.2]$$

The equivalence of these meanings can be seen from reasoning similar to that by which the genetic covariance of offspring and one parent was derived in the previous chapter. If we split the phenotypic value into breeding value and a remainder (R) consisting of the environmental, dominance, and interaction deviations, then $P = A + R$. Since A and R are uncorrelated, $\text{cov}_{AP} = V_A$ and so $b_{AP} = V_A/V_P = h^2$.

We may note also that the correlation between breeding values and phenotypic values, r_{AP} , is equal to the square root of the heritability. This follows from the general relationship between correlation and regression coefficients, which gives

$$r_{AP} = b_{AP} \frac{\sigma_P}{\sigma_A} = h^2 \frac{1}{h} = h \quad \dots [10.3]$$

By regarding the heritability as the regression of breeding value on phenotypic value we see that an individual's estimated breeding value is the product of its phenotypic value and the heritability

$$A_{(\text{expected})} = h^2 P \quad \dots [10.4]$$

breeding values and phenotypic values both being reckoned as deviations from the population mean. In other words, the heritability expresses the reliability of the phenotypic value as a guide to the breeding value, or the degree of correspondence between phenotypic value and breeding value. For this reason the heritability enters into almost every formula connected with breeding methods, and many practical decisions about procedure depend on its magnitude. These matters, however, will be considered in the next chapters; here we are concerned only to point out that the determination of the heritability is one of the first objectives in the genetic study of a metric character.

It is important to realize that the heritability is a property not only of a character but also of the population, of the environmental circumstance to which the individuals are subjected, and of the way in which the phenotype is measured. Since the value of the heritability depends on the magnitude of all the components of variance, a change in any one of these will affect it. All the genetic components are influenced by gene frequencies and may therefore differ from one population to another, according to the past history of the population. In particular, small populations maintained long enough for an appreciable amount of fixation to have taken place are expected to show lower heritabilities than large populations. The environmental variance is dependent on the conditions of culture or management: more variable conditions reduce the heritability; more uniform conditions increase it. And, finally, if the phenotype is the mean of two or more measurements the heritability will differ according to the number of measurements and will differ from that of a single measurement, for the reasons explained in connection with repeatability in Chapter 8. So, whenever a value is stated for the heritability of a given character it must be understood to refer to a particular population under particular conditions. Values found in other populations under other circumstances will be more or less the same according to whether the structure of the population and the environmental conditions are more or less alike.

Very many determinations of heritabilities have been made for a great variety of characters in animals and plants. Some examples are given in Table 10.1. Heritabilities cannot easily be estimated with any great precision, and most estimates have rather large standard errors. Different estimates for the same character in the same organism show a wide range of variation, some of which may reflect real differences between populations or the conditions under which they are studied. Nevertheless, within the range of sampling errors, estimates tend to be similar in different populations. Because of the large sampling errors, the estimates in Table 10.1 are given to the nearest 5 per cent. Despite the lack of precision, it is very clear that heritabilities differ greatly according to the character. There is, moreover, some connection between the magnitude of the heritability and the nature of the character. This can be seen in Table 10.1. On the whole, the characters with the lowest heritabilities are those most closely connected with reproductive fitness, while the

Table 10.1 Approximate values of the heritability of various characters in various animal species. The estimates are rounded to the nearest 5 per cent; their standard errors range from about 2 per cent to about 10 per cent.

	$h^2(\%)$	Ref.
<i>Man</i>		
Stature	65	(1)
Serum immunoglobulin (IgG) level	45	(2)
<i>Cattle</i>		
Body weight (adult)	65	(3)
Butterfat, %	40	(4)
Milk-yield	35	(4)
<i>Pigs</i>		
Back-fat thickness	70	(5)
Efficiency of food conversion	50	(5)
Weight gain per day	40	(5)
Litter size	5	(6)
<i>Poultry</i>		
Body weight (at 32 wks)	55	(7)
Egg weight (at 32 wks)	50	(7)
Egg production (to 72 wks)	10	(7)
<i>Mice</i>		
Tail length (at 6 wks)	40	(8)
Body weight (at 6 wks)	35	(8)
Litter size (1st litters)	20	(9)
<i>Drosophila melanogaster</i>		
Abdominal bristle number	50	(10)
Body size	40	(11)
Ovary size	30	(12)
Egg production	20	(11)

(1) West African population. Roberts, Billewicz, and McGregor (1978).

(2) US whites, Grundbacher (1974).

(3) Beef cattle; average of many estimates. Preston and Willis (1970).

(4) British Friesians, 1st lactations. Barker and Robertson (1966).

(5) British Large White. Smith, King and Gilbert (1962).

(6) British Large White. Strang and Smith (1979).

(7) White Leghorn strain-crosses. Emsley, Dickerson, and Kashyap (1977).

(8) Rutledge, Eisen, and Legates (1973).

(9) Falconer (1965b).

(10) Clayton, Morris, and Robertson (1957).

(11) Robertson (1957b).

(12) Robertson (1957a).

characters with the highest heritabilities are those that might be judged on biological grounds to be the least important as determinants of natural fitness. This relationship has been well substantiated by extensive surveys of the heritabilities of different characters in *Drosophila* (Roff and Mousseau, 1987) and in wild populations of a great variety of species (Mousseau and Roff, 1987). The reasons why different sorts of character should have different heritabilities will be considered in Chapter 20.

Some care is needed in applying the concept of heritability to plants. When defined as $h^2 = V_A/V_P$, the variances are those of individual values. Individual

values of plants, particularly of their yields, are often not available or, if available, are rendered largely meaningless by competition, which was mentioned as an environmental factor in the previous chapter. Yields are usually expressed per unit area of plot in which the plants are grown. The unit of measurement is therefore the plot yield, not the individual yield. If the individuals in a plot are members of one family – full or half sibs – the ‘heritability’ is the heritability of differences between families, the meaning of which will be explained in Chapter 13. The rest of this chapter refers only to the heritability of individual values.

Estimation of heritability

The heritability is estimated from the degree of resemblance between relatives. Table 10.2 shows again the composition of the phenotypic covariances derived in the previous chapter. The right-hand column gives the regression or correlation expressed in terms of the heritability, from which it can be seen that with any relationship

$$h^2 = b/r \quad \text{or} \quad t/r \quad \dots [10.5]$$

where r is the coefficient of the additive variance in the covariance, or the ‘theoretical’ correlation. Thus, when expressed in terms of the correlation (or regression) between relatives, the heritability is the observed correlation as a proportion of the correlation that would be found if the character were completely inherited, i.e., if all the variance were additive genetic.

The choice of what sort of relatives to use for the estimation of the heritability depends on the circumstances. In addition to the practical matter of which sorts of relatives are in fact available, there are two points to consider: precision and bias. In general, the closer the relationship, the more precise is the estimate. The reason for this is that the observed regression or correlation must be multiplied by a larger factor ($1/r$) with more distant relatives, and the standard error of the regression or correlation must be multiplied by the same factor to give the standard error of the estimated heritability. The statistical precision will be considered more fully later in this chapter. Bias in the estimate of the heritability is usually a more important consideration than precision. It is introduced by environmental sources of covariance and, in the case of full sibs, by dominance. From considerations of the biology of the character and the experimental design, we have to decide which covariance is least likely to be augmented by an environmental component, a matter already

Table 10.2

<i>Relatives</i>	<i>Covariance*</i>	<i>Regression (b) or correlation (t)</i>
Offspring and one parent	$\frac{1}{2} V_A$	$b = \frac{1}{2} h^2$
Offspring and mid-parent	$\frac{1}{2} V_A$	$b = h^2$
Half sibs	$\frac{1}{4} V_A$	$t = \frac{1}{4} h^2$
Full sibs	$\frac{1}{2} V_A + \frac{1}{4} V_D + V_{Ec}$	$t \geq \frac{1}{2} h^2$

*The contributions of epistatic interactions are ignored, and so are the possible environmental contributions to relatives other than full sibs.

discussed in the last chapter. Generally speaking, the half-sib correlation and the regression of offspring on father are the most reliable from this point of view. The regression of offspring on mother is sometimes liable to give too high an estimate on account of maternal effects, as it would, for example, with body size in most mammals. (Example 10.3 illustrates the bias due to a maternal effect.) The full-sib correlation, which is the only relationship for which an environmental component of covariance is shown in the table, is the least reliable of all. The component due to common environment is often present in large amount and is difficult to overcome by experimental design; and the full-sib covariance is further augmented by the dominance variance. The full-sib correlation can therefore seldom do more than set an upper limit to the heritability.

Example 10.1.

The heritability of abdominal bristle number in *Drosophila melanogaster* has been determined by three different methods, applied to the same population (Clayton, Morris, and Robertson, 1957), with the following results:

<i>Method of estimation</i>	<i>Heritability</i>
Offspring-parent regression	0.51 ± 0.07
Half-sib correlation	0.48 ± 0.11
Full-sib correlation	0.53 ± 0.07
Combined estimate	0.52

The estimates obtained by the three methods are in very satisfactory agreement. In this case, the character – bristle number – is free of complications arising from maternal effects and common environment.

Let us now consider briefly some technical matters concerning the translation of observational data into estimates of heritability. For the moment it will be assumed that all observations are made on a random-mating population with no selection of the parents. Later, the effects of assortative mating and of selection will be described.

Offspring-parent regression

The estimation of the heritability from the regression of offspring on parents is comparatively straightforward. The data are obtained in the form of measurements of parents – one or the mean of both – and the mean of their offspring. The covariance is then computed from the cross-products of the paired values. The following example illustrates the regression of mid-parent values.

Example 10.2.

Figure 10.1 illustrates the regression of offspring on mid-parent values for wing length in *Drosophila melanogaster* (Reeve and Robertson, 1953). There are 37 pairs of parents and a mean of 2.73 offspring were measured from each pair of parents. The parents were mated assortatively, with the result that the variance of mid-parent

Continued

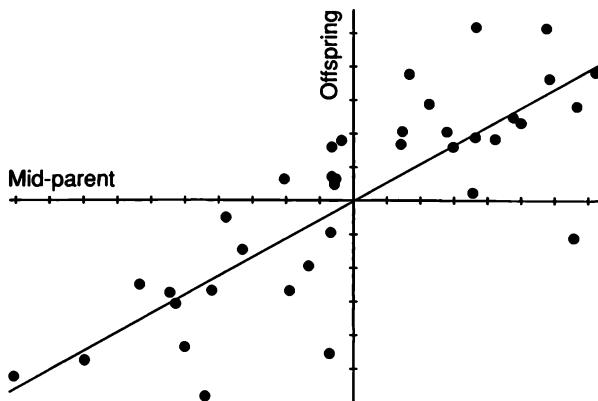


Fig. 10.1. Regression of offspring on mid-parent for wing length in *Drosophila*, as explained in Example 10.2. Mid-parent values are shown along the horizontal axis, and mean value of offspring along the vertical axis. (Drawn from data kindly supplied by Dr E. C. R. Reeve.)

Example 10.2 continued

values is greater than it would be if mating had been at random, as will be explained in a later section. Each point on the graph represents the mean value of one pair of parents (measured along the horizontal axis), and the mean value of their offspring (measured along the vertical axis). The axes are marked at intervals of 1/100 mm, and they intersect at the mean value of all parents and all offspring. The sloping line is the linear regression of offspring on mid-parent. The slope of this line estimates the heritability, and has the value (\pm standard error): $h^2 = b_{OP} = 0.58 \pm 0.07$.

A complication in the use of the regression of offspring on parents arises if the variance is not equal in the two sexes. It was noted in the previous chapter that the covariance of offspring and mid-parent values is equal to the additive genetic variance on condition that the sexes are equal in phenotypic variance. If the variances are not equal, the regression on mid-parent cannot, strictly speaking, be used, and the heritability must be calculated separately for each sex. The heritability in males, for example, is estimated from the regression of sons on fathers, and of daughters on fathers. The regression of daughters on fathers, however, must be adjusted for the difference in variation, multiplying it by the ratio of phenotypic standard deviations of males to females. Thus if b is the regression of daughters on fathers, the adjusted regression is $b' = b\sigma_d/\sigma_g$. Similarly, the heritability in females is estimated from the regression of daughters on mothers, and of sons on mothers adjusted by σ_g/σ_d . Estimations from the four regressions, and the adjustments for unequal variances, are illustrated in the following example.

Example 10.3.

The heritability of the body weight at 6 weeks of age was estimated in a random-bred strain of mice by offspring-parent regression (Falconer, 1973). The variances

Continued

Example 10.3 continued

of males and females were not equal, and so the regressions were calculated separately for each sex of offspring and of parent. The phenotypic standard deviations and their ratios were as follows:

$$\sigma_\delta = 3.786, \sigma_\varphi = 2.675, \sigma_\delta/\sigma_\varphi = 1.415, \sigma_\varphi/\sigma_\delta = 0.707$$

Table (i) gives the regression coefficients and their standard errors, with the factors by which both must be multiplied to adjust for the difference in variance. The regressions are all of offspring on one parent, so the regressions and their standard errors must be multiplied by two to obtain the heritabilities given in table (ii). The estimates do not differ significantly according to the sex of offspring, so male and female offspring are averaged in the third line of table (ii). The estimates do, however, differ significantly between male and female parents. The much higher estimate from females is attributable to bias from a maternal effect.

Table (i) Regression coefficients with standard errors and adjustment factors.

Parents		
Offspring	Male	Female
Male	0.110 ± 0.040	$(0.324 \pm 0.064) \times 0.707$ = 0.229 ± 0.045
Female	$(0.111 \pm 0.029) \times 1.415$ = 0.157 ± 0.041	0.237 ± 0.043

Table (ii) Heritabilities, per cent, with standard errors.

Parents		
Offspring	Male	Female
Male	22 ± 8	46 ± 9
Female	31 ± 8	47 ± 9
Both	27 ± 6	47 ± 6

Sib analysis

The estimation of heritability from half sibs is more complicated than appears at first sight and needs more detailed comment. A common form in which data are obtained with animals is the following. A number of males (sires) are each mated to several females (dams), the males and females being randomly chosen and randomly mated. A number of offspring from each female are measured to provide the data. The individuals measured thus form a population of half-sib and full-sib families. An analysis of variance is then made by which the phenotypic variance is divided into observational components attributable to differences between the progeny of different males (the between-sire component, σ_S^2), to differences between the progeny of females mated to the same male (between-dam, within-sire component, σ_D^2); and to differences between individual offspring of the same female (within-progeny component, σ_W^2). The form of the analysis is shown in Table 10.3. There are supposed to be s sires, each mated to d dams, which produce k

Table 10.3 Form of analysis of half-sib and full-sib families.

Source	d.f.	Mean square	Composition of mean square
Between sires	$s - 1$	MS_S	$= \sigma_W^2 + k\sigma_D^2 + dk\sigma_S^2$
Between dams (within sires)	$s(d - 1)$	MS_D	$= \sigma_W^2 + k\sigma_D^2$
Within progenies	$sd(k - 1)$	MS_W	$= \sigma_W^2$

s = number of sires

d = number of dams per sire

k = number of offspring per dam

offspring each. The values of the mean squares are denoted by MS_S , MS_D , and MS_W . The mean square within progenies is itself the estimate of the within-progeny variance component, σ_W^2 ; but the other mean squares are not the variance components. The compositions of the mean squares in terms of the observational components of variance are shown in the right-hand column of the table, consideration of which will show how the variance components are to be estimated. The between-dam mean square, for example, is made up of the within-progeny component together with k times the between-dam component; so the between-dam component is estimated as $\sigma_D^2 = (1/k)(MS_D - MS_W)$. Similarly, the between-sire component is estimated as $\sigma_S^2 = (1/dk)(MS_S - MS_D)$, where dk is the number of offspring per sire. If there are unequal numbers of offspring from the dams, or of dams in the sire-groups, the mean values of k and d can be used with little error, provided the inequality of numbers is not very great. The exact solution, which is too complicated for description here, can be found in Snedecor and Cochran (1967, Section 10.19), Turner and Young (1969), or Searle (1971).

The next step is to deduce the connections between the observational components that have been estimated from the data and the causal components, in particular the additive genetic variance, the estimation of which is the main purpose of the analysis. Though all the information needed has already been given, the interpretation of the observational components, which is given in Table 10.4, is not immediately apparent without explanation. The first point to note is that the estimate of the phenotypic variance is given by the sum (σ_T^2) of the three observational components: $V_P = \sigma_T^2 = \sigma_S^2 + \sigma_D^2 + \sigma_W^2$. This is not necessarily equal to the observed variance as estimated from the total sum of squares, though the two seldom differ by much. Now consider the interpretation of the between-sire component, σ_S^2 . This is the variance between the means of half-sib families and it therefore estimates the

Table 10.4 Interpretation of the observational components of variance in a sib analysis.

Observational component	Covariance and causal components estimated
Sires:	$\sigma_S^2 = \text{cov}_{(\text{HS})}$ $= \frac{1}{2}V_A$
Dams:	$\sigma_D^2 = \text{cov}_{(\text{FS})} - \text{cov}_{(\text{HS})}$ $= \frac{1}{2}V_A + \frac{1}{4}V_D + V_{Ec}$
Progeny:	$\sigma_W^2 = V_P - \text{cov}_{(\text{FS})}$ $= \frac{1}{2}V_A + \frac{3}{4}V_D + V_{Ew}$
Total:	$\sigma_T^2 = \sigma_S^2 + \sigma_D^2 + \sigma_W^2 = V_P$ $= V_A + V_D + V_{Ec} + V_{Ew}$
Sires + Dams:	$\sigma_S^2 + \sigma_D^2 = \text{cov}_{(\text{FS})}$ $= \frac{1}{2}V_A + \frac{1}{4}V_D + V_{Ec}$

phenotypic covariance of half sibs, $\text{cov}_{(\text{HS})}$, which is $\frac{1}{4} V_A$. Thus $\sigma_S^2 = \frac{1}{4} V_A$. Next consider the within-progeny component, σ_W^2 . Since any between-group variance component is equal to the covariance of the members of the groups, it follows that a within-group component is equal to the total variance minus the covariance of members of the groups. The progenies of the dams are full-sib families and so the within-progeny variance estimates $V_P - \text{cov}_{(\text{FS})}$. This leads to the interpretation $\sigma_W^2 = \frac{1}{2} V_A + \frac{3}{4} V_D + V_{Ew}$. Finally, there remains the between-dam component, and what it estimates can be found by subtraction as follows:

$$\sigma_D^2 = \sigma_T^2 - \sigma_S^2 - \sigma_W^2 = \text{cov}_{(\text{FS})} - \text{cov}_{(\text{HS})} = \frac{1}{4} V_A + \frac{1}{4} V_D + V_{Ec}$$

Consideration of the between-sire and between-dam components will show that their sum gives an estimate of the full-sib covariance, $\text{cov}_{(\text{FS})}$, but this provides no new information for estimating the causal components. These conclusions about the connection between observational and causal components of variance are summarized in Table 10.4. The contributions of the interaction variance to the observational components can be deduced from the contributions to the covariances given in Table 9.4.

The estimation of the heritability from sib analyses is illustrated in the two following examples. The calculation of the standard error of the estimate, which is complicated, is described by Turner and Young (1969).

Example 10.4

As an illustration of the estimation of heritability from a sib analysis, we refer to the study of Danish Landrace pigs based on the records of the Danish Pig Progeny Testing Stations (Fredeen and Jonsson, 1957). The data came from 468 sires each mated to 2 dams, the analysis being made on the records of 2 male and 2 female offspring from each dam. Only one such analysis is given here: that of body length in the male offspring. The analysis, shown in the table, was made within stations and within years, and this accounts for the degrees of freedom being fewer than would appear appropriate from the numbers stated above. The components of variance are calculated from the compositions of the mean squares as shown in Table 10.3; here $k = 2$, $d = 2$, $kd = 4$. The interpretation of the analysis, shown at the foot of the table, has been slightly simplified by the omission of some minor adjustments not relevant here. The between-dam component is not greater than the between-sire component, so there cannot be much non-additive genetic variance or variance due to common environment. The two estimates of the heritability, from the sire and dam components respectively, can therefore be regarded as equally reliable, and their combination based on the resemblance between full sibs may be taken as the best estimate.

Sib analysis of body length in Danish Landrace pigs; data for male offspring only.

Source	<i>d.f.</i>	<i>Mean square</i>	<i>Component of variance</i>
Between sires	432	6.03	$\sigma_S^2 = \frac{1}{4} (6.03 - 3.81) = 0.555$
Between dams,			
within sires	468	3.81	$\sigma_D^2 = \frac{1}{2} (3.81 - 2.87) = 0.47$
Within progenies	936	2.87	$\sigma_W^2 = \frac{2.87}{4}$
Total			$\sigma_T^2 = 3.895$

Continued

Example 10.4 continued

Interpretation of analysis

<i>Sib correlations</i>	<i>Estimates of heritability</i>
Half sibs: $t_{(HS)} = \frac{\sigma_S^2}{\sigma_T^2} = 0.142$	Sire-component: $h^2 = \frac{4\sigma_S^2}{\sigma_T^2} = 0.57$
	Dam-component: $h^2 = \frac{4\sigma_D^2}{\sigma_T^2} = 0.48$
Full sibs: $t_{(FS)} = \frac{\sigma_S^2 + \sigma_D^2}{\sigma_T^2} = 0.263$	Sire + Dam: $h^2 = \frac{2(\sigma_S^2 + \sigma_D^2)}{\sigma_T^2} = 0.53$

Example 10.5

We have not yet had an example to illustrate the effect of common environment in augmenting the full-sib correlation. This is provided by body size in mice. The analysis given in table (i) refers to the weight of female mice at 6 weeks of age (J. C. Bowman, unpublished). There were 719 offspring from 74 sires and 192 dams, each with one litter. These were spread over 4 generations and the analysis was made within generations. The analysis is complicated by the inequality of the number of offspring per dam and of dams per sire. The adjustments made for these inequalities are shown, without explanation, in the compositions of the mean squares from which the components are estimated. The dam component is much larger than the sire component, indicating a substantial bias due to common environment or dominance. Therefore only the sire component can be used to estimate the heritability. The estimate obtained is $h^2 = 4 \times (0.48/5.14) = 0.37$. (This estimate has a standard error of 0.26, so that it is not significantly different from zero. The experiment was on too small a scale to be of much practical use, though it serves to illustrate the method.) The causal components can now be estimated from the analysis according to the interpretation given in Table 10.4. It is not possible to discriminate between common environment and dominance as the cause of the difference between the dam and sire components. The estimates in table (ii) are based on the assumption that the difference is all due to common environment, and that $V_D = 0$. We can go a little further than this in the interpretation of the analysis and put an upper limit on the dominance variance as follows. The maximum possible value for V_D is set by the within-progenies component σ_W^2 ; it is possible, though very unlikely, that $V_{Ew} = 0$, which would make $\sigma_W^2 - 2\sigma_D^2 = \frac{4}{3}V_D$, from which $V_D = 1.64 = 32$ per cent as an upper limit. V_{Ec} would then be $\sigma_D^2 - \sigma_S^2 - \frac{4}{3}V_D = 1.58 = 31$ per cent as a lower limit. The true values of the causal components are, however, likely to be much nearer those in table (ii).

Table (i)

<i>Source</i>	<i>d.f.</i>	<i>Mean square</i>	<i>Composition of M.S.</i>	<i>Components</i>
Sires	70	17.10	$\sigma_W^2 + k'\sigma_D^2 + dk'\sigma_S^2$	$\sigma_S^2 = 0.48$
Dams	118	10.79	$\sigma_W^2 + k\sigma_D^2$	$\sigma_D^2 = 2.47$
Progeny	527	2.19	σ_W^2	$\sigma_W^2 = 2.19$
		$k = 3.48;$	$k' = 4.16;$	$d = 2.33$
				$\sigma_T^2 = 5.14$

Continued

Example 10.5 continued**Table (ii)**

$V_P = \sigma_T^2$	= 5.14 = 100%
$V_A = 4\sigma_S^2$	= 1.92 = 37%
$V_{Ec} = \sigma_D^2 - \sigma_S^2$	= 1.99 = 39%
$V_{Ew} = \sigma_W^2 - 2\sigma_S^2$	= 1.23 = 24%

Intra-sire regression of offspring on dam

The heritability can be estimated from the offspring-parent relationship in a population with the structure described in the foregoing section by the regression of offspring on dams calculated within sire-groups. That is to say, the regression of offspring on dams is calculated separately for each set of dams mated to one sire, and the regression from each set pooled in a weighted average. This regression estimates half the heritability, just as would the overall regression with sires ignored. The within-sire regression is preferable to the overall regression because it eliminates unwanted variation about the regression line due to sires, or to environmental differences between sire-groups. It has other advantages, explained by Lush (1940), the chief of which is the elimination of environmental covariance that arises if sire-groups are in different herds but the dams and progeny in each sire-group are reared in the same herd.

Combined estimates

For the classical experimental designs described above, causal components of variance are simple linear functions of the observed covariance between relatives. Estimates of variance components are obtained by least-squares statistical analyses (i.e., regression, analysis of variance) by solving the system of equations relating the observed variance to its expectation. Ideally, for statistical reasons, these designs should be balanced, and parents must be randomly sampled from the population for unbiased estimates of heritability based on sib covariances (see below). Often more information is available than can be accommodated by one of the classical designs. For example, when phenotypes of both parents and a number of their offspring are known, using the methods described above gives two estimates of heritability; one from offspring on mid-parent regression and the other from full-sib analysis. Similarly, information may be available on more distant relatives, and over several generations, from which variance components and heritability cannot be estimated using a standard design, or information is ignored by extracting only the part of the data that is appropriate for analysis. Furthermore, individuals used in animal breeding improvement programmes are usually a selected group, and estimates of variance components and heritability obtained by analysis of variance of their offspring are therefore biased.

Maximum likelihood (ML) statistical procedures can accommodate any structure of genetic relationships in the data, thus utilizing all available information, suitably weighted; they do not require balanced designs, and can take account of selection of parents. Essentially, given the observed relationships and parameters

(i.e., variance components, heritability) to be estimated, ML evaluates the probability that the observed data could be obtained given specific numerical values of the parameters. Initial values are chosen and an iterative computer algorithm is used to find the combination of parameters at which the likelihood is maximum; these are the maximum likelihood estimates (MLEs). However, MLEs are biased, for two reasons. First, estimates are constrained to lie within the range of the parameters, and for variance components cannot therefore be less than zero. Second, ML assumes fixed effects are known and does not take account of the loss of degrees of freedom from estimating fixed effects from the data. In the simplest case there will be only one fixed effect, the overall mean, but in more complicated data sets there may be many fixed effects; for example, herd, year, and season in dairy cattle data. This leads to underestimates of variance components in the same way that use of $\Sigma(X - \bar{X})^2/N$ underestimates the variance estimated from a sample. The second source of bias can be eliminated using a modification of ML, restricted ML (REML), which adjusts the observations for the estimates of the fixed effects. REML analysis is computationally intensive, but is now the method of choice for estimating heritability and variance components. General software packages such as SAS and specialized genetic analysis software (e.g., Shaw, 1987; Meyer, 1989a) using REML are available. For additional details of ML and REML analysis, see Kennedy (1981), Thompson (1982), Shaw (1987), and Meyer (1989b).

Twins and human data

Identical twins seem at first sight to provide, for man and cattle, a means of estimating the genotypic variance. They provide individuals of identical genotype, just as inbred lines, or crosses between lines, do for laboratory animals or for plants. Many studies of human twins have been made, and have shown the members of the pairs to be extremely alike in most characters, even when reared apart from childhood. Studies of cattle twins, though on a much smaller scale, show the same thing (see Hancock, 1954; Brumby, 1958). Taken at their face value, these studies seem to indicate a very high degree of genetic determination – up to 90 per cent or even more – for many characters. The use of identical twins in this way is, however, vitiated by the additional similarity due to common environment. Twins share a common environment from conception to birth and over the period during which they are reared together, so that the between-pair variance contains the variance due to common environment, V_{Ec} , confounded with the genetic variance, V_G . This difficulty may be partly overcome by comparison of the two sorts of twins, identical or monozygotic (MZ) and fraternal or dizygotic (DZ). Dizygotic twins are full sibs that share a common environment to approximately the same extent as monozygotic twins. To estimate the amount of genetic variance, we ask how much less alike are DZ than MZ twins. Table 10.5 shows the composition of the components of variance between and within pairs, on the assumption that both components of the environmental variance, V_{Ec} and V_{Ew} , are the same in MZ as in DZ twins. The contributions from the interaction variance, which are omitted for simplicity, can be added from Table 9.4. The difference between MZ and DZ twins in both components estimates half of the

Table 10.5 Composition of the components of variance between and within pairs of twins, omitting interaction components.

	<i>Between pairs, σ_b^2</i>	<i>Within pairs, σ_w^2</i>
Identical (MZ)	$V_A + V_D + V_{Ec}$	V_{Ew}
Fraternal (DZ)	$\frac{1}{2}V_A + \frac{3}{4}V_D + V_{Ec}$	$\frac{1}{2}V_A + \frac{3}{4}V_D + V_{Ew}$
Difference	$\frac{1}{2}V_A + \frac{3}{4}V_D$	$\frac{1}{2}V_A + \frac{3}{4}V_D$

additive variance together with three-quarters of the dominance variance. It may be noted that the difference between the between-pairs mean squares has the same expectation as the difference between the components, i.e., $(MS_{MZ} - MS_{DZ}) = (\sigma_b^2_{b(MZ)} - \sigma_b^2_{b(DZ)}) = \frac{1}{2}V_A + \frac{3}{4}V_D$. The correlation between co-twins is the between-pair component divided by the phenotypic variance, so twice the difference between the MZ correlation and the DZ correlation estimates $(V_A + 1\frac{1}{2}V_D)/V_P$. This is nearer to the degree of genetic determination (broad-sense heritability) than it is to the heritability (narrow-sense), which is perhaps what is wanted from human data. It should be noted, however, that the twin analysis does not provide a strictly valid estimate of either V_A/V_P or of V_G/V_P , even with the assumption of equality of the environmental components. If the epistatic components are added to the covariances it will be seen that the bias is increased. Example 10.6 illustrates the twin-analysis applied to four human characters.

The analysis of twin data outlined above rests critically on two assumptions. The first, already mentioned, is that the environmental components of variance are the same in the two types of twins. The second, not yet mentioned, is that the total genetic variance is the same in the two types. Furthermore, the object of the analysis is to estimate parameters of the population, most of whom are not twins, so for these estimates to be valid the environmental components of variance of twins must be the same as those of single-born individuals. There are many possible causes of differences in the environmental components, of which the following are some (Stern, 1973, explains and discusses these more fully).

(1) Genotype-environment interaction: as explained in Chapter 8, this is formally included with the environmental variance. It will contribute different amounts to the MZ and DZ environmental components.

(2) MZ twins are of three types according to the arrangement of the foetal membranes – a single amnion and single chorion, a single chorion, or separate amnions and chorions; all DZ twins are of the last type.

(3) Competition between co-twins *in utero*, which is probably more severe in MZ than in DZ pairs.

(4) Exact contemporaneity of twins as opposed to singletons.

(5) Parental treatment of twins, which may either enhance or diminish the similarity, and may affect MZ and DZ twins differently.

(6) Errors in the diagnosis of zygosity.

(7) The inclusion of unlike-sexed pairs among the DZ twins.

Differences between the total genetic variance of MZ and DZ twins can arise in the following way (Nance, 1976). The frequency of DZ twinning is influenced by genetic factors including racial differences, whereas the frequency of MZ twinning is little, if at all, influenced by genetic or racial factors. Therefore the different sections

or strata of the population may be differently represented among samples of MZ and DZ twins, and the genetic variances may differ in consequence. The requirement of equality of variances may be tested by comparison of the total variances estimated as $\sigma_b^2 + \sigma_w^2$ though counterbalancing differences of genetic and environmental components cannot be ruled out. If the total variances prove to be equal and there is no obvious preference for the between-pair or within-pair comparison, the information from the two can be combined by averaging them (Christian *et al.*, 1974), i.e., $(\sigma_{b\text{MZ}}^2 - \sigma_{b\text{DZ}}^2) + (\sigma_{w\text{DZ}}^2 - \sigma_{w\text{MZ}}^2) = V_A + 1\frac{1}{2} V_D$. To estimate the 'heritability', the value obtained for $V_A + 1\frac{1}{2} V_D$ is divided by the total variance V_P . If the total variance of twins is not the same as that of singletons, the 'heritability' applicable to the population would be obtained by taking V_P from singletons.

Despite all the difficulties in twin analyses, there is probably less bias from inequality of environmental variances than there is from the common-environment component V_{Ec} in full-sib correlations. The following example illustrates the point.

Example 10.6

The table gives the correlations of MZ twins, like-sexed DZ twins, and full sibs for four characters, from Huntley (1966). The characters, all measured on children, are the total ridge count on ten fingers, height adjusted for age, a verbal IQ test, and a social-maturity score which 'assesses the individual's ability to look after his practical needs and to take responsibility in relation to his age'. These were chosen to represent characters that would be expected to be, in the order stated, increasingly subject to environmental influences. The 'heritabilities' estimated from the twin-differences, shown at the foot of the table, are consistent with this expectation. The estimates from doubling the full-sib correlation are obviously too high, except for the ridge count, being biased upwards by common environment V_{Ec} . The twin analyses have, at least partially, removed this bias. The heritability of the finger-ridge count has been estimated from offspring-parent regressions as about 0.8 (Mi and Rashad, 1975). The heritabilities of the counts of single fingers are lower, ranging from 0.58 to 0.68 for different fingers. The high value for the total count results from the multiple measurement, which eliminates all but one-tenth of the environmental component V_{Es} affecting each finger separately, as explained in Chapter 8.

	<i>Finger-ridge count</i>	<i>Height</i>	<i>IQ score</i>	<i>Social-maturity score</i>
MZ twins	0.96	0.90	0.83	0.97
DZ twins	0.47	0.57	0.66	0.89
Full sibs	0.51	0.50	0.58	0.32
$2(t_{\text{MZ}} - t_{\text{DZ}})$	0.98	0.66	0.34	0.16
$2t_{\text{FS}}$	1.02	1.00	1.16	0.64

The effects of common environment present serious difficulties in the interpretation of the correlations between relatives in man, especially for characters influenced by cultural transmission. These difficulties in arriving at a meaningful estimate of the heritability cannot be discussed here. It must suffice to say that they may be at least

partly overcome by utilizing correlations of several different sorts of relatives and having an index that quantifies the environment to which each family is subject (see Morton, 1974; Rao, Morton, and Yee, 1974, 1976; Elston, 1988 and references therein). Methods of estimating the effects of cultural transmission are described by Eaves (1976) and by Cloninger, Rice, and Reich (1979). These last authors conclude, for example, that the heritability of IQ scores in their data was 33 per cent but the 'total transmissible variance' was 69 per cent. Rather than trying to estimate genetic parameters such as the heritability, it is perhaps more important to test whether the parameters are non-zero. This is done by 'model-fitting'. A 'model' is simply a series of expectations for correlations between relatives based on the hypothesis to be tested. The hypothesis might be, for example, that there is variation due to common environment but no genetic variance. If the data give a significantly bad fit to the expectations of the model, the hypothesis is disproved. The application of these methods to psychological characters in man is reviewed by Eaves *et al.* (1978).

Assortative mating

Assortative mating means mating 'like with like' and is seen in a correlation between the phenotypic values of mated individuals. Mating in human populations is assortative with respect to many metric characters, such as stature and IQ scores, though not necessarily by deliberate choice of mates. The questions to be considered in this section are how assortative mating affects the estimation of heritability, and whether the use of assortative mating as a deliberate breeding policy has any advantages in this respect. The genetic consequences of assortative mating are rather complex and only the conclusions can be given here, with no more than brief indications of how they are arrived at. Full explanations are given by Crow and Kimura (1970).

The degree of assortative mating is expressed as the correlation r between the phenotypic values of the mated individuals, and this is what can be observed. The genetic consequences, however, depend on the correlation m between the breeding values of the mates. To deduce the connection between m and r it is necessary to know what governs the choice of mates – whether the primary cause of the resemblance is phenotypic, genetic, or environmental. Primary phenotypic resemblance means that the mates are chosen on the basis of their phenotypic values of the character under consideration. This is how assortative mating would be applied in a breeding programme. The relationship between the two correlations can then be shown to be $m = rh^2$, where h^2 is the heritability of the character by which the mates are chosen. (The derivation of this relationship will be explained later.) The consequences to be described are restricted to primary phenotypic resemblance as a cause of assortative mating. Assortative mating in man, however, probably seldom arises purely in this way and caution is needed in applying the results to human data, particularly in assuming the relationship $m = rh^2$ to be applicable.

Primary genetic or primary environmental resemblance occurs if matings take place within groups that are differentiated from each other genetically or environmentally. This is probably how much of the assortative mating in man arises. The observed phenotypic correlation r is then a 'secondary' correlation resulting from

the 'primary' correlation of breeding values or of environmental deviations. The primary correlations cannot be deduced from r unless one of them can be estimated by other means, and the genetic consequences of the assortative mating cannot be deduced without a knowledge of m . If the primary correlation is wholly environmental ($m = 0$), there will be no genetic consequences of the assortative mating (except that the increased variance of mid-parent phenotypic values will reduce the regression of offspring on mid-parent). Environmental correlation may be the basis of the assortative mating for IQ in man. An analysis of family data on IQ scores (Rao, Morton, and Yee, 1976) showed that the phenotypic correlation between husband and wife of $r = 0.5$ could be largely, perhaps wholly, attributed to people choosing a spouse from those with a family background similar to their own.

Returning to assortative mating by phenotypic value, the genetic consequences are, in summary, as follows. The resulting correlation m between breeding values causes an increase of the additive variance, and consequently of the heritability. The correlations between relatives, however, are increased by more than would result from the increased heritability alone. There is therefore a possible ambiguity in the meaning of heritability under assortative mating. It may be thought of as the determination of the resemblance between relatives, as expressed in equation [10.5], or as the ratio of variance components, V_A/V_P , and the two are not the same under assortative mating. The definition as V_A/V_P will be retained here. The questions with which we shall be mainly concerned are: by how much is the heritability increased, and how is the heritability (defined as V_A/V_P) to be estimated from the resemblance between relatives?

Other aspects of assortative mating that must be noted are the following. (1) The full effects are not immediate; it takes some generations following random mating to reach an equilibrium state. (2) The effects are dependent on the number of loci influencing the character: it will be assumed that the number is large. (3) The effect on the dominance variance is small and may be neglected. Attention will be restricted to pair-matings producing full-sib families in the progeny. Linkage will be disregarded.

The consequences of assortative mating can be worked out by consideration of the covariances of mated pairs, of which three are needed. These are given in Table 10.6 in terms of the two correlations, r (between phenotypic values) and m (between breeding values), and the variance components in the generation to which the mated pairs belong. The relationship $m = rh^2$, stated earlier, can now be derived as follows: $\text{cov}(A_1 A_2) = \text{cov}(h^2 P_1, h^2 P_2) = h^4 \text{cov}(P_1 P_2) = h^4 r V_P = rh^2 V_A$; by (2) of Table 10.6, $\text{cov}(A_1 A_2) = m V_A$, so $m = rh^2$. It is important to note that h^2 here is the heritability of the character measured at the age at which the choice of mates takes place. The variance in the progeny is obtained as follows. The covariance of breeding values of the parents increases the variance of mid-parent breeding values and so increases the variance between family means. The variance within families is due to segregation and is not affected provided the number of segregating loci is not small. Adding together the between-family and the within-family components gives the total variance in the offspring generation. Equations relating the additive and phenotypic variances to those in the random breeding base population are given in Table 10.6. In each case the first equation, (4) and (6), refers to the offspring of one

Table 10.6 Assortative mating. Approximate expressions for variances and covariances. (For meanings of symbols, see notes below.)**Covariances of mates:**

$$\text{phenotypic values, } \text{cov}(P_1 P_2) = rV_P \quad (1)$$

$$\text{breeding values, } \text{cov}(A_1 A_2) = mV_A = mh^2 V_P \quad (2)$$

breeding value of one with environmental deviation of the other,

$$\text{cov}(A_1 E_2) = (r - m)V_A = (r - m)h^2 V_P \quad (3)$$

Variances:

	<u>Additive</u>	<u>Phenotypic</u>	<u>Heritability</u>
1 generation	$V_{A1} = V_{A0}(1 + \frac{1}{2}m)$ (4)	$V_{P1} = V_{P0}(1 + \frac{1}{2}mh^2)$ (6)	$h_1^2 = h_0^2 \left[\frac{1 + \frac{1}{2}m}{1 + \frac{1}{2}mh^2} \right]$ (8)
equilibrium	$V_{A0} = V_A(1 - m)$ (5)	$V_{P0} = V_P(1 - mh^2)$ (7)	$h_0^2 = h^2 \left[\frac{1 - m}{1 + mh^2} \right]$ (9)

Relatives:

	<u>Covariance</u>	<u>Regression (b) or correlation (t)</u>
Offspring, mid-parent	$\frac{1}{2}V_A(1 + r)$ (10)	$b = h^2$ (13)
Offspring, one parent	$\frac{1}{2}V_A(1 + r)$ (11)	$b = \frac{1}{2}h^2(1 + r)$ (14)
Full sibs	$\frac{1}{2}V_A(1 + m)$ (12)	$t = \frac{1}{2}h^2(1 + m)$ (15)

Notes:

r = correlation between phenotypic values of mates.

m = correlation between breeding values of mates. When choice of mates is purely by phenotypic values, $m = rh^2$.

h^2 = heritability, defined as V_A/V_P , at the age of mating.

Covariances of mates: subscripts 1 and 2 refer to the two mated individuals; E includes non-additive genetic deviations; V_A and V_P refer to the generation of the mated pairs.

Variances: subscript 0 refers to the random breeding base, 1 refers to the offspring of 1 generation of assortative mating.

Relatives: dominance V_D , and common environment, V_{Ec} , are omitted; V_A and h^2 refer to the parental generation with correlations r and m . Equations (10) to (14) apply to any generation. Eq. (15) applies only to an equilibrium population; otherwise $t = \text{eq. (12)}/\text{eq. (6)} = \text{eq. (15)}/(1 + \frac{1}{2}mh^2)$.

generation of assortative mating, and the second, (5) and (7), to a population that has reached equilibrium, when the variances remain constant. Dividing the additive by the phenotypic variance gives the heritability in equations (8) and (9).

With these equations we can answer two questions about the heritability. First, by how much does one generation of assortative mating increase the heritability? Equation (8) with substitution of $m = rh^2$ shows that it increases it by a factor of $(1 + \frac{1}{2}h_0^2r)/(1 + \frac{1}{2}h_0^4r)$, where h_0^2 is the original heritability. The increase may be useful in improving the accuracy with which individuals' breeding values can be predicted from their phenotypic values. The increase of the heritability, however, is never very great – at most about 10 per cent. For an experiment with *Drosophila* on the use of assortative mating in this way, see McBride and Robertson (1963). The second question is this: if we have a population in equilibrium and estimate the heritability in it, what would the heritability be if the population were mating at random? Equation (9) with substitution of $m = rh^2$ shows that if, for example, the heritability were 0.50 under assortative mating of $r = 0.5$, the random-mating heritability would be 0.43. This question is relevant to human populations if comparisons are to be made with other species, but equation (9) can be applied to

human data only if m is known or guessed, because $m = rh^2$ is probably seldom true for the reasons already given.

A final question to consider is the estimation of the heritability, defined as V_A/V_P , in a population with assortative mating. The covariances of relatives can be worked out in the manner described in Chapter 9, taking account of the parental covariances given in (1), (2), and (3) of Table 10.6. The covariance and regression or correlation are given for three relationships in Table 10.6. (For the correlations of other relatives, see Nagylaki, 1978.) These covariances apply to any generation, V_A and h^2 being the values in the parental generation. V_A is increased over its random breeding value, as shown by equation (5), and the covariances are increased by a further factor of $(1 + r)$ for offspring and parents and by $(1 + m)$ for full sibs. As before, the offspring-parent covariance is the same for mid-parent values as for single parents. The variance of mid-parent values, however, is increased by the same amount as the covariance; so the regression of offspring on mid-parent values is equal to the heritability, as in a random-breeding population. This conclusion has important practical consequences for the estimation of the heritability. Assortative mating among the parents does not affect the regression of offspring on mid-parent values and so the regression provides a valid estimate of the heritability in the population from which the parents came. Assortative mating, however, has the advantage of increasing the precision of the estimate, the standard error being reduced because the variance of mid-parent values is increased, as will be explained in the next section (for details see Reeve, 1961).

The regression of offspring on single parents and the full-sib correlation are both affected by assortative mating. The variance of single parents is simply the phenotypic variance, but because of the correlation with the unmeasured parent the regression of offspring on single parents is increased by the factor $(1 + 1/r)$, and with perfect assortative mating ($r = 1$) it would be the same as the regression on mid-parent values. The correlation of full sibs in equation (15) of Table 10.6 omits dominance and common environment. If these were assumed to be negligible, the heritability (in an equilibrium population) could be estimated by substituting $m = rh^2$. The equation is then quadratic with the solution $h^2 = [-1 + \sqrt{1 + 8rt}]/2r$.

Precision of estimates and design of experiments

The precision of an estimate of heritability, indicated by its standard error, is easily obtained from the standard error of the regression or correlation from which the heritability is estimated. Standard errors of heritability estimates are uncomfortably large unless the regression or correlation is based on very large numbers, so it is important to do everything possible to minimize the standard error. In planning an experiment to estimate a heritability, one wants to know how many observations are needed to achieve a given degree of precision; and to achieve the greatest possible precision, within the limitations imposed by the available facilities, one needs to know what is the best method and the best design of the experiment. These are the problems to be considered now. The choice of method is between regression of offspring on one or on both parents, and sib-correlations. The choice of method, however, is usually determined more by practical considerations and by freedom

from bias, than by precision. We shall therefore not give much attention to the comparison of methods. The question of design concerns the number of individuals per family. The total number of individuals that can be measured is limited by space, labour, or cost. Increasing the number of individuals per family therefore reduces the number of families. The problem is to find the best compromise between large families and many families that will minimize the sampling variance of the regression or correlation.

In assessing the relative efficiencies of different methods and designs, we have to compare experiments made on the same scale; that is to say, with the same total expenditure in labour or cost. We must therefore decide first what are the circumstances that limit the scale of the experiment. If the labour of measurement is the limiting factor, as for example in experiments with *Drosophila*, then the limitation is in the total number of individuals measured, including the parents if they are measured. If, on the other hand, breeding and rearing space is the limiting factor, as it generally is with larger animals, the limitation may be either in the number of families or in the total number of offspring that can be produced for measurement, and measurements of the parents may be included without additional cost.

We cannot take account here of all the ways in which the scale of an experiment may be limited. For the sake of illustration, the limitation will be taken to be the number of individuals that can be measured in one generation, implying that equal numbers in the parental and offspring generations can be measured. The principles of finding the optimal design are described by Latter and Robertson (1960) for offspring-parent regressions and by A. Robertson (1959a) for sib-correlations. The conclusions will be given without full explanation of how they are arrived at.

Offspring-parent regression

Let N be the number of families giving paired observations of the means of offspring and of parents; let k be the number of parents of each family, which is 1 or 2; and let n be the number of offspring in each family. Then the sampling variance of the regression coefficient of mean of offspring on mean of parents can be shown to be

$$\sigma_b^2 = \frac{k[1 + (n - 1)t]}{nN} \quad (\text{approx.}) \quad \dots [10.6]$$

This approximate expression for the sampling variance allows one to compare the methods – one or both parents measured – and to decide how many offspring should be measured per family. The intra-class correlation of sibs, t , affects the precision because additional offspring give more information about the family mean when it is low than they do when it is high.

One parent Consider first the measurement of only one parent. The denominator, nN , of equation [10.6] is the total number of offspring measured. If this is what limits the scale of the experiment, then nN is fixed and the sampling variance is minimal when $n = 1$, i.e., $(n - 1)t = 0$. Thus the most efficient design under these circumstances is to have as many families as possible and to measure only one offspring per family. The standard error of the estimate of the heritability will then be as follows:

$$\text{s.e.}(h^2) = 2\sigma_b = 2/\sqrt{N} \quad (\text{approx.}) \quad \dots [10.7]$$

To achieve a standard error of 0.1 it is necessary to measure 400 parents and 400 offspring. This illustrates the fact that large numbers are needed to give estimates of even very modest precision. If only 100 families could be measured, the standard error would be about 0.2 and no estimates under about 0.4 would be significantly different from zero.

Both parents Now consider the measurement of both parents for the regression on mid-parent values. If only one offspring is measured per family, substitution of $k = 2, n = 1$ in equation [10.6] gives

$$\text{s.e.}(h^2) = \sigma_b = \sqrt{(2/N)} \quad (\text{approx.}) \quad \dots [10.8]$$

However, if both parents are measured, the same facilities will allow two offspring per family to be measured. Substituting $k = 2, n = 2$ into equation [10.6] gives the standard error of the estimate as $\sqrt{[(1 + r)/N]}$, where r is the full-sib correlation. Comparison will show that, under most circumstances, regression on mid-parent gives better precision than regression on one parent.

Assortative mating Mating the parents assortatively increases the precision. Both parents must, of course, be measured, so only the regression on mid-parent values need be considered. The effect comes from the increase of the variance of mid-parent values. The variance of offspring is also increased but not by much, and this will be neglected for the sake of simplicity. The variance of mid-parent values under assortative mating is $\frac{1}{2} V_p(1 + r)$, where r is the correlation between mates. The consequence is that the sampling variance of the regression with assortative mating is approximately $1/(1 + r)$ times the sampling variance with random mating. Thus the precision, in terms of standard errors, is increased by a factor of $\sqrt{1 + r}$, or by $\sqrt{2}$ if assortative mating is complete, i.e., if $r = 1$.

Weighting families of unequal size It is often possible to measure as many offspring as there are in each family without reducing the number of families. The number of offspring per family then varies among families and this introduces the problem of how to weight the families according to the number of offspring. The appropriate weighting depends on the phenotypic correlation r between the offspring in the families. The principle of the weighting is that families of size n are weighted in proportion to the reciprocal of the variance of the regression that would be obtained if all families were of size n . The weighting is described by Kempthorne and Tandon (1953). The following procedure (Falconer, 1963) is a modification which adjusts the weights so that families of size $n = 1$ always have a weight of 1. First, the intraclass correlation r must be calculated from an analysis of variance between and within families of offspring. Second, the regression coefficient to be estimated must be guessed at, or estimated approximately from unweighted means of families. The weight w_n to be given to the mean of n offspring is then

$$w_n = (n + nB)/(1 + nB) \quad \dots [10.9]$$

where $B = (t - b^2)/(1 - t)$ for regression on single parents, and $B = (t - \frac{1}{2}b^2)/(1 - t)$ for regression on mid-parent values. The weighting does not have much effect on the precision unless n varies substantially. Bohren, McKean, and Yamada (1961) examine its merits.

Sib analyses

Now let us consider estimates obtained from the intraclass correlation of full-sib or half-sib families. We shall at first suppose for simplicity that half-sib families are not subdivided into full-sib families, i.e., that only one offspring from each dam is measured in paternal half-sib families. Let N be the number of families, and n the number of individuals per family, so that the total number of individuals measured is $T = nN$. Let the intraclass correlation be t . The sampling variance of the intra-class correlation is then

$$\sigma_t^2 = \frac{2[1 + (n-1)t]^2(1-t)^2}{n(n-1)(N-1)} \quad \dots [10.10]$$

When the value of $T = nN$ is limited by the size of the experiment, it can be shown that the sampling variance of the intraclass correlation is minimal when $n = 1/t$, approximately. Thus the optimal family size depends on the correlation and therefore on the heritability. Assuming that variance due to dominance and common environment are negligible, with full sibs $t = h^2/2$, and with half sibs $t = h^2/4$. So the family sizes giving the most efficient design are $n = 2/h^2$ for full-sib families, and $n = 4/h^2$ for half-sib families. In the case of half sibs we are assuming that only one offspring per dam is measured, so n is the optimal number of dams per sire. Since prior knowledge of the heritability will be at the best only approximate, the optimal family size cannot be exactly determined beforehand. The loss of efficiency, however, is much greater if the family size is below the optimum than if it is above. It is therefore better to err on the side of having too large families. A. Robertson (1959a) shows that, in the absence of prior knowledge of the heritability, half-sib analyses should generally be designed with families of between 20 and 30.

The sampling variance of the correlation when the experiment has the optimal design is obtained by substituting $n = 1/t$ in equation [10.10]. Making some approximations, this leads to

$$\sigma_t^2 = 8t/T \quad (\text{approx.}) \quad \dots [10.11]$$

To get the sampling variance of the heritability, the variance of the full-sib correlation must be multiplied by 4, and the variance of the half-sib correlation by 16. Then, by substituting $t = h^2/2$ in equation [10.11], the sampling variance of the heritability estimated from full sibs becomes

$$\sigma_h^2 = 4\sigma_t^2 = 16h^2/T \quad (\text{approx.}) \quad \dots [10.12]$$

And, by substituting $t = h^2/4$ in equation [10.11], the sampling variance of the estimate from half sibs becomes

$$\sigma_{h^2}^2 = 16\sigma_t^2 = 32h^2/T \quad (\text{approx.}) \quad [10.13]$$

Thus, other things being equal, an estimate from full-sib families is twice as precise, in terms of their variances, as one from half-sib families.

It is sometimes desirable to design an experiment for estimating the heritability both from offspring-parent regression and from sib-correlation. Hill and Nicholas (1974) show that the optimal design does not differ much from what would be the best for either method alone.

Selection of parents

In experimental populations and in farm animals the parents used are often a selected group. They may be selected on the basis of the character whose heritability is being estimated, or on the basis of some other character correlated with it. The selection causes the variance between parents to be reduced and consequently the covariance of sibs to be reduced. As a result, the heritability estimated from intraclass correlations is biased downwards, and can be as much as 50 per cent below its true value (see Ponzoni and James, 1978). If the selection of parents is based on the character whose heritability is being estimated, it does not affect the regression of offspring on parents, either single parents or mid-parent values, but it reduces the precision because it reduces the variance of the parents (see A. Robertson, 1977a). Selection can, however, improve the precision if two groups of parents are selected, one with high values and one with low values, and offspring are reared only from these selected groups. The gain in precision comes from devoting all the available facilities to the more extreme families, which give the most information about the regression. When equal numbers of offspring and selected parents are measured, the optimal proportion of parents to select in each group is about 5 per cent. For details see Hill and Thompson (1977).

Problems

10.1 What would be the heritability estimated from each of the following correlations or regressions, assuming that resemblance due to environment or dominance was negligible?

- | | |
|---|--------|
| (1) Regression of offspring on father | = 0.21 |
| (2) Regression of offspring on mother | = 0.27 |
| (3) Correlation of full sibs | = 0.34 |
| (4) Regression of offspring on mean of parents | = 0.32 |
| (5) Correlation of half sibs | = 0.02 |
| (6) Regression of female offspring on mother's sister | = 0.03 |
| (7) Regression of daughters on dams, within sires | = 0.09 |

[Solution 48]

10.2 The following data were obtained in a study of the adult height of people in two West African villages. Female heights were adjusted to male equivalents so that the means were the same in males and females. Derive what you regard as the most reliable estimate of the heritability, and its standard error. What other component of covariance, in addition to V_A , can be derived from the data?

<i>Offspring-parent regressions ± standard errors</i>			
	<i>Father</i>	<i>Mother</i>	<i>Mid-parent</i>
Sons	0.323 ± 0.058	0.454 ± 0.057	0.705 ± 0.085
Daughters	0.291 ± 0.044	0.420 ± 0.048	0.683 ± 0.063
Both	0.303 ± 0.036	0.424 ± 0.038	0.654 ± 0.052

Standard deviations (inches): Males 2.5; Females 2.3

Data from Roberts, D.F. *et al.* (1978) *Ann. Hum. Genet.*, 42, 15–24.

[Solution 58]

10.3 In the study used for Problem 10.2 the sib correlations given below were also obtained, the marriage customs of the people providing both paternal and maternal half sibs. The sexes did not differ in their correlations and are combined. Use these data to partition the variance of height in this population. (Standard errors of the components are not given in the solution.) How do the components estimated here compare with those estimated in Problem 10.2?

Full sibs	0.406 ± 0.035
Paternal half sibs	0.140 ± 0.056
Maternal half sibs	0.257 ± 0.101

[Solution 68]

10.4 Show that the intraclass correlation of twins can be estimated from an analysis of variance by $t = (B - W)/(B + W)$, where B and W are the mean squares between pairs and within pairs respectively. [Solution 78]

10.5 Skin-fold thickness provides a useful measure of (human) fatness. The table gives the correlation of skin-fold thickness in twins aged under 10 and between 10 and 15. Estimate the heritabilities in the two groups. What can be deduced about resemblance due to common environment?

	<i>Under 10</i>	<i>10–15</i>
MZ	0.64	0.91
DZ	0.38	0.42

Data from Brook, C.G.C. *et al.* (1975) *Brit. Med. J.*, 1975, 2, 719–21.

[Solution 88]

10.6 The table gives the mean squares from an analysis of variance of a random-breeding population of *Drosophila melanogaster*. The character was the number of sternopleural bristles. These are bristles on the sides of the thorax, the numbers on one side being counted. There were 62 males (sires) each mated to 3 females (dams). Each female laid eggs in one vial. The bristles of 10 male and 10 female offspring of each dam were counted. Calculate the correlation of half sibs and of full sibs, and estimate the components of variance that can be separated by these data.

	<i>Males</i>	<i>Females</i>
Between sires	3.894	4.461
Between dams within sires	2.198	2.061
Within dams	1.125	0.893

Data from Sheridan, A. K. *et al.* (1968) *Theor. Appl. Genet.*, **38**, 179–87. [Solution 98]

10.7 Show that if the correlation of full sibs is 0.75, the heritability of the character cannot be greater than 0.5. The full-sib correlation of weaning weight in mice is 0.8; what is the maximum heritability compatible with this? [Solution 108]

10.8 A study of morphological variation in a population of *Geospiza fortis*, one of Darwin's Finches in the Galapagos, provides the following data on the depth of the bill. How would you interpret these data?

Regressions, ± s.e.

Offspring–midparent	0.82 ± 0.15
Offspring–father	0.47 ± 0.17
Offspring–mother	0.48 ± 0.13

Correlations, ± s.e.

Full sibs	0.71 ± 0.12
Father–mother	0.33

Data from Boag, P. T. & Grant, P. R. (1978) *Nature*, **274**, 793–4. [Solution 118]

10.9 Suppose that a population has bred with assortative mating for long enough to reach equilibrium. There is a correlation of $r = 0.4$ between mates, the choice of mates being based purely on phenotypic values of a particular character. The correlation of full sibs with respect to this character is $t = 0.3$. The character is known to have negligible dominance variance and to be negligibly affected by environment common to sibs. What is the estimate of the heritability in the population, and what would the heritability be if there were no assortative mating? [Solution 128]

10.10 If the heritabilities given below were estimated by the methods indicated, and in every case the total number of individuals measured was 400, what would be approximately the standard errors of the estimates, assuming that there was no environmental resemblance between sibs, and that the data came from unselected individuals of a random breeding population?

- (1) $h^2 = 0.5$ from regression of sons on fathers; 200 fathers.
- (2) $h^2 = 0.6$, from regression of the mean of 3 offspring (full sibs) on the mean of their parents.
- (3) $h^2 = 0.4$, from correlation of full sibs in families of 5.
- (4) $h^2 = 0.2$, from correlation of half sibs in 20 families of half sibs with no full sibs among them.

[Solution 138]

11 Selection:

I. The Response and its Prediction

Up to this point the treatment of metric characters has been mainly concerned with the description of the genetic properties of a population as it exists under random mating, with no influences tending to change its properties; now we have to consider the changes brought about by the action of a breeder or experimenter. There are two ways in which the action of the breeder can change the genetic properties of the population; the first by the choice of individuals to be used as parents, which constitutes selection, and the second by control of the way in which the parents are mated, which embraces inbreeding and crossbreeding. Selection in one form or another is the means whereby all improvement of domesticated animals and plants has been made. In this chapter, therefore, we start consideration of the most important application of quantitative genetics. Selection means breeding from the 'best' individuals, whatever 'best' may be. The ways in which the theory of quantitative genetics can help in this are, first, by showing how to choose individuals with the best breeding values and, second, by predicting the outcome so that different breeding schemes can be compared. The simplest form of selection is to choose individuals on the basis of their own phenotypic values. This is the form of selection to be considered in this chapter. Chapter 13 will show how information from relatives can help to identify individuals with the best breeding values. Experimental selection in laboratory animals provides a means of studying the genetics of metric characters. This aspect of selection will be dealt with in the next chapter.

In any practical selection programme the number of parents used is more or less restricted, with the result that some inbreeding inevitably takes place, and its effects are superimposed on those of the selection. Any inbreeding effects that there may be will at first be ignored, but they will have to be taken into consideration later.

The basic effect of selection is to change the array of gene frequencies in the manner described in Chapter 2. The changes of gene frequency themselves, however, are now almost completely hidden from us because we cannot deal with the individual loci concerned with a metric character. The effects of selection that can be observed are therefore restricted mainly to changes of the population mean. Let us, however, consider the underlying changes of gene frequencies a little further in general terms.

To describe the change of the genetic properties from one generation to the next we have to compare successive generations at the same point in the life-cycle of the individuals, and this point is fixed by the age at which the character under study is measured. Most often the character is measured at about the age of sexual maturity or

on the young adult individuals. The selection of parents is made after the measurements, and the gene frequencies among these selected individuals are different from what they were in the whole population before selection. If there are no differences of fertility among the selected individuals or of viability among their progeny, then the gene frequencies are the same in the offspring generation as in the selected parents. Thus artificial selection – that is, selection resulting from the action of the breeder in the choice of parents – produces its change of gene frequency by separating the adult individuals of the parent generation into two groups, the selected and the discarded, that differ in gene frequencies. Natural selection, operating through differences of fertility among the parent individuals, or of viability among their progeny, may cause further changes of gene frequency between the parent individuals and the individuals on which measurements are made in the offspring generation. Thus there are three stages at which a change of gene frequency may result from selection: the first through artificial selection among the adults of the parent generation; the second through natural differences of fertility, also among the adults of the parent generation; and the third through natural differences of viability among the individuals of the offspring generation. Though natural differences of fertility and viability are always present, they are not necessarily always relevant, because they are not necessarily connected with the genes concerned with the metric character.

Response to selection

The change produced by selection that chiefly interests us is the change of the population mean. This is the *response* to selection, which will be symbolized by R ; it is the difference of mean phenotypic value between the offspring of the selected parents and the whole of the parental generation before selection. The measure of the selection applied is the average superiority of the selected parents, which is called the *selection differential*, and will be symbolized by S . It is the mean phenotypic value of the individuals selected as parents expressed as a deviation from the population mean, that is from the mean phenotypic value of all the individuals in the parental generation before selection was made. To deduce the connection between response and selection differential, let us imagine two successive generations of a population mating at random, as represented diagrammatically in Fig. 11.1. Each point represents a pair of parents and their progeny, and is positioned according to the mid-parent value measured along the horizontal axis and the mean value of the progeny measured along the vertical axis. The origin represents the population mean, which is assumed to be the same in both generations. The sloping line is the regression line of offspring on mid-parent. (A diagram of this sort, plotted from actual data, was given in Fig. 10.1.) Now let us regard a group of individuals in the parental generation as having been selected – say those with the highest values. These pairs of parents and their offspring are indicated by solid dots in the figure. The parents have been selected on the basis of their own phenotypic values, without regard to the values of the progeny or of any other relatives. Let S be the mean phenotypic value of these selected parents, expressed as a deviation from the population mean. And similarly let R be the mean deviation of their offspring from the population mean. Then S is the selection differential and R is the

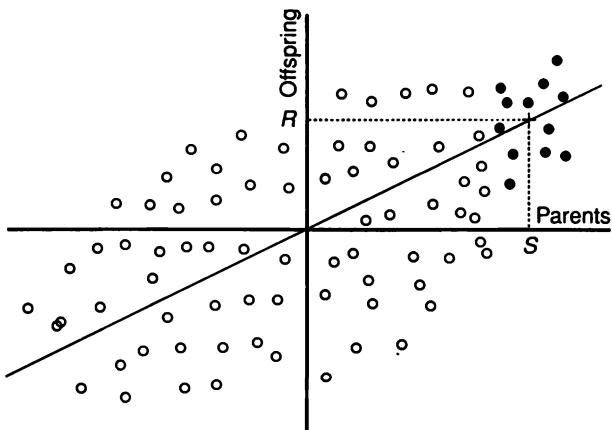


Fig. 11.1. Diagrammatic representation of the mean values of progeny plotted against the mid-parent values, to illustrate the response to selection, as explained in the text.

response. The point marked by the cross represents the mean value of the selected parents and of their progeny, and its expected position is on the regression line as shown. Thus the ratio R/S is equal to the slope of the regression line. The connection between the response and selection differential is therefore given by

$$R = b_{OP}S \quad [11.1]$$

We saw in the last chapter that the regression of offspring on mid-parent is equal to the heritability, provided there is no non-genetic cause of resemblance between offspring and parents. To this we must add the further condition that there should be no natural selection: that is to say, that fertility and viability are not correlated with the phenotypic value of the character under study. Provided these conditions hold, therefore, the ratio of response to selection differential is equal to the heritability, and the response is given by

$$R = h^2S \quad [11.2]$$

The connection between the response and the selection differential, expressed in equation [11.2], follows directly from the meaning of the heritability. We noted in the last chapter (equation [10.2]) that the heritability is equivalent to the regression of an individual's breeding value on its phenotypic value. The deviation of the progeny from the population mean is, by definition, the breeding value of the parents, and so the response is equivalent to the breeding value of the parents. Thus it follows that the expected value of the progeny is given by $R = h^2S$.

There is one point at which the situation envisaged in deducing the equations of response does not coincide with what is actually done in selection. We supposed the individuals of the parent generation to have mated at random and the selection to have been applied subsequently. In practice, however, the selection is usually made before mating, on the basis of the individuals' values and not the mid-parent values. The effect of this is that the individuals, when regarded as part of the whole parental population, have been mated assortatively. Assortative mating, however,

has very little effect on the mid-parent regression, as we noted in the last chapter, and this feature of selection procedure can therefore be disregarded.

Another point that should be mentioned concerns the linearity of the regression. It is drawn as a straight line in Fig. 11.1 and assumed to be linear in equation [11.1]. In most circumstances this assumption is justified and equation [11.1] is valid to a near approximation. Non-linearity could be produced by dominance. Consideration of Fig. 7.2 will show that if all the variance were due to a single locus with dominance, the regression of breeding value on genotypic value would be non-linear. However, when there are more than a few loci the distribution of genotypic values becomes nearly normal, as can be seen from Fig. 6.1, and the regression is effectively linear (Gimelfarb, 1986). For a discussion of non-linear regressions see also Robertson (1977b).

Prediction of response

The chief use of these equations of response is for predicting the response to selection. Let us consider a little further the nature of the prediction that can be made. First, it is clear that equation [11.1] is not a prediction but simply a description, because the regression of offspring on parent cannot be measured until the offspring generation has been reared. The equation $R = h^2S$, however, provides a means of prediction from knowledge of the heritability obtained from previous generations. The heritability for use in the prediction can be estimated by any method, such as a sib-correlation, and does not have to be estimated from the offspring-parent regression. The selection differential S cannot be known till after the parents have been selected, but its expected value can be predicted, as will be explained in the next section. The following example illustrates the calculation of the selection differential and response, and the prediction of the response by equation [11.2].

Example 11.1

The data in the table come from the experiment of Clayton, Morris, and Robertson (1957) on selection for abdominal bristle number in *Drosophila melanogaster*. The heritability of bristle number was first estimated in the base population before selection and found to be 0.52, as stated in Example 10.1. The parents selected for high bristle number had a mean superiority of $S = 40.6 - 35.3 = 5.3$ bristles. The predicted response, by equation [11.2], is $0.52 \times 5.3 = 2.8$. The observed response was $37.9 - 35.3 = 2.6$ bristles.

Generation	Mean of all measured	Mean of those selected	Selection differential	Response	
				Exp.	Obs.
Parents	35.3	40.6	5.3	2.8	—
Offspring	37.9	—	—	—	2.6

The prediction of response is valid, in principle, for only one generation of selection. The response depends on the heritability of the character in the generation from which the parents are selected, so responses in later generations cannot, strictly speaking, be predicted without redetermining the heritability in each

generation. There are two reasons why the heritability is expected to change. First, if there is a response the gene frequencies must change, and the heritability depends on the gene frequencies. This change is not likely to be apparent for some considerable time because gene frequency changes are small unless only a few loci are involved. Second, the selection of parents reduces the variance and the heritability. This takes place in the early generations. It will be explained briefly later and will be ignored meantime. These expected changes in the heritability are not large, however, and experiments have shown that the response is usually maintained with little change over several generations – up to five, ten, or even more. This will be seen in the graphs of responses to selection given later in this chapter and in the next.

Selection differential and intensity of selection

The selection differential can be predicted in advance provided that two conditions hold: the phenotypic values of the character being selected are normally distributed, and selection is by *truncation*. Truncation selection means that individuals are chosen strictly in order of merit as judged by their phenotypic values, no individual being selected that is less good than any of those rejected. Under these conditions the selection differential depends only on the proportion of the population included among the selected group, and the phenotypic standard deviation of the character. The dependence of the selection differential on these two factors is illustrated diagrammatically in Fig. 11.2. The graphs show the distribution of phenotypic values, which is assumed to be normal. The individuals with the highest values are supposed to be selected, so that the distribution is sharply divided at a point of truncation, all individuals above this value being selected and all below rejected. The arrow in each figure marks the mean value of the selected group, and S is the selection differential. In graph (a) half the population is selected, and the selection differential is rather small: in graph (b) only 20 per cent of the population is selected, and the selection differential is much larger. In graph (c) 20 per cent is again selected, but the character represented is less variable and the selection differential is consequently smaller. The standard deviation in (c) is half as great as in (b) and the selection differential is also half as great.

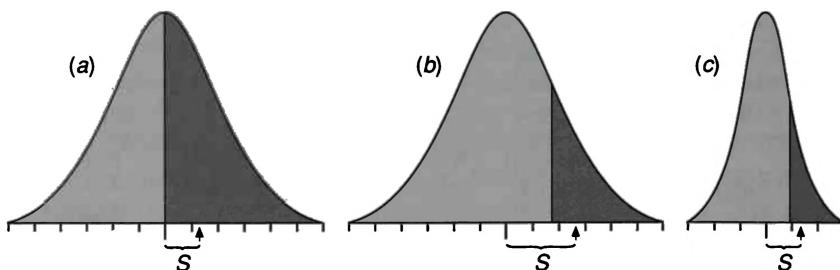


Fig. 11.2. Diagrams to show how the selection differential, S , depends on the proportion of the population selected, and on the variability of a normally distributed character. All the individuals in the stippled areas, beyond the points of truncation, are selected. The axes are marked in hypothetical units of measurement.

- (a) 50 per cent selected; standard deviation 2 units: $S = 1.6$ units.
- (b) 20 per cent selected; standard deviation 2 units: $S = 2.8$ units.
- (c) 20 per cent selected; standard deviation 1 unit: $S = 1.4$ units.

The standard deviation, which measures the variability, is a property of the character and the population, and it sets the units in which the response is expressed, i.e., so many pounds, millimetres, bristles, etc. The response to selection may be generalized if the selection differential is expressed in terms of the phenotypic standard deviation, σ_P . This standardized selection differential S/σ_P is called the *intensity of selection*, symbolized by i . Then the selection differential is

$$S = i\sigma_P$$

and the expected response in equation [11.2] becomes

$$R = ih^2\sigma_P \quad \dots [11.3]$$

By noting that $h = \sigma_A/\sigma_P$, where σ_A is the standard deviation of breeding values (square root of the additive genetic variance), we may write this equation in the form

$$R = ih\sigma_A \quad \dots [11.4]$$

which is sometimes used in comparisons of different methods of selection.

The intensity of selection, i , depends only on the proportion of the population included in the selected group and, provided the distribution of phenotypic values is normal, it can be determined from tables of the properties of the normal distribution. If p is the proportion selected, i.e., the proportion of the population falling beyond the point of truncation, and z is the height of the ordinate at the point of truncation, then it follows from the mathematical properties of the normal distribution that

$$\frac{S}{\sigma_P} = i = \frac{z}{p} \quad \dots [11.5]$$

Thus, given only the proportion selected, p , we can find out by how many standard deviations the mean of the selected individuals will exceed the mean of the population: that is to say, the intensity of selection, i . The graphs in Fig. 11.3 show the relationship between i and p . Values of i for given values of p are tabulated in Appendix Table A. The relationship between i and p given in equation [11.5] applies, strictly speaking, only to a large sample: that is to say, when a large number of individuals have been measured, among which the selection is to be made. When selection is made out of a small number of measured individuals, the mean deviation of the selected group is a little less. The intensity of selection can be found from tables of deviations of ranked data (Table XX of Fisher and Yates, 1963). The two lower curves in Fig. 11.3 show the intensity of selection when selection is made from samples of 20 and of 10 measured individuals. Appendix Table B gives some values of i when selection is made from small numbers.

Example 11.2

A comparison of the expected and observed responses under different intensities of selection was made by Clayton, Morris, and Robertson (1957), studying abdominal bristle number in *Drosophila*. The heritability was first determined by three methods,

Continued

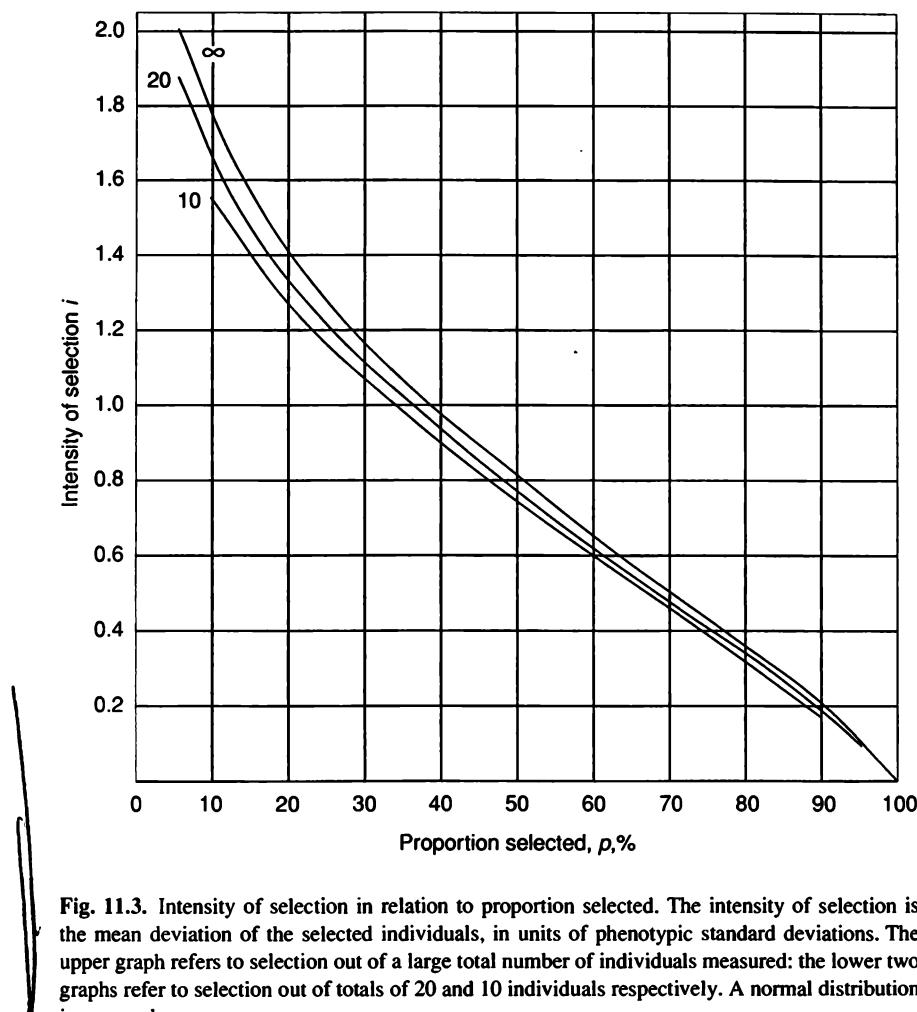


Fig. 11.3. Intensity of selection in relation to proportion selected. The intensity of selection is the mean deviation of the selected individuals, in units of phenotypic standard deviations. The upper graph refers to selection out of a large total number of individuals measured; the lower two graphs refer to selection out of totals of 20 and 10 individuals respectively. A normal distribution is assumed.

Example 11.2 *continued*

which yielded a combined estimate of 0.52 (see Example 10.1). The standard deviation of bristle number (average of the two sexes) was 3.35. Selection at four different intensities was carried on for five generations, both upward and downward (i.e., both for increased and for decreased bristle number). In each case 20 males and 20 females were selected as parents, the intensity being varied by the number out of which these were selected, as shown in the first column of the table. The intensities of selection corresponding to these proportions selected are given in the second column of the table. The expected responses are then found from equation [11.3]. Under the most intense selection, for example, it is $R = 1.4 \times 3.35 \times 0.52 = 2.44$. The observed responses are given in the last two columns of the table. Although they do not agree very precisely with expectation, they show how the change made by selection falls off as the intensity of selection is reduced.

Continued

Example 11.2 continued

<i>Proportion selected, p</i>	<i>Intensity of selection, i</i>	<i>Mean response per generation</i>		
		<i>Expected</i>	<i>Up</i>	<i>Down</i>
20/100 = 0.20	1.40	2.44	2.62	1.48
20/75 = 0.267	1.23	2.14	2.20	1.26
20/50 = 0.40	0.97	1.65	1.46	0.79
20/25 = 0.80	0.34	0.59	0.28	-0.08

The selection differential, S in equation [11.2], and the intensity of selection, i in equation [11.3], refer to the mean superiority of all the parents used. Males and females may differ in the amount of selection that can be applied to them. Some characters, for example, can be measured only on one sex, so that no selection can be applied to the other sex. If the selection applied to males and females differs, the values of S or i to be used are the unweighted means for the two sexes, i.e.,

$$S = \frac{1}{2}(S_m + S_f) \quad \dots [11.6a]$$

$$\text{or} \quad i = \frac{1}{2}(i_m + i_f) \quad \dots [11.6b]$$

Thus if only females, for example, can be selected, $S = \frac{1}{2} S_f$, and the expected response is $R = \frac{1}{2} h^2 S_f$. This can be related to equation [11.1] by noting that $\frac{1}{2} h^2$ is the regression of offspring on single parents. The sexes may also differ in the numbers used as parents. The value of S or i is then again as given in equations [11.6] because half the genes in the offspring come from each sex of the parents regardless of the numbers.

Improvement of response

The ways in which the breeder might improve the rate of response can be seen from the equation $R = ih^2\sigma_p$. The phenotypic standard deviation, σ_p , merely specifies the units of measurement. The heritability can be increased by reducing the environmental variation through attention to the techniques of rearing and management, by multiple measurements when these are possible, and to a small extent by assortative matings as explained in the last chapter. Increasing the intensity of selection seems at first sight to be a straightforward way of improving the response, but there are two factors that limit what the breeder can do in this way. First, the reproductive rate of the organism limits the intensity of selection because the proportion selected for breeding can never be less than the proportion needed for replacement. That is to say, two individuals are needed on average to replace each pair of parents. So the more prolific the organism the more intense the selection that can be applied. If males mate with more than one female, males have more offspring than females, and selection can be more intense on males than on females. Suppose, for example, that each male mates with 10 females, and the females have on average 5 daughters

each. To allow for replacement of the females the proportion of females selected cannot be less than 1/5, but males have on average 50 sons, allowing selection of 1/50 to replace the males. The upper limits of the intensity of selection in this case would be $i_f = 1.40$ for females and $i_m = 2.42$ for males, giving a net intensity of $i = 1.91$ by equation [11.6b]. The second factor that limits the intensity of selection is the consequence of population size and inbreeding. Inbreeding almost always reduces reproductive fitness and characters related to it, as will be explained in Chapter 14. So the number of parents used must be large enough to keep this inbreeding depression to an acceptable level when balanced against the gain from selection. In experimental work, for example, one might decide to use no fewer than 10 or 20 pairs of parents. When the number of parents to be used is fixed in this way, the intensity of selection can be increased only by measuring more individuals out of which to select the parents.

Generation interval The number of offspring available for selection depends not only on the parents' reproductive rate but, in many organisms, also on how long the breeder is willing to wait before he makes the selection. The progress per unit of time is usually more important than progress per generation which has been dealt with so far. The interval of time between generations is therefore an important factor in reckoning the response to selection. By waiting until more offspring have been reared before he makes the selection, the breeder can increase the intensity of selection and the response per generation, but in doing so he inevitably increases the generation interval and may thereby reduce the response per unit of time. There is thus a conflict of interest between intensity of selection and generation interval, and the best compromise must be found between the two. Increasing the number of offspring will pay up to a certain point, and beyond this point it will not. The optimal number of offspring cannot be stated in general terms, and each case must be worked out according to its special circumstances.

In reckoning the generation interval under any scheme of selection, distinction must be made between discrete and overlapping generations. When generations are discrete the offspring are kept till the last-born are mature; selection is then made and the selected individuals are all mated at more or less the same time. The generation interval is the interval between the matings made in successive generations. When generations overlap, replacement of the parents by selected offspring is a more or less continuous process, the selected offspring being mated as soon as they are mature. The generation interval can be calculated as the average age of the parents at the birth of their selected offspring. The problem is to find the optimal age for discarding the parents. Example 11.3 below illustrates the calculation of the optimal procedure both when generations are discrete and when they are overlapping. When fewer male parents are used than female, the generation intervals of males and females, L_m and L_f , must be distinguished as well as the intensities of selection, i_m and i_f . What has to be maximized is the ratio $(i_m + i_f)/(L_m + L_f)$. The solution, which can be found graphically, is explained by Ollivier (1974), where the solutions for the main farm animals are given. Sometimes it is necessary to distinguish four intensities of selection and generation intervals, according to whether the male and female parents are used to breed sons or daughters. The overall

ratio i/L is then calculated as $\Sigma i/\Sigma L$, where Σi is the sum of the four intensities and ΣL is the sum of the four generation intervals (Rendel and Robertson, 1950).

Example 11.3

Let us suppose that selection is to be applied to some character in mice, and that speed of progress per unit of time is the aim. The question is: how many litters should be raised? To find the number of litters that will give the maximum speed of progress, we have to find the intensity of selection and the generation interval. The ratio of the two will then give the relative speed. The actual speed could be obtained by multiplying by the heritability and the standard deviation, but these factors will be assumed to be independent of the number of litters raised. A comparison of the expected rates of progress per week is made in the table. The comparison is made for two different average sizes of litter, meaning the number of young reared per litter. It is assumed that the character to be selected can be measured before sexual maturity, and that first litters are born when the parents are 9 weeks old, subsequent litters following at intervals of 4 weeks. It is assumed also that the population is large enough to be treated as a large sample in reckoning the intensity of selection, and that equal numbers of males and females are selected.

The generation interval depends on the procedure for selection and mating. Two different procedures are considered. First, selection is deferred till all the litters have been measured. All the selected mice are then mated at the same time, and generations are discrete. The generation interval, tabulated under L , is the age of the parents at the birth of the last litter to be raised. This is a realistic procedure for laboratory experiments. Second, the mice required are selected equally from all the litters raised. For example, if two litters are raised, one per litter is selected from first litters and one per litter from second litters, making a total of two per family. The intensity of selection is the same as by the first procedure provided the total numbers are large. The selected mice are mated as soon as they are mature, and generations are therefore overlapping. The generation interval, tabulated under \bar{L} , is the parents' mean age at the birth of their litters. This procedure is more realistic for a practical breeding programme.

The optimal number of litters is shown by the maximal value of the ratio i/L or i/\bar{L} . It differs according to the litter size and the procedure. With the first procedure,

$n = 6$						$n = 4$					
N	L	\bar{L}	p	i	i/L	i/\bar{L}	p	i	i/L	i/\bar{L}	
1	9	9	0.333	1.10	0.122	0.122	0.500	0.80	0.089	0.089	
2	13	11	0.167	1.50	0.115	0.136	0.250	1.27	0.098	0.115	
3	17	13	0.111	1.71	0.101	0.132	0.167	1.50	0.088	0.115	
4	21	15	0.083	1.85	0.088	0.123	0.125	1.65	0.079	0.110	

n = number of young reared per litter.

N = number of litters raised.

L = generation interval, in weeks, to last litter.

\bar{L} = mean generation interval, all litters (see text).

p = proportion selected.

i = intensity of selection.

if 6 young are raised per litter the maximum rate of response is attained by rearing only one litter; if 4 young are reared it is worth while to wait for second litters but not for third litters. With the second procedure, if 6 young are reared the parents should be discarded after their second litters; if 4 young are reared, the rate of progress is the same when parents are discarded after their second or their third litters. These conclusions could hardly have been guessed at without the computations shown in the table.

Measurement of response

When one or more generations of selection have been made, the measurement of the response actually obtained introduces several problems. These are matters of procedure rather than of principle and will be only briefly discussed.

Variability of generation means

The first problem arises from the variability of generation means. Inspection of any graph of selection shows that the generation means do not progress in a simple regular fashion, but fluctuate erratically and more or less violently. The consequence of this variation between generation means is that the response can seldom be measured with any pretence of accuracy until several generations of selection have been made. The best measure of the average response per generation is then obtained from the slope of a regression line fitted to the generation means, as illustrated in the following example, the assumption being made that the true response is constant over the period.

Example 11.4

Figure 11.4 shows the results of 11 generations of two-way selection for body weight in mice (Falconer, 1953). On the left the 'up' and 'down' lines are shown separately, and on the right the divergence between the two is shown. Linear regression lines are fitted to the observed generation means. (The first generation of selection is disregarded because the method of selection was different.) The estimates of the average response per generation, with their standard errors, are as follows:

Up	0.27 ± 0.050
Down	0.62 ± 0.046
Divergence	0.88 ± 0.036

The difference between the upward and downward responses will be discussed in the next chapter.

The causes of variation of the generation means will be considered more fully in the next chapter. Here we simply note what the causes are, and consider what can be done to reduce this variation in the response from generation to generation. The causes of the variation are: random genetic drift, sampling errors in estimating the generation means, differences in the selection differential, and environmental factors. Variation due to random drift and sampling errors can be reduced only by increasing the numbers selected and measured. Differences in the selection differential can be allowed for in a way to be explained in the next sections.

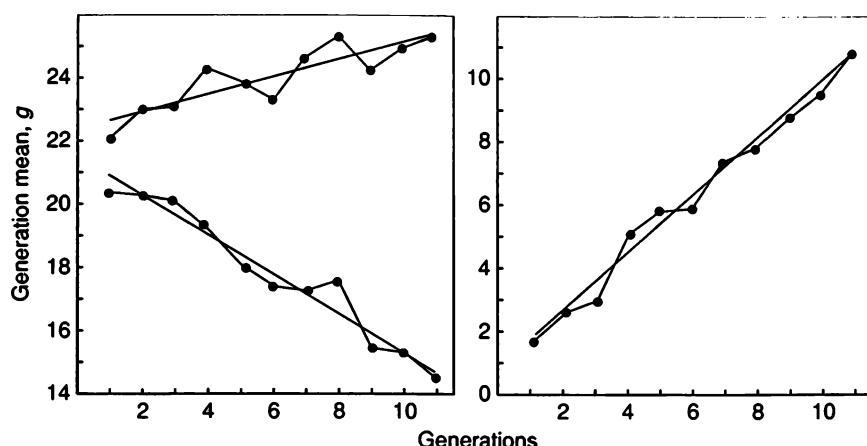


Fig. 11.4. Two-way selection for 6-week weight in mice. On the left the response of the two lines are shown separately. On the right the 'divergence' is shown, i.e., the difference between the upward- and downward-selected lines. See Example 11.4. (Based on Falconer, 1953.)

Environmental differences between generations can arise from many causes, climatic, nutritional, and general management. The obvious way of eliminating environmental fluctuations from an assessment of the rate of response is by keeping an unselected control population. On the assumption that environmental differences affect the selected and control populations alike, the difference between them estimates the genetic improvement made by selection. The use of a control, however, does not always improve the precision with which the response is estimated. Both populations are subject to random drift and to sampling errors, and the sampling variance of the difference between the two lines is the sum of the sampling variance of each line separately. Furthermore, the scale of an experiment is usually limited by the facilities available, so that the use of a control necessitates a reduced population size of the selected line. If the selected line and the control both have half the population size of a single selected line, then the use of a control quadruples the sampling variance of the response measured as deviations from control, and so doubles the standard error. This loss of accuracy may counterbalance the gain from eliminating environmental differences. The relative accuracy of the response measured by use of a control can be improved if the 'control' is not an unselected population but is selected in the opposite direction. This is known as 'two-way', or 'divergent', selection and is illustrated in Fig. 11.4. Each selected line acts as a 'control' for the other and the response is measured as the divergence between the two lines. The elimination of some of the variation from generation to generation by this means is clearly seen in Fig. 11.4. In the absence of environmental differences between generations, the precision is the same, relative to the magnitude of the response, as that of a single line occupying the same total facilities. The reason for this is that the standard error of the difference between the lines is doubled, as explained above, but the response is also approximately doubled because both lines are selected. An unselected control, however, is preferable to two-way selection if, for practical reasons, one is interested only in the change in one direction, because the response is not always equal in the two directions, a point that will be discussed in the next chapter.

Random changes of environment reduce the precision with which the response is estimated, but they do not bias the estimate. A more serious difficulty arises from environmental trends, i.e., progressive changes with time, because what looks like a response to selection may really be due to an environmental trend. This makes it difficult to assess the effectiveness of selection in the improvement of domesticated animals and plants, because without a control there is no sure way of deciding how much of the improvement is due to selection and how much to improved management. However, when generations overlap, as with farm animals, it is possible to assess the genetic improvement without an unselected control by making comparisons between contemporary individuals belonging to different generations (see Smith, 1962). For detailed consideration of the measurement of responses and the use of controls, see Hill (1972a) and Muir (1986). Experimental evidence about the usefulness of controls is reviewed by Hill (1972b).

Weighting the selection differential

In experimental selection the selection differential as well as the response has to be measured because it is the relationship between the two, and not the response alone, that is of interest from the genetic point of view. We have to distinguish between the expected and the effective selection differential, because in practice the individual parents do not contribute equally to the offspring generation. Differences of fertility are always present, so that some parents contribute more offspring than others. To obtain a measure of the selection differential that is relevant to the response observed in the mean of the offspring generation, we therefore have to weight the deviations of the parents according to the number of their offspring that are measured. The expected selection differential is the simple mean phenotypic deviation of the parents as defined at the beginning of this chapter; the effective selection differential is the weighted mean deviation of the parents, the weight given to each parent, or pair of parents, being their proportionate contribution to the individuals that are measured in the next generation.

The weighting of the selection differential takes account of a good part of the effects of natural selection. If the differences of fertility are related to the parents' phenotypic values for the character being selected, then this natural selection will either help or hinder the artificial selection. If, for example, the more extreme phenotypes are less fertile, or more frequently sterile, then natural selection is working against artificial selection. By weighting the selection differential we measure the joint effects of natural and artificial selection together. A comparison of the effective (i.e., weighted) with the expected selection differential may thus be used to discover whether natural selection is operative.

Example 11.5

The experiment with mice, as shown in Fig. 11.4, was carried through 30 generations in the upward direction and 24 generations in the downward direction (see Falconer, 1955). Comparisons are made in the table between the effective

Example 11.5 continued

(weighted) and the expected (unweighted) selection differentials in the two lines. The period of selection is divided into two parts and the comparisons are made separately in each. Throughout the whole of the upward selection there was virtually no difference between effective and expected selection differentials, and we can conclude that natural selection was unimportant as a factor influencing the response.

The situation in the downward selected line, however, is different, the effective selection differential being less than the expected, especially in the second part. From this we can conclude that natural selection was operating in favour of large size, thus hindering the artificial selection and reducing the response obtained, particularly in the latter part of the experiment. The main way in which natural selection acted in the small line was through fertility. The smaller mice tended to have fewer young in their litters and to be more often sterile, with the result that the smallest of the selected parents were represented by fewer measured offspring. There was also another way in which the effective selection differential was reduced which was formally equivalent to natural selection. Smaller mice tend to be more reactive and 'jumpy' than larger mice, and very small mice often escape and are lost during the changing of cages. Those lost in this way before they reproduced proved to be the smallest of the selected mice.

Direction of selection	Generation numbers	Selection differential per generation (g)		
		Expected	Effective	Effective Expected
Upwards	1-22	1.39	1.36	0.98
	23-30	1.08	1.09	1.01
Downwards	1-18	1.03	0.96	0.93
	19-24	0.82	0.70	0.86

The weighting of the selection differential does not take account of the whole effect of natural selection, because it makes no allowance for any differences of viability among the offspring that may be related to their phenotypic values.

Realized heritability

The response per generation, such as is illustrated in Fig. 11.4, describes what happened, but it takes no account of the amount of selection applied. A means is therefore needed of showing how the response is related to the selection differential. This is done by expressing the response as a proportion of the selection differential, i.e., the ratio R/S , in the following way. The general means are plotted against the cumulated selection differential. That is to say, the selection differentials, appropriately weighted, are summed over successive generations so as to give the total selection applied up to the generation in question. Responses plotted in this way are illustrated in Fig. 11.5. The average value of the ratio R/S is then given by the slope of the regression line fitted to the points.

The response to selection can be used as a means of estimating the heritability in the base population, because the expected value of the ratio R/S is the heritability, rearrangement of equation [11.2] giving

$$h^2 = R/S$$

... [11.7]

The heritability estimated in this way is called the realized heritability because it is primarily a description of the response and may, for several reasons, not provide a valid estimate of the heritability in the base population. First, for reasons to be explained at the end of this chapter, the responses of characters with high heritabilities are expected to be somewhat reduced after the first generation of selection, so that the realized heritability after the first generation will underestimate the heritability in the base population. Second, if there are systematic changes due to environmental trends or inbreeding depression, these will be included in the response unless they are removed by comparison with a control line. Changes due to random drift are also confounded with the response. The effects of random drift, which will be discussed in the next chapter, can be assessed empirically by replication of the selection. Figure 11.5 provides a clear example of realized heritabilities being disturbed by other factors. Selection in the two directions yielded very different realized heritabilities; each is a valid description of the response, but they cannot both be valid estimates of the heritability in the base population. The reasons for responses being different in the two directions will also be discussed in the next chapter. Unbiased estimates of the heritability in the base population can be obtained from response to selection by REML, which uses information from the selection response as well as genetic relationships among all individuals within each generation and across generations (e.g., Meyer and Hill, 1991). REML is the best method for estimating realized heritability, since it takes account of drift and selection.

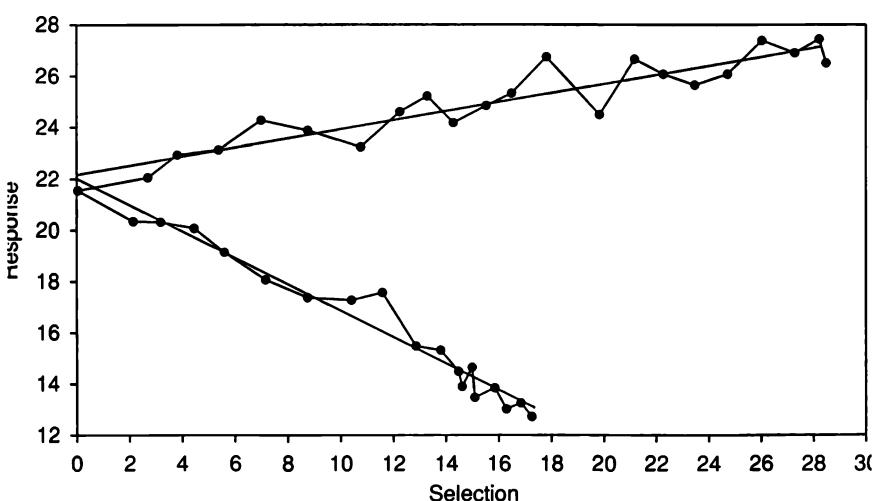


Fig. 11.5. Two-way selection for 6-week weight in mice. The generation means are plotted against the cumulated selection differentials, as explained in the text. The slopes of the regression lines fitted to the points measure the realized heritabilities, which were 0.175 for upward selection and 0.518 for downward selection. (After Falconer, 1954.)

Maternal effects

Maternal effects as a source of resemblance between mothers and offspring were described in Chapter 9. They can lead to anomalous responses to selection, which can be greater or smaller than would be expected without the maternal effect, and they can even cause the response to be in the ‘wrong’ direction, or maladaptive (Kirkpatrick and Lande, 1989). An example of a character that may respond in the ‘wrong’ direction is litter size in mice (Falconer, 1960a, 1965b). When females were selected for having had large litters, their offspring reared in those large litters had to share the milk among a larger number of litter-mates. Consequently the offspring grew more slowly and were smaller as adults. Smaller mice tended to have smaller litters, so this maternal effect worked in the direction opposite to the selection. In this two-way experiment the upward-selected line had smaller litters in the first and second generations than the downward-selected line.

If a character is subject to a maternal effect, detailed knowledge of the maternal effect is needed before the response to selection can be reliably predicted, or an estimate of the heritability from the observed response can be relied on.

Change of gene frequency under artificial selection

It was pointed out at the beginning of this chapter that the change of the population mean resulting from selection is brought about through changes of the gene frequencies at the loci that influence the character selected. But since the effects of the loci cannot be individually identified, the changes of gene frequency cannot be followed in practice. It is possible, however, to deduce an approximate expression connecting the intensity of selection, i , with the coefficient of selection, s , acting on individual loci. The approximate change of gene frequency can then be found by substituting the appropriate value of s in the formulae given in Chapter 2.

The effect of selection for a metric character on one of the loci concerned may be pictured in the manner illustrated in Fig. 11.6. This refers to a locus with two alleles and shows only the two homozygous genotypes, A_1A_1 and A_2A_2 . The position of

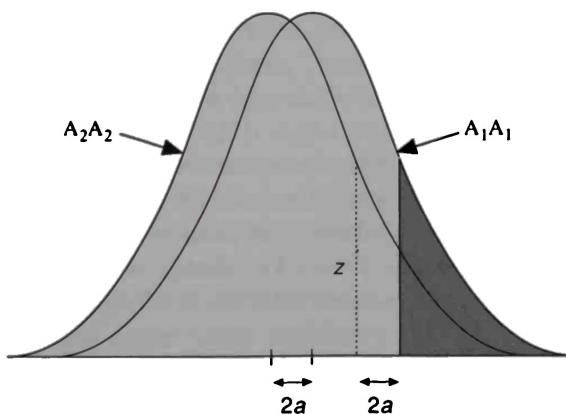


Fig. 11.6. Selection for a metric character operating on one of the loci concerned.

the heterozygous genotype will be considered later. The two genotypes are shown as having equal frequencies, but this is not necessary to the argument. The homozygous genotypes differ in their mean phenotypic values by $2a$ units of measurement in the notation of earlier chapters (see Fig. 7.1). The distribution of phenotypic values within each genotype is depicted, this variation arising from other loci as well as from environmental causes. It is assumed that both distributions are normal and that the variance within each genotype is the same. The solid vertical line marks the point of truncation, to the right of which all individuals of both genotypes are selected.

The coefficient of selection is deduced by finding the relative fitness of the two genotypes, i.e., the relative proportions that survive through being selected. Let p be the proportion of A_1A_1 that survive, shown by stippling in the figure. Now imagine the truncation point is moved down by $2a$ units, as shown by the broken line, so that the same proportion p is cut off from the A_2A_2 genotype by this new truncation. The proportion of the A_2A_2 genotype that is actually selected is p minus the proportion lying between the two truncation lines. Provided the separation between the two genotypes, i.e., $2a$, is small relative to the standard deviation, the area of the A_2A_2 curve between the two truncation lines is $2az$, where z is the height of the ordinate. The proportion of the A_2A_2 genotype corresponding to this area is $2az/\sigma_p$, where σ_p is the phenotypic standard deviation. From equation [11.5], $z = ip$, and so the proportion of A_2A_2 actually selected is $p - 2ai/\sigma_p = p(1 - 2ai/\sigma_p)$. In Chapter 2 the coefficient of selection referred to the reduced fitness of the genotype selected against, which is here A_2A_2 . The coefficient of selection against A_2A_2 is obtained from its relative fitness as

$$1 - s = \frac{\text{fitness of } A_2A_2}{\text{fitness of } A_1A_1} = \frac{p(1 - 2ai/\sigma_p)}{p}$$

from which the coefficient of selection against A_2A_2 becomes

$$s = i \frac{2a}{\sigma_p} \quad (\text{approx.}) \quad \dots [11.8]$$

This relationship is valid for any degree of dominance, though only two genotypes have been considered in its derivation. If A_1 is completely dominant, the heterozygotes are included with the A_1A_1 genotype, and if A_1 is completely recessive they are included with A_2A_2 . In either case the change of gene frequency is given approximately by equation [2.8], which is $\Delta q = -sq^2(1 - q)$, where q is the frequency of A_2 . If there is no dominance, the coefficient of selection acting on the heterozygote is defined in Chapter 2 as $\frac{1}{2}s$. The difference in mean between A_1A_2 and A_1A_1 is a , and the relationship equivalent to equation [11.8] is $\frac{1}{2}s = ia/\sigma_p$, which is the same as equation [11.8]. The change of gene frequency can therefore be obtained by substituting s from equation [11.8] into equation [2.7], which is $\Delta q = -\frac{1}{2}sq(1 - q)$. The conditions under which equation [11.8] provides a reasonable approximation for s are examined by Latter (1965), and a more general derivation is given by Kimura and Crow (1978).

Equation [11.8] shows how the two ways of expressing the 'strength' of selection – by the intensity and by the coefficient of selection – are related to each other.

The change of mean of a quantitative character can be derived in the two corresponding ways, and the equivalence of the two derivations provides a check on equation [11.8]. The change of mean can be derived from s and Δq as follows. Consider a single locus with no dominance. From equation [7.2], the mean with $d = 0$ is $M = a(p - q) = a(1 - 2q)$, where q is the initial gene frequency. The change of mean is $\Delta M = a(1 - 2q_1) - a(1 - 2q)$, where q_1 is the new gene frequency. This reduces to $\Delta M = -2a\Delta q$. Substituting for Δq from equation [2.7] gives $\Delta M = asq(1 - q)$. Equation [11.8] allows us to put s into terms of i and this gives $\Delta M = 2ia^2q(1 - q)/\sigma_P$. Now, when $d = 0$, $2a^2q(1 - q) = V_A$, by equation [8.5], V_A being the additive variance due to the locus under consideration. Summing over all loci gives the change of mean in terms of the total additive variance as $\Delta M = iV_A/\sigma_P = (iV_A/V_P)\sigma_P = ih^2\sigma_P$, and this is the response to selection given by equation [11.3]. Thus equation [11.8] provides a connection between the change of mean derived from s and Δq , and the response derived from i and h^2 . The same equivalence can be demonstrated for a dominant gene if the approximation of neglecting $(\Delta q)^2$ is made.

The quantity $2a/\sigma_P$ in equation [11.8] is the difference of value between the two homozygotes, expressed in terms of the phenotypic standard deviation. This quantity will be referred to as the *standardized effect* of the locus. Equation [11.8] will be used in the next chapter to draw some tentative conclusions about the standardized effects of loci giving rise to selection responses.

Effects of selection on variance

The genetic variance depends on the gene frequencies, as shown in Fig. 8.1. A change of genetic variance is therefore expected when gene frequencies change in response to selection. The change of variance cannot be predicted, but it is likely to be small during the first few generations because gene frequencies change slowly unless there are genes with large effects. Changes of variance over a longer period are described in the next chapter.

There is, however, one cause of change which operates immediately, with the first selection. For reasons explained below, selection reduces the variance and the heritability in the progeny of the first selection. There is a further, but progressively smaller, reduction in subsequent generations. This reduction of variance caused by selection is known as the *Bulmer effect*. How it happens is, briefly, as follows; for a full explanation, see Bulmer (1985, Ch. 9).

A group of selected parents represents one tail of the phenotypic distribution, and in consequence their phenotypic variance must be less than that of the whole population from which they are selected, as was pointed out in Chapter 10. If V_P is the phenotypic variance before selection and k the factor by which it is reduced, then the phenotypic variance, V_P^* , in the selected parents is

$$V_P^* = (1 - k)V_P$$

The factor k depends on the intensity of selection. When selection is by truncation of a normal distribution, then

$$k = i(i - x) \quad \dots [11.9]$$

where i is the intensity of selection and x is the corresponding deviation of the point of truncation from the population mean. (Values of i and x are given in Appendix Table A.) The additive variance among the selected individuals can be deduced as follows. The correlation between breeding values, A , and phenotypic values, P , is h (equation [10.3]). The square of the correlation is the proportion of the variance of A that is associated with variation of P . Thus only the proportion h^2 of the additive variance is affected by the reduced phenotypic variance in the selected individuals. V_P is reduced by the factor k and the proportion h^2 of V_A is reduced by the same factor. Thus the additive variance among the selected individuals is

$$V_A^* = (1 - h^2 k) V_A$$

where V_A is the additive variance in the population before selection.

The reduction of the additive variance can be described in terms of gametic phase disequilibrium. This was mentioned in Chapter 8 as the consequence of one form of non-random mating, and is represented by the covariance term in equation [8.10]. The covariance due to disequilibrium here is $-h^2 k V_A$; being negative, it reduces the variance. The reason why negative disequilibrium is generated can be understood in the following way. Suppose we could choose a set of individuals all with the same genotypic value, and suppose we could record the magnitude of the effect on the character of each gene in every individual. We would then find that the gene-effects were negatively correlated in the individuals; in other words, there would be a negative covariance of gene-effects. (This is essentially the same phenomenon as the one explained at the end of Chapter 9 in the section on 'Competition'.) Of course individuals selected by their phenotypic values do not have identical genotypic values, but their genotypic values are more alike than those of a randomly chosen set of individuals, and so a negative disequilibrium covariance is generated by the selection.

Table 11.1 Variance components in selected parents and their progeny. V_P and V_A are the variances and h^2 the heritability in the parental generation before selection; $k = i(i - x)$, equation [11.9]. Families are full sibs.

Component	Parents after selection	Progeny (Generation 1)
Phenotypic	$(1 - k) V_P$	$(1 - \frac{1}{2} h^4 k) V_P$
Additive	$(1 - h^2 k) V_A$	Between families $\frac{1}{2}(1 - h^2 k) V_A$ Within families $\frac{1}{2} V_A$ Total $(1 - \frac{1}{2} h^2 k) V_A$
Disequilibrium	$-h^2 k V_A$	$-\frac{1}{2} h^2 k V_A$

Now consider the additive variance in the progeny of the selected individuals, when they are mated at random to produce full-sib families. The disequilibrium due to unlinked genes is halved in the progeny, as explained in Chapter 1, but it appears only in the between-family variance for the following reason. The variance within families due to unlinked genes is not affected by the phenotypic values of the parents and so is unaffected by the selection. It is therefore simply $\frac{1}{2} V_A$. The additive variance of the means of full-sib families is half the additive variance of the

selected parents. It is therefore $\frac{1}{2}(1 - h^2k)V_A$, the disequilibrium covariance being $-\frac{1}{2}h^2kV_A$. Adding the between-family and within-family variances gives the total additive variance due to unlinked genes of $(1 - \frac{1}{2}h^2k)V_A$. The consequences of one generation of selection outlined above are summarized in Table 11.1.

Dominance variance is ignored in the above treatment; but in any case, if present, it would be very little affected by disequilibrium because only one-quarter of it appears in the between-family component. The environmental variance is, of course, the same in the progeny as in the parents before selection. With V_D and V_E unchanged, or nearly so, the reduced additive variance results in a reduced heritability. If h_1^2 and h^2 are the heritabilities in progeny and parental generations respectively, the ratio of the two can be shown from the quantities in Table 11.1 to be

$$\frac{h_1^2}{h^2} = \frac{1 - \frac{1}{2}h^2k}{1 - \frac{1}{2}h^4k} \quad \dots [11.10]$$

The first generation of response to selection depends on the heritability in the parental generation, and is predicted by equation [11.3]. The second generation of response is reduced because both the heritability and the phenotypic variance are reduced. If R_1 and R_2 are the first two generations of response the ratio of the two can be shown from equation [11.10] and Table 11.1 to be

$$\frac{R_2}{R_1} = \frac{1 - \frac{1}{2}h^2k}{\sqrt{1 - \frac{1}{2}h^4k}} \quad \dots [11.11]$$

Some representative values of this ratio are given in Table 11.2. It will be seen that with high heritabilities and high intensities of selection the expected response is about 20 per cent less in the second generation than in the first. With low heritabilities, however, the reduction is much less.

Table 11.2 The response to selection in the second generation relative to that in the first, calculated by equation [11.11], for some representative values of the heritability h^2 in the base population and of the proportions selected, p per cent.

<i>p</i> %	Heritability, h^2				
	0.9	0.7	0.5	0.3	0.1
5	0.76	0.79	0.83	0.89	0.96
20	0.78	0.81	0.85	0.90	0.96
50	0.83	0.85	0.88	0.92	0.97

Though half the disequilibrium (with unlinked genes) is lost by recombination in the progeny, more is regenerated by the next selection. The additive variance in any generation ($t + 1$) can be expressed in terms of that of the previous generation (t) by the recurrence equation

$$V_{A(t+1)} = \frac{1}{2}[1 - h_{(t)}^2k]V_{A(t)} + \frac{1}{2}V_A$$

where V_A is the additive variance in the base population (see Bulmer, 1985, eq. 9.30). The reduction of additive variance, however, does not go on indefinitely. A balance is soon reached where the increase of disequilibrium due to selection is balanced by the loss due to recombination. In the absence of linkage three or four generations are sufficient to bring the population very near to this balance, though with linked genes it takes longer. After the state of balance is reached the response is expected to remain constant until gene-frequency changes become large enough to affect it. The constancy of response usually found in experiments is therefore not in conflict with the effect of selection on variance, at least after the first generation. But the response observed after the first generation is expected to be somewhat less than would be predicted by equation [11.3] from the heritability in the base population. The discrepancy will be small when the heritability and selection intensity are low, and greater when they are higher.

Example 11.6

An experiment with sheep described by Atkins and Thompson (1986) provides an excellent verification of the effects expected from gametic phase disequilibrium generated by selection. Two-way selection was made for the length of the cannon-bone (a bone in the foreleg) in a population of Scottish Blackface sheep, the length being adjusted for body weight. The selection was applied for about 8 generations in a period of 19 years. The response was estimated from the divergence between the upward and downward selected lines. There was an unselected control line from which the parameters of the base population were estimated. The heritability in the base population was 0.56 ± 0.04 . The realized heritability was 0.52, calculated by equation [11.7] after allowance for complications which need not concern us. As expected from the effects of gametic phase disequilibrium, the realized heritability was less than that of the base population. To test whether the observed response agreed with what would be expected when disequilibrium is allowed for, the authors calculated the base-population heritability that would be required to give the observed response when disequilibrium is taken into account. They found this to be 0.57, which agrees very well with the observed value of 0.56, showing that the reduction of the response due to disequilibrium was almost exactly as expected.

The phenotypic variance was also reduced by the expected amount. It was reduced by 9 per cent in the high line and 11 per cent in the low, while the expected reduction was 10 per cent.

Problems

The effects of selection on variance, described at the end of the chapter, are to be ignored in all these problems except, as a refinement, in 11.3.

- 11.1 What would be the expected rate of progress per generation if selection were applied to the characters in the table, individuals being selected on the basis of their own phenotypic merit?

	<i>Heritability</i>	<i>Phenotypic variance</i>	<i>Proportion selected (%)</i>
(1) Body weight of mice (g)	0.37	10.7	(a) 25 (b) 50 (c) 75
(2) Development time in <i>Tribolium</i> (days)	0.18	1.7	10
(3) Female fertility of mice (litter size)	0.22	4.3	30

[Solution 9]

- 11.2** The species of Darwin's Finch in Problem 10.8 suffered severe mortality as a result of a drought in 1977. This species eats seeds, and the seeds available during the drought were mainly large and hard ones. The surviving birds, in comparison with the population before the drought, were larger in several dimensions, particularly of the bill. The mean depth of the bill in 642 birds before the drought was 9.42 mm and in 85 birds after the drought was 9.96 mm. What change in bill depth would you predict from this selective survival and the data in Problem 10.8?

Data from Boag, P.T. & Grant, P.R. (1981) *Science*, **214**, 82–4.

[Solution 19]

- 11.3** Suppose that selection for weight gain from 5 to 9 weeks in a flock of broiler chickens is planned. From the following data predict the mean weight gain after five generations of selection. In each generation 4 males and 8 females will be selected, each out of 60 birds measured. Base population: mean = 738 g, standard deviation = 111 g, heritability (from sib analysis) = 0.81.

Data based on Pym, R.A.E. & Nichols, P.J. (1979) *Brit. Poult. Sci.*, **20**, 73–86.

[Solution 29]

- 11.4** The data in the table refer to selection for increased and for decreased plasma cholesterol levels in mice. Calculate the realized heritability from the two lines separately and from the divergence. M = generation mean, P = mean of selected individuals to be used as parents of the next generation. The units are log (mg/100 ml). The sexes are averaged.

<i>Generation</i>	<i>High</i>		<i>Low</i>	
	<i>M</i>	<i>P</i>	<i>M</i>	<i>P</i>
0	2.16	2.32	2.16	2.02
1	2.26	2.34	2.06	2.00
2	2.26	2.37	2.03	1.97
3	2.33	2.41	2.02	1.96
4	2.45	2.47	2.05	2.01
5	2.44	—	2.01	—

Data from Weibust, R.S. (1973) *Genetics*, **73**, 303–12.

[Solution 39]

- 11.5** The table gives the data on the selection of mice for small body size in the last generation of the experiment shown in Fig. 11.5. Calculate the unweighted and the weighted

selection differentials. Treat female and male parents separately and then combine them. What conclusion can be drawn about natural selection?

<i>Mating number</i>	<i>Weights (g) of parents</i>		<i>Number of offspring measured</i>
	<i>Female</i>	<i>Male</i>	
1	7.6	12.4	1
2	12.4	14.5	9
3	13.5	11.6	0
4	13.7	11.6	15
5	13.2	14.3	5
6	17.2	17.1	14
7	10.7	13.8.	10
8	12.9	11.6	9
9	14.2	10.1	0
10	10.5	13.1	6

Mean of population from which parents were selected:

Females, 13.14; Males, 14.80

[Solution 49]

11.6 Suppose that you are selecting sheep for growth rate in an experiment with the following procedure. Equal numbers of males and females are selected and mated in single pairs, the numbers selected being large. Both sexes breed first when they are 2 years old, and subsequently produce lambs once each year. The average number of lambs reared to maturity is 1.2 per ewe per breeding season. Equal numbers are selected each year. For how many years should you keep the parents before replacing them by selected offspring in order to maximize the rate of progress per year? What proportion of lambs will then be selected in each year?

[Solution 59]

11.7 The breeding scheme for sheep in Problem 11.6 is not a practically realistic one. To be more realistic, assume that instead of mating each male to only one female, males are mated each to 10 females. This affects the optimal procedure, which is now to discard females when they are 4 years old, having had 3 breeding seasons, and to discard males when they are 3 years old, having had 2 breeding seasons. How much better would this be than the optimal procedure with single-pair matings? Why is the optimal age for discarding both sexes lower than in Problem 11.6?

[Solution 111]

11.8 If sows are to be selected for litter size, selection can be based on the size of their first litter or on the mean size of two or more litters. Increasing the number of litters has the advantages of increasing the intensity of selection and of increasing the heritability, but it has the disadvantage of increasing the generation length. What is the optimum number of litters for maximizing the expected response per year? Take the repeatability of litter size to be 0.409 from Problem 8.6. Assume that (i) sows have their first litters when they are 1 year old and subsequently have litters at 6-month intervals, (ii) the average number of individuals reared per litter is 8, (iii) the number selected is the number required to replace the parents. For simplicity, assume further that (iv) the number selected is large and (v) generations are non-overlapping, the offspring of selected individuals all having their first litters when the youngest is 1 year old.

[Solution 121]

- 11.9 Suppose that one of the genes affecting sternopleural bristle score in *Drosophila* is additive, that the two homozygotes differ by 0.3 bristles, and that the increasing allele is at a frequency of 0.4. What will be the frequency of this allele after the 10 per cent highest-scoring flies have been selected in two successive generations in a population with a phenotypic standard deviation of 2.0 bristles?

[Solution 131]

12 Selection: II. The Results of Experiments

In the last chapter we saw that the theoretical deductions about the effects of artificial selection are limited to the change of the population mean, and strictly speaking over only one generation. By changing the gene frequencies, selection changes the genetic properties of the population upon which the effects of further selection depend. And, because the effects of the individual loci are unknown, the changes of gene frequency cannot be predicted, and so the response to selection can be predicted only for as long as the genetic properties remain substantially unchanged. Thus there are many consequences of selection that can be discovered only by experiment. The object of this chapter is to describe briefly what seem to be the most general conclusions about these consequences that have emerged from experimental studies of selection. The most important questions to be answered by experiment concern the long-term effects of selection. For how long does the response continue? By how much can the population mean ultimately be changed? What is the genetic nature of the limit to further progress? Before dealing with the long-term effects, however, there are two questions to be considered concerning the earlier generations, during which the rate of response remains more or less constant. These are the repeatability of responses and asymmetry of responses to selection in opposite directions.

Short-term results

Repeatability of response

The variability of the responses from one generation to the next was commented on in the last chapter, and four causes were given: random drift due to the restricted number of parents, sampling error in estimating the generation mean, variation of selection differentials, and environmental factors. The question to be considered now is the variability of the overall response: if the experiment were repeated, how closely would the results agree? An answer to this question is needed before a standard error can be attached to the realized heritability as an estimate of the heritability in the base population, or to allow comparisons to be made between different experiments. We are concerned here only with the period of selection during which the response remains constant enough for a linear regression to be fitted to the generation means without significant error. The standard error of the slope of the fitted regression line can, of course, be calculated. But this does not tell us how much variation in slope there would be between replicates, because it does not take

account of the variation between replicates arising from random drift. Random drift causes changes of gene frequencies which are reflected in changes of the generation mean. In consequence, replicate lines selected independently come to drift apart in the manner that was illustrated in Fig. 3.2. The changes due to drift are cumulative, any change in one generation being carried on as the starting point for the change in the next generation. Because of the cumulative nature of the changes due to drift, the deviations from regression of any one line do not include all the variation due to drift. For this reason the standard error of the realized heritability is underestimated by the standard error of the regression. This point is illustrated in Fig. 12.1. In the experiment illustrated there were six replicates. Fig. 12.1(a) shows the response of all the replicates together treated as if they were a single large population. Fig. 12.1(b) shows the responses in three of the six replicates. Regression lines were fitted to each of the six replicates and their slopes are given in Table 12.1. The realized heritabilities can be estimated either from the single regression lines in Fig. 12.1(a) or from the means of the six replicates in Table 12.1; there is little difference between them. The standard errors, however, differ greatly.

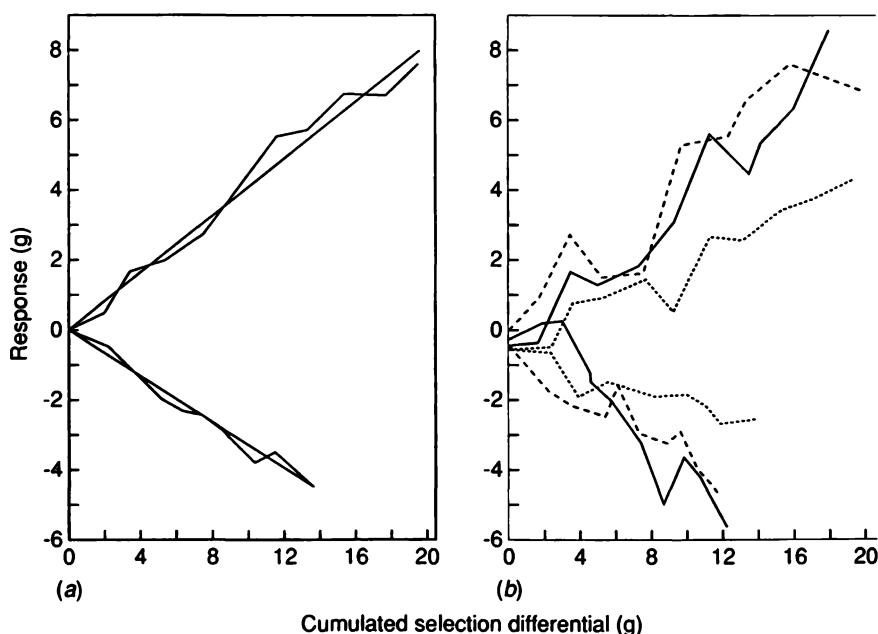


Fig. 12.1. Ten generations of two-way selection for six-week weight in mice (Falconer, 1973). Generation means, measured as deviations from controls, are plotted against cumulated selection differentials (*original data*).

- (a) The whole 'population' consisting of six replicates selected in each generation. The fitted regression lines have slopes \pm s.e. of: Upward, $b = 0.398 \pm 0.020$; Downward, $b = 0.328 \pm 0.014$.
- (b) Three of the six replicates selected in each direction. Each replicate was bred from 8 pairs of parents with minimal inbreeding, giving $N_e = 31$ (by equation [4.9]). The realized heritabilities of these and the other replicates are given in Table 12.1.

Table 12.1 Regression coefficients estimating realized heritability in replicate selection lines. The replicates are listed in order of the magnitude of their responses; those shown in Fig. 12.1(b) are marked*.

	<i>Upward selection</i>	<i>Downward selection</i>
0.457*	.	0.501*
0.448	.	0.376
0.438	.	0.365
0.390	.	0.301
0.385*	.	0.288*
0.251*	.	0.159*
Mean	0.395 ± 0.031	0.331 ± 0.046
Difference		0.064 ± 0.055

The standard errors of the single regression lines are 0.020 upwards and 0.014 downwards; the empirical standard errors calculated from the actual variation between replicates are 0.031 upwards and 0.046 downwards.

Sampling variance

The sampling variance of a realized heritability is not a straightforward matter. The following simplified account will allow an approximate standard error to be obtained. For details see Hill (1971, 1972c, d, 1980). The important conclusion is that the standard error of the regression seriously underestimates the standard error of the realized heritability; the latter can be between three and five times the former under a wide range of circumstances. Consider first the response in a single selected line, measured as the mean of the last generation, the base population mean being assumed to be known without error. Environmental differences between generations will be assumed to be negligible. There are then two sources of error in the estimation of the response: variance due to random drift, σ_d^2 , and variance due to measurement error, σ_e^2 . The first depends on the effective number of parents, N_e , and the second on the number of individuals measured, M , from which the mean is estimated. The drift variance of a line bred without selection is approximately equal to $2FV_A$ for reasons to be explained in Chapter 15 (see Table 15.1). The inbreeding coefficient F is approximately equal to $t\Delta F$, where t is the number of generations and ΔF is the rate of inbreeding, which is equal to $1/2 N_e$ (equation [4.1]). So $\sigma_d^2 = tV_A/N_e$, approximately. The drift variance of a selected line is not so simple but the same expression is likely to be a good approximation (Hill, 1980). The sampling variance from measurement error is simply V_p/M , where M is the number of individuals measured. The sampling variance of the response is therefore

$$\begin{aligned}\sigma_R^2 &= \sigma_d^2 + \sigma_e^2 \\ &= V_p \left(\frac{th^2}{N_e} + \frac{1}{M} \right) \text{ (approx.)}\end{aligned}$$

If the response is estimated as the difference between two means, as with two-way selection or a selected and a control line, the sampling variance of the response is the sum of the variances of the two lines. If the numbers measured and bred from are the same in the two lines the sampling variance of the response is twice the

above expression. If the realized heritability is obtained by dividing the response by the cumulated selection differential ΣS , then its standard error is $\sigma_R/\Sigma S$. It makes no difference to the standard error if a fixed number of parents is bred as a single population or is divided into replicate lines; an advantage of having replicate lines, however, is that an empirical standard error can then be obtained (Hill, 1971). Estimates of realized h^2 made by REML account for correlation of generation means, drift, and measurement error by including the above expressions in the variance-covariance matrix of response. Approximate 95% confidence limits are obtained as the two values of h^2 that give a log likelihood 2 less than the maximum (e.g., Shaw, 1987).

Selection experiments often yield no response over the first one or two generations, or even longer, but give a clear response later. The reason is usually that the numbers have been too small and random drift in the 'wrong' direction has nullified the response. Because of drift, a reliable estimate of the realized heritability cannot be obtained from a small population selected over a few generations. The scale of an experiment required to achieve a given degree of precision can be calculated approximately (see Nicholas, 1980).

Asymmetry of response

The experiment illustrated in Figs. 11.4 and 11.5 showed different rates of response to selection in opposite directions. Selection for increased body weight was only one-third as effective as selection for decreased body weight, when compared by the realized heritabilities. Asymmetrical responses have been found in many two-way selection experiments, and indeed most experiments show asymmetry in some degree. Asymmetry of response has important practical consequences for the following reason. The prediction of a response is made from the heritability estimated in the base population. This can be presumed to predict the mean of the responses in the two directions, and if there is asymmetry the response in one direction will fall short of expectation. Thus if a character of economic importance is selected in one direction only, the response may disappoint the breeder by being less than was expected. It would be useful to be able to predict when asymmetry is likely to occur, and particularly its direction, but this can be done only to a very limited extent. The reason is that there are several possible causes of asymmetrical responses, and only a few of these can be revealed by observations made before selection has been applied. The main causes that may generate asymmetrical responses are as follows.

1. *Random drift* If there is only one selection line in each direction, asymmetry of response can easily result from random drift, as explained in the preceding section. In any particular case, therefore, the first question must be whether the asymmetry is real in the sense that the realized heritabilities in the two directions are significantly different. Without replication of the selection lines it is not easy to prove the reality of the asymmetry. In Fig. 11.5 there was no replication and the reality of the asymmetry is therefore doubtful. In Fig. 12.1(a) there was replication and the asymmetry was proved to be no more than was expected by chance. Asymmetry due to random drift cannot be predicted.

2. *Selection differential* The selection differential may differ between the upward and downward selected lines, for several reasons. (i) Natural selection may aid artificial selection in one direction or hinder it in the other. (ii) The fertility may change so that a higher intensity of selection is achieved in one direction than in the other. (iii) The variance may change as a result of the change of mean: the selection differential will increase as the variance increases and decrease as it decreases. This is a 'scale-effect', to be discussed more fully in Chapter 17. Differences of the selection differential influence the response per generation, and the agreement between observed and predicted responses, but they affect the realized heritability only a little (Falconer, 1954). Therefore asymmetry of realized heritabilities cannot be attributed to any cause operating through the selection differential.

3. *Inbreeding depression* Most experiments on selection are made with populations not very large in size, and there is usually therefore an appreciable amount of inbreeding during the progress of the selection. If the character selected is one subject to inbreeding depression, there will be a tendency for the mean to decline through inbreeding. This will reduce the rate of response in the upward direction and increase it in the downward direction, thus giving rise to asymmetry. An unselected control population, subject to the same inbreeding depression, will reveal how much asymmetry can be attributed to this cause. Prior knowledge of the rate of inbreeding depression would allow the asymmetry of response to be predicted.

4. *Maternal effects* Characters complicated by a maternal effect may show an asymmetry of response associated with the maternal component of the character. The asymmetry in the experiment of Fig. 11.5 was of this sort. The character selected – 6-week weight of mice – may be divided into two components, weaning weight and post-weaning growth, the former being maternally determined. The weaning weights increased hardly at all in the large line but decreased very much in the small line. Thus the asymmetry of response was all in the maternal component of the character. To attribute asymmetry of response to a maternal effect, however, only transfers the problem from the character selected to another and does not explain the asymmetry.

5. *Genetic asymmetry* The additive genetic variance and the heritability depend on the gene frequencies. Additive genes contribute maximally to the heritability when the gene frequency is 0.5, and recessive genes when the recessive allele has a frequency of 0.75 (see Fig. 8.1). These will be called the 'symmetrical' gene frequencies. If all the genes affecting the character were at these symmetrical frequencies in the initial population, the realized heritabilities would gradually diminish as the gene frequencies became changed, but the diminution would be roughly equal in lines selected in opposite directions and there would be no asymmetry. Suppose, however, that the population starts with gene frequencies above or below these values. In one line the frequencies will then move away from the symmetrical values and the heritability will diminish. But in the line selected in the opposite direction the gene frequencies will move toward the symmetrical values and the heritability will increase. Thus asymmetry will develop as the gene frequencies become different in

the up- and down-lines. The response observed depends on the combined effects of all the loci, and asymmetry is to be expected if the 'average' gene frequencies are different from the symmetrical values of 0.5 for additive genes and 0.75 for recessive genes, the 'averages' being weighted for the gene effects. Asymmetry of response from this cause, however, would not be expected to appear immediately in the first few generations because it depends on differentiation in gene frequencies. Furthermore, it would be associated with non-linear responses, because it depends on the response decelerating in one line and accelerating in the other. So it could not readily explain asymmetry of responses that are not detectably non-linear. Genetic asymmetry can be looked at in a different way as the relation of the starting point to the selection limits. The theoretical limits to selection are when all favourable alleles have been fixed. Asymmetry of response will result if the initial population is not mid-way between the two limits in phenotypic value, so that the selection response has further to go in one direction than in the other. If selection favours heterozygotes, the situation is a little different because the limit in one direction is not fixation but is the equilibrium gene frequency. Asymmetry will result if the initial population is not at the point, in respect of gene frequencies, where the additive variance is maximal.

6. *Genes with large effects* Asymmetry of response that appears immediately in the first generation can result from genetic asymmetry of genes with large effects. The reason why the asymmetry is immediate is that the first selection of parents produces a large change of gene frequency, equivalent to many generations of selection on genes with small effects. The asymmetry results from the initial gene frequencies not being at the symmetrical points. If the first response is asymmetrical it follows that the regression of offspring on mid-parent values in the base population will be non-linear (Robertson, 1977b). Asymmetrical responses of this sort should therefore be predictable.

7. *Scalar asymmetry* The genetic and environmental variation may be skewed to different degrees or in opposite directions. The genetic variation will then make up a larger proportion of the total at one end of the distribution than at the other. In consequence the offspring-parent regression in the base population will be non-linear and the response asymmetrical in the first generation. The situation envisaged is shown diagrammatically in Fig. 12.2(a), where the genetic and environmental variances are skewed in opposite directions. The difference in skewness may be a scale effect, as will be explained in Chapter 17, or it may be due to genotype-environment interaction in the following way. Individuals that experience a good environment may exhibit less genetic variation than those that experience a poor environment; this is illustrated in Fig. 12.2(b). Or, individuals with high genetic values may be more susceptible to environmental variation than individuals with low genetic values, as in Fig. 12.2(c). In either case, individuals with high values will exhibit a lower heritability than those with low values. The difference in skewness could equally well be the other way round from that shown in Fig. 12.2, in which case the upward heritability would be greater than the downward. This form of asymmetrical response should, again, be predictable from a non-linear offspring-parent regression in the base population. For details see Robertson (1977b).

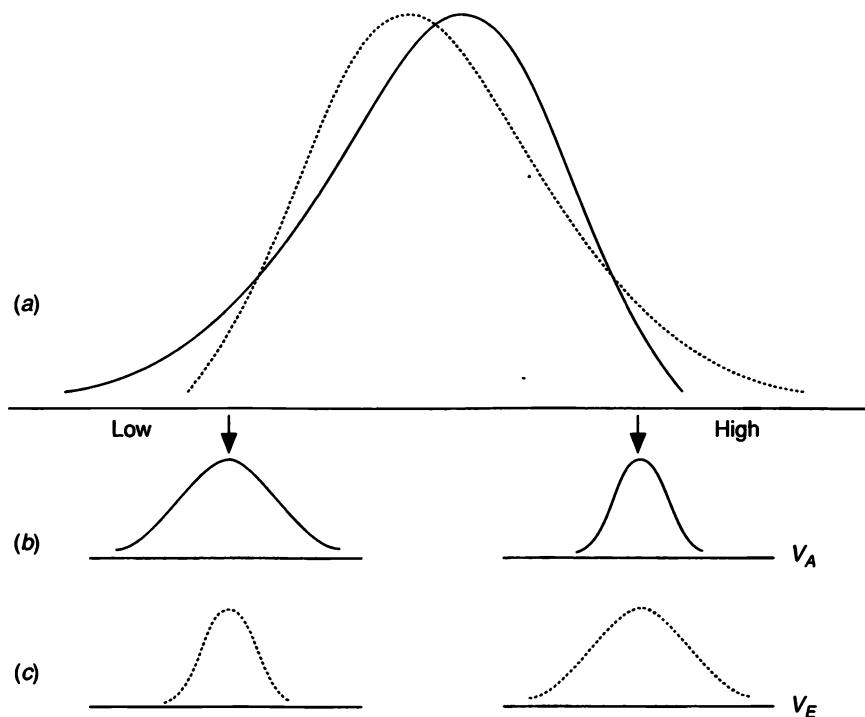


Fig. 12.2. Frequency distributions illustrating scalar asymmetry. (a) shows the additive genetic variation (solid line) with negative skewness, and the environmental variation (dotted line) with positive skewness. (b) shows the additive genetic variation among individuals whose environmental values are at the points marked by the arrows. (c) shows the environmental variation among individuals whose breeding values are at the points marked by the arrows. In both situations upward selection will give a lower realized heritability than downward selection. The figure is drawn roughly to scale, and if the distributions in (b) and (c) represented selected individuals the upward heritability would be about 0.1 and the downward about 0.4.

8. Indirect selection Sometimes the criterion of selection is not quite the same as the character measured for assessing the response. Then, if the measured character is not linearly related to the selection criterion, asymmetry of response may result. Baptist and Robertson (1976) selected *Drosophila* for body size by inducing them to crawl as far as they could through a series of slits of decreasing diameter. The criterion of selection was the number of slits traversed, and this responded symmetrically. The procedure, however, selected not only for body size but also for activity. Small flies are more active than large and this led to a non-linear relation between body size and slit score. In consequence, body size responded less to upward selection than to downward.

With all these possible causes it is not surprising that asymmetrical responses are often found. Nor is it surprising that the cause operating in a particular case is hard to identify. Some of the causes make prediction of asymmetry possible but others do not and, until asymmetrical responses are better understood, the prediction of rates of response from the heritability in the base population will remain somewhat

unreliable. There is, however, one generalization that can be made. It is that if the character selected is a component of natural fitness, asymmetry should be expected, with selection towards increased fitness giving a slower response than selection towards decreased fitness. There are three reasons for this expectation. First, these characters usually show inbreeding depression, though an unselected control would reveal this cause. Second, characters subjected to natural selection in the past are likely to have favourable alleles at frequencies above their symmetrical points. Third, inbreeding depression indicates directional dominance, which leads to non-linear offspring-parent regressions, especially if there are genes with large effects. The expectation of asymmetrical responses, with increased fitness responding less, has been confirmed by experiments. A survey of published experiments on *Drosophila*, *Tribolium*, mice, chickens, and quail (Frankham, 1990) found that 24 out of 30 experiments confirmed the expectation, and the 6 where the asymmetry was in the opposite direction were readily accounted for by special features of the experimentation. Inbreeding was not the cause of the asymmetry in the experiments that had suitable controls.

Long-term results

The outcome of selection over a long period is unpredictable, at least with our present understanding. There are two reasons for this: first, the outcome depends on the properties of the individual genes contributing to the response, which cannot be determined by observation at the outset; and, second, because mutation produces new variation whose nature we cannot predict. There is, however, a body of theory that allows us to predict what would happen if certain conditions were present, and consequently to say what were the probable reasons for what actually happened. This theory will now be explained in outline. We shall deal first with responses in the absence of mutation, and then we shall consider the effects of mutation. Some features commonly found in experiments are shown in Fig. 12.3. These will be commented on when they bear on the theory.

Selection limits

Without the creation of new variation by mutation, the response to selection cannot be expected to continue indefinitely. Sooner or later the genes segregating in the base population will be brought to fixation (or equilibrium if there is over-dominance) by the selection or the accompanying inbreeding. The response will therefore slowly diminish and finally cease. The population is then at a 'plateau' or selection limit. Examples of this type of long-term result are shown in Fig. 12.3(b) and (c). The diminishing responses in several selection experiments have been found to fit well to exponential curves (Bünger and Herrendörfer, 1994; Bünger, Renne, and Dierl, 1994). The parameters of such a fitted curve provide better estimates of the initial realized heritability and of the population mean at the selection limit. The questions to be asked about selection limits are: how large is the total response in relation to the initial variation, and how long does it take to get to the limit? First, some empirical answers from experiments. We consider only two-way selection because of the complications of asymmetry. The total response, R_T , is the

difference between the divergent lines when both are at their limits; it will be referred to as the *range*. The number of generations taken to get to a limit is not easy to decide because the response gradually decreases as the limit is approached. The time-scale can, however, be more precisely expressed as the *half-life* of the response. This is the number of generations taken to go half-way to the limit. The results of four experiments are summarized in Table 12.2; two refer to *Drosophila* and two to mice. The ratios of the two means at the limits varied widely. The litter size of the high line of mice was only 1.6 times that of the low line (column 4), but the high line of *Drosophila* had 8 times as many bristles as the low (column 1). The range varied from 3.6 to 28 additive genetic standard deviations, or from 1.7 to 20 phenotypic standard deviations. All the experiments took roughly 20–30 generations to reach the limits, and the half-lives varied from 7 to 12 generations.

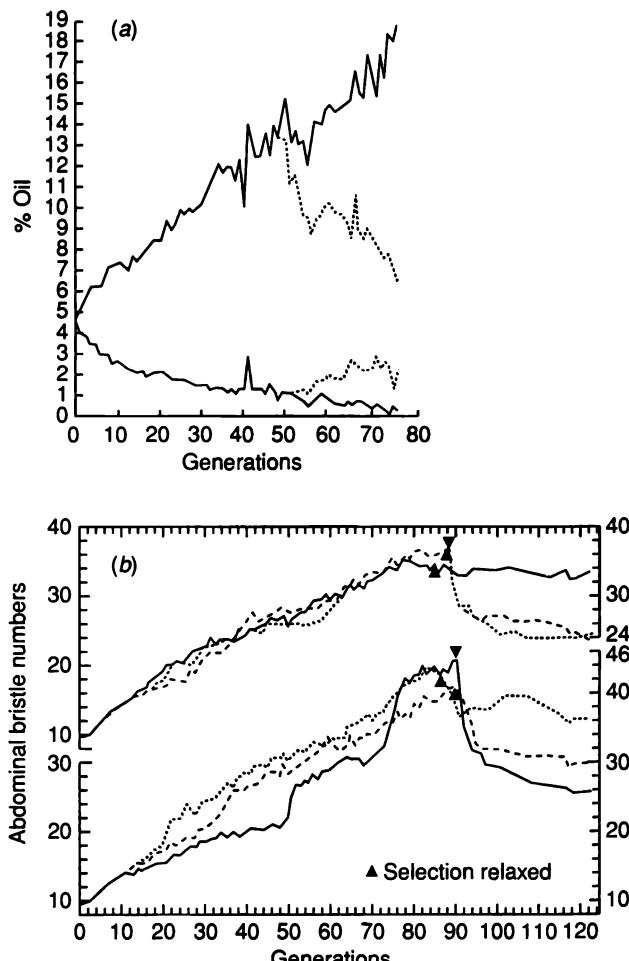
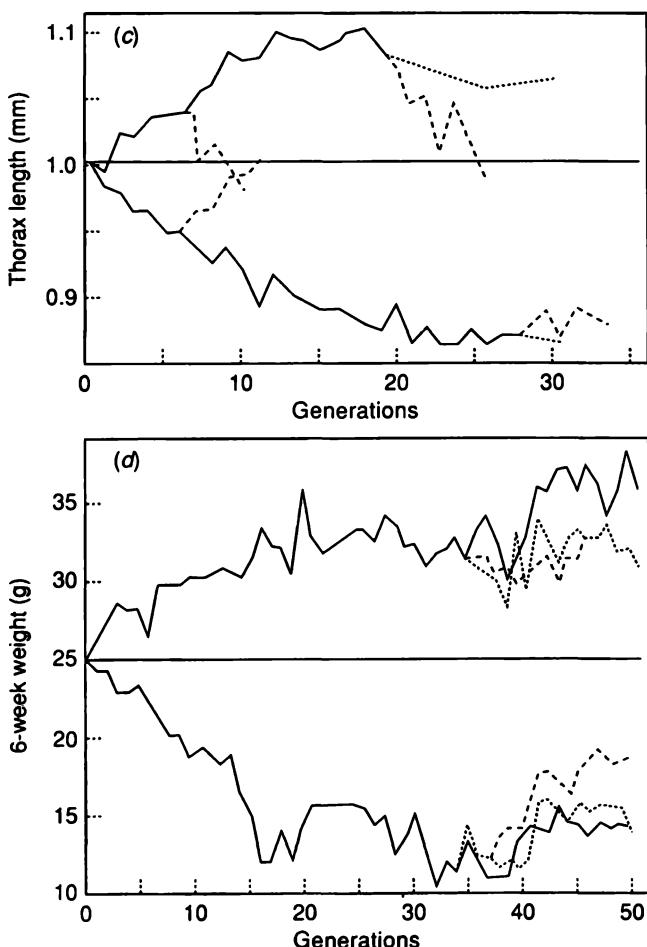


Fig. 12.3. Four experiments illustrating long-term responses.

- (a) Two-way selection for oil-content of maize seeds. Broken lines are reversed selection. (After Dudley, 1977.)
- (b) Six replicate lines of *Drosophila melanogaster* selected upwards for abdominal bristle number. Selection was suspended at the points marked. (After Yoo, 1980a.)

In these and most other experiments, selection has taken the mean far beyond the range of variation in the base population. Though the total responses in Table 12.2 may be impressive when reckoned in terms of the variation present in the original population, they are not at all spectacular when compared with the achievements of the breeders of domestic animals. For example, after selection to the two limits, the large mice were 2.5 times the weight of the small mice. In contrast, the weights of the largest breeds of dogs are about 100 times the weights of the smallest breeds (Stockard, 1941). The reason for the disappointing results of experimental selection when viewed against the differences between the breeds of domestic animals is that experiments are carried out with closed populations, usually of not very large size. The breeder of domestic animals in contrast, by intermittent crossing, casts his net



(c) *Drosophila melanogaster*, thorax length. (After F. W. Robertson, 1955.)

(d) Mouse, six-week body weight. (Adapted from Roberts, 1966b.)

Dashed lines are responses to selection in the reverse direction; dotted lines are responses to natural selection, with artificial selection suspended.

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far wider in the search for genes favourable to his purpose and can utilize new mutations that have occurred elsewhere, some of which may have large effects.

What, then, can theory tell us about long-term selection?

Table 12.2 Limits to selection in four experiments. Explanation in text.

		Experiment			
		(1)	(2)	(3)	(4)
Observed ratio of means	H/L	8.0	1.3	2.5	1.6
Observed range	R_T/σ_A	28	20	16	3.6
Theoretical maximum	R_T/σ_P	20	12	8	1.7
Effective population size	$R_{(\max)}/\sigma_P$	82	52	22	8
Duration (generations):					
	Total (approx.)	30	20	25	20
	Half-life	10	7	9	12
	Half-life/ N_e	0.4	0.3	0.6	0.4
Observed/Maximum:	Range	0.24	0.22	0.36	0.21
	Half-life	0.29	0.19	0.43	0.36
$n = R_T^2/8\sigma_A^2$		98	50	32	2
Standardized effect:	$2a/\sigma_P$	0.21	0.23	0.24	0.95

Experiments and sources

- (1) *Drosophila*, abdominal bristles: Clayton and Robertson (1957).
- (2) *Drosophila*, thorax length (Fig. 12.3c): F.W. Robertson (1955).
- (3) Mouse, 6-week weight (Fig. 11.5): Falconer (1955), Roberts (1966a).
- (4) Mouse, litter size: Falconer (1965b, 1971, 1977).

Population size in the *Drosophila* experiments is taken to be $N_e = 0.7N$.

Theory of limits The total response relative to the initial genetic variation, R_T/σ_A , depends primarily on the number of loci contributing to the variation. If, for example, there were only one additive locus with gene frequencies of 0.5, the most extreme genotypes would each appear in the base population with frequencies of 1/4; or if there were two such loci, with frequencies of 1/16. The selection limits, which are represented by the most extreme genotypes, would then be well within the range of variation found in the base population. With larger numbers of loci, the extreme genotypes are rarer in the base population and the selection limits are further removed, in σ_A units, from the original mean. It is very clear that in at least three of the experiments in Table 12.2 there are many more than 'a few' loci contributing to the variation in the base populations. The numbers of genes and their effects are inversely related because, with a given amount of genetic variation, if there are few genes they must have large effects and if there are many genes they must have small effects. Since neither the number of genes nor their effects are known in advance it is not possible to predict the limits. It is possible, however, to predict a 'theoretical maximum' for the limit, so let us pursue the theoretical consideration of the limits a little further, to find out first how the limit depends on the number of loci and then to see what the theoretical maximum can tell us.

First suppose that the population being selected is bred from a very large number of parents, so that no random fixation occurs; and suppose also that there are no overdominant loci. Then the favourable alleles at all relevant loci will be made

homozygous at the limits. In the notation of Chapter 7, the range is $\Sigma 2a$ units of measurement, i.e., the homozygote difference summed over all loci. How then does the range relate to the original additive genetic variance? In order to express this relationship in a simple way we have to make two assumptions that are certainly not true, but we can see later how the error may affect the conclusions. The first assumption is that all the loci have the same magnitude of effect on the character selected. The range is then $R_T = 2na$, where n is the number of loci, each having a homozygote difference of $2a$. The second assumption is that all the genes start at frequencies of 0.5. With these assumptions the original additive variance, by equation [8.7], is $\sigma_A^2 = \frac{1}{2} \Sigma a^2 = \frac{1}{2} na^2$. (The symbol σ_A^2 is used here rather than V_A because it simplifies the formulation when the standard deviation σ_A is involved.) Note that when gene frequencies are 0.5 the dominance deviation d does not appear in the formulation of σ_A^2 , so no assumption about the degree of dominance needs to be made. The relationship between the range and the additive variance is obtained by squaring the range, which gives

$$\frac{R_T^2}{\sigma_A^2} = \frac{4n^2 a^2}{\frac{1}{2} na^2} = 8n \quad \dots [12.1]$$

This equation will be considered later as a possible way of estimating the number of loci. The responses to be expected with other assumptions about the distributions of gene effects and gene frequencies are examined by Hill and Rasbash (1986).

The total response considered above depends on the effective population size being very large. In practice the number of parents used is seldom large enough for random drift to be ignored. Some inbreeding therefore occurs, which leads to random fixation at some loci. In other words, unfavourable alleles are fixed at some loci despite the selection against them, with the result that the total response is less than that indicated by equation [12.1]. The limit achieved then depends on the chance of fixation of the favourable allele at each locus, this chance being determined partly by the selection and partly by the inbreeding. The way in which the inbreeding and selection interact has been worked out by Robertson (1960), Hill and Robertson (1966), and Robertson (1970). The main conclusions are as follows.

The number of loci affects the issue through the coefficient of selection s acting on each locus. The larger the number of loci, the smaller are their effects and the smaller the coefficient of selection. The chance of fixation of a favourable allele depends on its initial gene frequency; the rarer it is the more likely it is to be lost. Given the initial gene frequency, the chance of fixation is a function of $N_e s$, which is the product of the effective population size and the coefficient of selection in favour of the allele. The coefficient of selection is equal to $i(2a/\sigma_p)$, where i is the intensity of selection (equation [11.8]). Therefore with a given initial frequency and a given gene effect ($2a/\sigma_p$) the chance of fixation of a favourable allele is a function of $N_e i$, the product of the effective population size and the intensity of selection. Thus the total response should be greater with larger population sizes and with more intense selection. This expectation has been confirmed by an experiment with *Drosophila* (Jones, Frankham, and Barker, 1968). Selection was carried out for 50 generations for increased abdominal bristle number in a number of lines with different intensities of selection and different population sizes. The lines with the

greatest total responses were those with the largest population size and the greatest intensity of selection. In practice, increasing the intensity of selection usually necessitates a reduction in the number of parents, which is the population size. The best compromise is to select 50 per cent. This maximizes the total response, though the rate of progress will be less than it could be with more intense selection (Robertson, 1960; Jódar and López-Fanjul, 1977).

When the population size is not large, and there is consequently some inbreeding, it is still true that the larger the number of loci the larger the response will be in relation to the original variance. If the number of loci is very large their effects must be very small and most loci become fixed by random drift before selection can fix the favourable alleles. In spite of this, the greatest response would be attained if the genetic variance were caused by a very large number of loci (strictly speaking an infinite number), even though only a small proportion of them are fixed by the selection. This is the theoretical maximum response; it is the total response that would be attained if the genetic variance were generated by an infinite number of loci. With additive genes, the theoretical maximum response is shown to be (Robertson, 1960)

$$R_{(\max)} = 2N_e ih^2 \sigma_P \quad \dots [12.2]$$

All the terms in this expression can be estimated, so the maximum response can be predicted. Note that $ih^2 \sigma_P$ is the predicted response in one generation (equation [11.3]) or the observed response over the first few generations. The maximum response to divergent selection is obtained simply by putting i as the sum of the intensities of selection in the two directions. With recessive genes, however, the maximum response may be much greater, particularly if favourable recessives have low initial frequencies. The theoretical maximum response has a half-life of $1.4N_e$ generations if all the genes are additive, or up to about $2N_e$ generations if the genes are recessive.

The theoretical maximum response is not something that can be achieved by optimal selection procedures. The response that can be achieved depends on the number of genes. The theoretical maximum is what would be achieved in the most favourable genetic situation, which is a very large number of genes – in fact an impossibly large number. As a prediction, therefore, the theoretical maximum does no more than set an upper limit to what can be expected. There is, however, some interest in comparing observed responses with their theoretical maxima because the comparison gives some idea of how far the assumptions underlying the theoretical maximum are valid. If the observed response falls far short of the maximum it cannot have been produced by a very large number of loci of equal effects and at equal gene frequencies. Ratios of observed to maximum responses are given in Table 12.2 in respect of the range and of the half-life. The ratios are between about 0.2 and 0.4, which shows that none of these responses were due to a very large number of genes having equal effects.

The extent to which fixation has been produced by inbreeding rather than selection has a bearing on the differences between replicate selection lines at the limits. If there has been much fixation by inbreeding, different replicates will have different alleles fixed at many loci. The replicates will then reach different limits and,

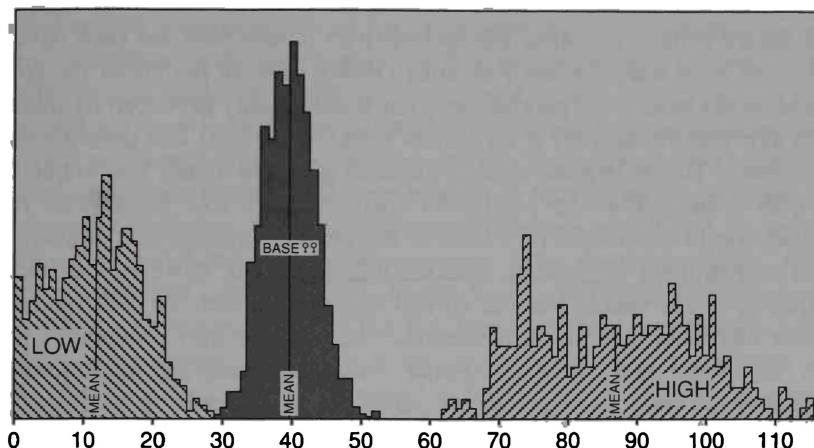


Fig. 12.4. Frequency distributions of abdominal bristle number in *Drosophila melanogaster* (females), in the base population and in the most extreme high and low lines after 35 and 34 generations of selection. (After Clayton and Robertson, 1957.)

furthermore, if they are crossed, some genetic variance will be restored on which further selection could act. If there has not been much fixation by inbreeding, selection will have fixed the same alleles at most loci. All replicates will then have the same limit and no genetic variation will be generated by crossing them.

Phenotypic variance The loss of genetic variance expected by the theory outlined above should lead to a reduced phenotypic variance. The phenotypic variance, however, is seldom found to decline as expected; often it increases. An example from *Drosophila* is provided by the experiment on abdominal bristle number in Table 12.2. The phenotypic variance in the base population and in the most extreme of the replicate high and low lines is illustrated by frequency distribution in Fig. 12.4. Selection in both directions resulted in a much increased variance. Similar increases have been found in many other experiments. The following are some possible reasons for the phenotypic variance increasing or not decreasing. First, the variance of many characters is not independent of the mean: when the mean changes under selection, the variance automatically changes with it. This is a 'scale effect' which will be more fully discussed in Chapter 17. Second, the environmental variance may increase. With the approach to fixation the frequency of homozygotes will increase. There is evidence, mentioned in Chapter 8 and to be discussed more fully in Chapter 15, that homozygotes are sometimes more variable from environmental causes than are heterozygotes. Third, if there is genotype-environment interaction, the selection is expected to increase the environmental variance, for reasons to be explained in Chapter 19. An increase of phenotypic variance from these causes might counterbalance a declining heritability and so, as can be seen from equation [11.3], maintain a more or less constant rate of response. And, fourth, the genetic variance may not decline as expected, for reasons outlined later in this chapter.

Mutation

The theory of how mutation affects responses to selection has been developed by Hill (1982a, b) and Hill and Keightley (1988); only an outline of the conclusions can be given here. New genetic variation is continually produced by mutation, but each new mutant has only a very small effect in the next few generations after its occurrence. This is because a newly mutated gene has a very low frequency, equal to $1/2N$ (where N is the population size). At such low frequencies the newly mutated genes contribute very little to the genetic variance and without selection most new mutants are lost by random drift. Selection, however, can increase the frequency of favourable mutants so that they are not lost. As their frequencies are further increased by continued selection, the variance they produce increases and they contribute more to the response. New mutations are introduced at every generation so that the response per generation attributable to mutation gradually builds up over time and eventually reaches a stable value which is not negligible. When this stable value is reached the increase of variance due to the continuous occurrence of new mutations is balanced by the loss of variance due to mutant genes being fixed by the selection or inbreeding. It may take 20 generations before mutation begins to contribute appreciably to the response, and much longer before the rate of response becomes constant. Thus mutation is important only for long-term responses. This has a practical implication: attempts to improve the rate of response by the artificial induction of mutation cannot be expected to show any success unless both the mutagenesis and the selection are continued for very many generations (Hill, 1982b).

The rate of response, when it has become constant, depends on the effective population size, N_e , the intensity of selection, i , the phenotypic standard deviation, σ_P , and the additive variance arising from new mutants in each generation, V_M . If some reasonable assumptions are made about the way mutants vary in their effects (the distribution of gene effects), and if the genes are additive (no dominance) and do not affect natural fitness, then the response per generation is expected to be

$$R = 2N_e i V_M / \sigma_P$$

(This is analogous to equation [11.3] which can be written as $R = iV_A/\sigma_P$.) Thus the rate of response is greater in a large population than in a small one, but it takes longer to reach the maximum rate because in a large population each mutant gene starts at a lower frequency. The mutational variance, V_M , can only be determined by experiment. Several experiments with *Drosophila* show that for both abdominal and sternopleural bristle numbers it is about $V_E \times 10^{-3}$ (see Hill, 1982b; Lynch, 1988); V_E is the environmental variance, which provides a convenient standard. This makes it possible to test the expectation against the observed responses in long-term selection of *Drosophila*. For the experiment illustrated in Fig. 12.3(b) the predicted rate of response from mutation was 0.3 bristle per generation and the observed rate between generations 50 and 80 was 0.4 bristle per generation (Hill, 1982b). Thus the theory of how mutation contributes to long-term responses seems to be well supported by this experiment. The generation of new variation by mutation is discussed more fully in Chapter 20.



The general picture of what ought to happen under long-term selection when mutation is taken into account is this. At first the response comes from the existing additive genetic variance in the base population. The rate of response should diminish gradually as the additive variance is depleted. Then, after perhaps 20 generations, new variance from mutated genes begins to contribute to the response, which should diminish more slowly. After some further time all the genes segregating in the base population should have been brought to fixation by the selection or the accompanying inbreeding, and further response depends entirely on the mutations that have accumulated during the selection. The response should then continue at a constant rate indefinitely: a selection limit is not expected when there is mutation affecting the selected trait but not fitness. A few experiments have shown responses continuing over very many generations without any sign of approaching a limit. One of these is illustrated in Fig. 12.3(a) in which maize was selected for oil content. The experiment was continued beyond the point shown and the high line showed no sign of reaching a limit up to generation 90 (Dudley and Lambert, 1992). Another example is the selection for high pupa weight in *Tribolium*, which continued responding for at least 75 generations (Enfield, 1977). And one of the six replicate lines in Fig. 12.3(b) was still responding at generation 88. Most experiments, however, have shown responses that end at a limit. Furthermore, most populations at a selection limit do not lack genetic variance though the response has ceased. We must therefore consider the possible reasons for these facts.

Causes of selection limits

We have to distinguish two situations: limits where no genetic variance remains, and limits where genetic variance is present but the population fails to respond. In the first situation the problem is why there is no response from mutation. The reason may be simply that the new variation generated by mutation is not enough to produce a detectable response; or, perhaps, that most mutants have an adverse effect on natural fitness. The second situation, where genetic variance is present, is a common one; why, then, does the population not respond?

The presence of genetic variance can be detected by reversing the direction of selection, or by suspending selection so that natural selection alone operates, or by inbreeding. The first two tests were applied to the selected lines in Fig. 12.3(c) and (d). The low line in Fig. 12.3(c) failed to respond to either, suggesting that no genetic variance remained. The same was true of the high line in Fig. 12.3(d), but here a renewed response occurred later in the upward-selected line which led to a new and higher limit. This was probably due to a new mutation. The high line in Fig. 12.3(c) and the low line in Fig. 12.3(d), however, responded to reversed selection, showing that additive genetic variance was present.

The following are some possible reasons for failure to respond when genetic variance is present.

1. The limit may be an extrinsic one imposed by the nature of the character or the way in which it is measured. For example, percentages have limits of 0 and 100; *Drosophila* bristle number cannot go below 0. These limits may be reached, or closely approached, with little fixation of the genes concerned. The experiment of

Fig. 12.3(a) shows this type of limit very clearly. The low line was near to a limit of zero oil content, while the high line, with no such extrinsic limit, continued to respond.

2. Fertility is often reduced in selected lines, and the selection differential may be drastically reduced in the later generations. A plot of means against generations may then show a clear approach to a limit, but a plot against the cumulated selection differential may reveal little evidence that the line has really ceased to respond. Figure 11.5 illustrates this, more particularly in the low line. In this situation the line will respond to reversed selection, though it may take some time to do so.

3. Favourable alleles may be dominant. When the unfavourable recessives are brought to low frequencies most of the variance they cause is non-additive (see Fig. 8.1). In this situation the mean will change in the unfavourable direction on inbreeding, for reasons to be explained in Chapter 14. The presence of rare unfavourable recessives was thought to be the situation in two experiments on mouse litter size, the one of Table 12.2 (Falconer, 1971) and one described by Eklund and Bradford (1977). In both cases, inbreeding and crossing, which was thought to have eliminated the unwanted recessives, produced a mean well above the original limit.

4. There could be overdominance at some loci for the character selected. At the selection limit overdominant genes would be in equilibrium at more or less intermediate frequencies. The variance they give rise to would be non-additive only. There would be an immediate change of mean towards the base level on inbreeding. There is, however, no evidence that this is a common feature of selection limits.

5. The artificial selection may be opposed by natural selection. This should be detectable by the effective (weighted) selection differential being less than the expected (unweighted). This loss of selection differential was illustrated in Example 11.5. Natural selection will also be detected by suspending the artificial selection. Selection was suspended, or 'relaxed', in all the lines in Fig. 12.3(c) and (d). With the possible exception of the high line in Fig. 12.3(c), none responded, suggesting that natural selection was not a cause of the limits.

6. Natural selection may favour heterozygotes through the joint action of artificial and natural selection. This situation occurs commonly, in contrast to simple overdominance for the character selected. It can result from a gene affecting the selected trait with deleterious fitness effects that was present in the initial base population and was increased in frequency by selection, or from new mutations arising during the course of selection. The theory of the contribution of new mutations to selection response outlined above assumes mutations affecting the selected trait are neutral with respect to fitness. However, it is likely that most mutations are deleterious. They will not then be fixed by artificial selection and a selection limit at which genetic variance remains will result from the balance between artificial and natural selection. [The pygmy gene of mice, referred to in Chapter 7, is an example.] The gene arose by mutation in a line selected for small size (MacArthur, 1949) and heterozygotes were selected because they are smaller in size. Homozygotes are smaller still but natural selection prevented the fixation of the gene because homozygotes are sterile. Thus, under combined artificial and natural selection, heterozygotes were favoured. When the selection limit is reached under this situation, there is genetic variation due to the gene but no further response. If

artificial selection is relaxed, the line responds to the natural selection. If selection is reversed, the artificial and natural selection both act in the same direction and there is an immediate and often rapid response. This may be regarded as an extreme form of asymmetrical response.

Natural selection acting through lethality rather than sterility has often been found in selected *Drosophila* lines. In the line selected for high bristle number illustrated in Fig. 12.4, a gene was present which was lethal in homozygotes and which increased bristle number by 22 in the heterozygotes, which was 5.8 times the original phenotypic standard deviation. Five of the six lines in Fig. 12.3(b) were found to contain lethals with large effects on bristle number, of up to nearly $5\sigma_p$ (Yoo, 1980b). These lethals accounted for the reduction of mean on suspension of selection. They arose by mutation during the selection and they accounted for the accelerated responses seen particularly clearly in one of the lines. The nature of the genetic variation in these lines at the end of the experiment was further analysed by Yoo (1980c). Heritabilities estimated from resemblances between relatives were found to be as high in some of the lines as in the base population.

Relevance to practical breeding It may be thought that experimental studies of long-continued selection are of little relevance to the practice of animal and plant improvement, because the breeder is concerned only with responses in the short term. Breeds of livestock, however, have already been under selection for a very long time and, in the case of broiler chickens, recent selection has been very intense. If they behave like some laboratory populations they might now be at selection limits and no longer responding to selection. If this were the case, an understanding of the nature of selection limits would be very relevant to the exploration of methods of overcoming the limit and making further progress. Fortunately, however, the main animal species do not seem to be at selection limits, because continued improvement is being made (Smith, 1984, 1988; and see further at the end of the next chapter). For discussions of the bearing of laboratory experiments on animal breeding, see Roberts (1967a, b), Falconer (1971), Eklund and Bradford (1977), Hill (1982b) and, reviewing experiments with mice, Eisen (1980).

Number of loci (effective factors) and standardized effects

Since the total response depends primarily on the number of loci, it is tempting to try to use the observed response to estimate the number of loci that have contributed to it. There are, however, serious difficulties in interpreting any number so obtained, centring on what is meant by a locus in this context. There are two main difficulties. First, genes affecting metric traits do not have equal effects; evidence described in Chapter 21 shows that there are a few genes with large effects and increasing numbers with smaller and smaller effects. Then where do we stop counting a locus as one affecting the character? The second difficulty concerns linkage. What we count as a locus is a segment of chromosome that has not recombined in the course of the selection. In recognition of linkage, loci in this context are referred to as *effective factors* and their number as the effective number. Despite these difficulties it is worth while to consider briefly how the number of effective factors may be estimated.

The effective number of loci can be estimated by equation [12.1] as $n = R_T^2/8\sigma_A^2$, where R_T is the difference between the upper and lower selection limits, and σ_A^2 is the additive variance in the base population. The estimate made by equation [12.1] is valid on three conditions: (1) all the favourable alleles have been fixed at both limits; (2) all the genes have equal effects; and (3) all the genes have initial frequencies of 0.5. Failure of conditions (1) or (2) leads to the estimate of n being too low. Failure of condition (3) leads to n being overestimated, because σ_A^2 will then be less than it would be with gene frequencies of 0.5 as required. The requirement of condition (3) can be met by estimating σ_A^2 not in the base population but in the F_2 and subsequent generations of a cross between lines at the upper and lower limits. All genes by which the lines differ are then at frequencies of 0.5. But the problem of linkage is then magnified, since all relevant genes are in complete linkage disequilibrium in the F_1 . With the reduction of disequilibrium by recombination, the genetic variance will decrease progressively in the generations following the F_2 and the number of effective factors will correspondingly increase. Some of the difficulties arising from the failure of the conditions can be overcome if data from F_1 , F_2 and backcross generations are available (Lande, 1981).

The numbers estimated by equation [12.1] are given for the four experiments in Table 12.2. They range from 2 to 98. The estimate of 2 for litter size seems too low to be believed, which suggests that the assumptions made were seriously in error. A similar experiment, but selecting only upward, yielded an estimate of $n = 164$ on the assumption that all the genetic variation was due to recessive genes at initial gene frequencies of 0.25 (Eklund and Bradford, 1977). Analysis of the upward response of the experiment in Table 12.2 with the same assumptions gives $n = 25$. This large difference according to the assumptions made emphasizes the dubious value of these estimates of gene numbers.

From the number of effective factors it is possible to obtain the standardized effects of the genes, subject to the same conditions and qualifications. Rearrangement of the expression for the additive variance given earlier, $\sigma_A^2 = \frac{1}{2}na^2$, leads to the standardized effects of the genes as $2a/\sigma_P = 2h\sqrt{(2/n)}$, where h is the square root of the heritability. The values obtained are close to 0.2 in three of the experiments in Table 12.2; the litter size experiment gives a value of 0.95 for $n = 2$, or 0.21 for $n = 25$. The coefficients of selection, s , acting on the individual genes can be estimated approximately from equation [11.8]. The intensities of selection, i , are not very different from 1, so the values of s are, very roughly, 0.2. The use of marker genes makes it possible to locate some of the genes that have contributed to a selection response. The question of how many loci cause the variation of quantitative traits will be considered more fully in Chapter 21.

Problem

- 12.1 Calculate the quantities listed in Table 12.2 from the results of the following experiment. (The last two quantities will have to be based on a guess.) Mice were selected for increased 3-6 week weight gain over 43 generations. There was no selection for decreased gain but there was an unselected control. The response was linear over the first 19 generations and reached a limit at about generation 34. The data needed are in the table, males and

females being averaged. The figures in parentheses are the generations to which the data refer.

Realized heritability (1–19)	0.20
Phenotypic standard deviation (1–19)	2.10 g
Mean selection differential per generation (1–19)	2.25 g
Mean of selected line (34–43)	23.55 g
Mean of control line (34–43)	11.90 g
Effective population size	33

Data from Barria, N, & Bradford, G.E. (1981) *J. Anim. Sci.*, **52**, 729–38. [Solution 67]

13 Selection:

II. Information from Relatives

In our consideration of selection we have up to now supposed that individuals are measured for the character to be selected and that the best are chosen to be parents in accordance with the individual phenotypic values. An individual's own phenotypic value, however, is not the only source of information about its breeding value; additional information is provided by the phenotypic values of relatives, particularly by those of full or half sibs. With some characters, indeed, the values of relatives provide the only available information. Milk-yield, to take an obvious example, cannot be measured in males, so the breeding value of a male can only be judged from the phenotypic values of its female relatives.

The use of information from relatives is of great importance in the application of selection to animal breeding, for two reasons. First, the characters to be selected are often ones of low heritability, and with these the mean value of a number of relatives often provides a more reliable guide to breeding value than the individual's own phenotypic value. And, second, when the outcome of selection is a matter of economic gain, even quite a small improvement of the response will repay the extra effort of applying the best technique. In this chapter we shall outline the principles underlying the use of information from relatives and the choice of the best method of selection.

If the family structure of the population is taken into account we can compute the mean phenotypic value of each family; this is known as the *family mean*. Suppose, then, that we have a population in which the individuals are grouped in families, which may be full or half sibs, and we have measurements of each individual and of the means of every family. How then is the additional information from the family means to be used? The problem may best be explained by reference to a specific example. Table 13.1 gives some hypothetical but realistic values of litter size in mice. There are 16 individuals whose phenotypic values are entered in the body of the table. The individuals are grouped in four full-sib families, A to D, with 4 individuals in each family. We have to choose the best 4 of these 16 individuals. Basing the choice on the individual phenotypic values we have no difficulty in choosing individuals A1, B1, and A2 with values, 13, 11, 10 respectively. But now there are two with values of 9, B2 in a good family and D1 in a bad family. Which do we choose? The decision rests on whether the differences between families are mainly genetic or mainly environmental. If they are genetic we choose B2, on the grounds that its better family mean indicates a better breeding value. If, on the other hand, the differences between families are mainly environmental we would choose D1, on the grounds that its low family mean indicates a poor environment and that

it has performed well despite this disadvantage. The problem is not only in discriminating between individuals with the same phenotypic values, but is a matter of finding the right weight to be given to the family means. With the correct weighting we might be led to choose A3 with 8 in place of B2 with 9. Application of the principles to be developed shows that this would in fact be the best procedure if these values were litter sizes of mice (see Example 13.1).

Table 13.1 Examples of individual values and family means for selection, as explained in the text.

<i>Individual</i>	<i>Family</i>			
	A	B	C	D
1	13	11	7	9
2	10	9	7	5
3	8	6	6	3
4	5	6	4	3
Family mean	9	8	6	5
Overall mean		7		

To calculate the best weighting of the family means, only three things need be known: the kind of family (whether full or half sibs), the number of individuals in the families (i.e., the family size), and the phenotypic correlation between members of the families with respect to the character. The information needed to solve what seems a complex problem is thus surprisingly simple; but the explanation of the underlying principles is not so simple. The explanation will be presented in two ways. First we shall extend the concept of heritability as a determinant of the response to selection. This introduces no new principles and leads fairly easily to a solution of the problem posed above; but it is not convenient for the solution of more complex problems found in practice. Then, under the heading of 'Index selection', a more general solution will be briefly explained. This allows information from different sorts of relatives to be combined, for example from parents as well as sibs. It also allows information from correlated characters to be used as an aid to selection, in a way to be explained in Chapter 19.

Criteria for selection

The phenotypic value of an individual, P , measured as a deviation from the population mean, is the sum of two parts: the deviation of its family mean from the population mean, P_f , and the deviation of the individual from the family mean, P_w (the within-family deviation); so that

$$P = P_f + P_w \quad \dots [13.1]$$

The procedure of selection, then, varies according to the attention paid, or the weight given, to these two parts. There are three simple procedures that can be followed. First, we may select on the basis of individual values only, as assumed in the last two chapters, giving equal weights to the two components P_f and P_w . This

is known as *individual selection*. Second, we may select on the basis of the family mean P_f only, giving zero weight to the within-family deviation P_w . This is known as *family selection*. Applied to Table 13.1, all four individuals in family A would be selected. Third, we may select on the basis of the within-family deviation P_w alone, giving zero weight to the family mean P_f . This is known as *within-family selection*. Applied to Table 13.1, the best individual in each of the four families would be selected.

Instead of one or other of these three simple procedures, we may take account of both components, P_f and P_w , but give them different weights chosen so as to make the best use of the two sources of information. This is known as selection by optimum combination or *combined selection* or, more generally, *index selection*. It represents the general solution for obtaining the maximum rate of response, and the other three simpler methods are special cases in which the weights given to the two sources of information are either 1 or 0. It is therefore in principle always the best method. The appropriate weighting of P_f and P_w will be explained later.

Simple methods

The salient features of the three simpler methods are as follows.

Individual selection Individuals are selected solely in accordance with their own phenotypic values. This method is usually the simplest to operate and in many circumstances it yields the most rapid response. It should therefore be used unless there are good reasons for preferring another method. *Mass selection* is a term often used for individual selection, especially when the selected individuals are put together *en masse* for mating, as for example *Drosophila* in a bottle. The term 'individual selection' is used more specifically when the matings are controlled or recorded, as with mice or larger animals.

Family selection Whole families are selected or rejected as units, according to the mean phenotypic value of the family. Individual values are thus not acted on except in so far as they determine the family mean. In other words, the within-family deviations are given zero weight. The families may be of full sibs or half sibs, families of more remote relationship being of little practical significance.

The chief circumstance under which family selection is to be preferred is when the character selected has a low heritability. The efficacy of family selection rests on the fact that the environmental deviations of the individuals tend to cancel each other out in the mean value of the family. So the phenotypic mean of the family comes close to being a measure of its genotypic mean, and the advantage gained is greater when environmental deviations constitute a large part of the phenotypic variance, or in other words when the heritability is low. On the other hand, environmental variation common to members of a family impairs the efficacy of family selection. If this component is large it will tend to swamp the genetic differences between families, and family selection will be correspondingly ineffective. Another important factor in the efficacy of family selection is the number of individuals in the families, or the family size. The larger the family, the closer is the correspondence between mean phenotypic value and mean genotypic value. So the conditions

that favour family selection are low heritability, little variation due to common environment, and large families.

There are practical difficulties in the application of family selection, particularly in laboratory populations. They arise from the conflict between the intensity of selection and the avoidance of inbreeding. It is generally desirable to keep the rate of inbreeding as low as possible. If the minimum number of parents is fixed by considerations of inbreeding – say at ten pairs – then under family selection ten families must be selected, since each family represents only one pair of parents in the previous generation. And, if a reasonably high intensity of selection is to be achieved, the number of families bred and measured must be perhaps twice to four times this number. Family selection is thus costly of space, and if breeding space is limited the intensity of selection that can be achieved under family selection may be quite small. The two following methods are variants of family selection.

Sib selection Some characters, as we have already noted, cannot be measured on the individuals that are to be used as parents, and selection can only be based on the values of relatives. This amounts to family selection but with the difference that now the selected individuals have not contributed to the estimate of their family mean. The difference affects the way in which the response is influenced by family size. Where the distinction is of consequence we shall use the term *sib selection* when the selected individuals are not measured, and family selection when they are measured and included in the family mean. When families are very large the two methods are equivalent, and the term family selection is then to be understood to cover both.

Progeny testing is a method of selection widely applied in animal breeding. We shall not discuss it in detail, except in so far as it can be treated as a form of family selection. The criterion of selection, as the name implies, is the mean value of an individual's progeny. At first sight this might seem to be the ideal method of selection and the easiest to evaluate because, as we saw in Chapter 7, the mean value of an individual's offspring comes as near as we can get to a direct measure of its breeding value, and it is in fact the practical definition of breeding value. In practice, however, it suffers from the serious drawback of a much-lengthened generation interval, because the selection of the parents cannot be carried out until the offspring have been measured. The evaluation of selection by progeny testing is apt to be rather confusing because of the inevitable overlapping of generations and because of a possible ambiguity about which generation is being selected, the parents or the progeny. The progeny, whose mean is used to judge the parents, are ready to be used as parents just when the parents have been tested and await selection. Thus both the selected parents and their progeny are used concurrently as parents. The difficulty of interpretation may be partially overcome by regarding progeny testing as a modified form of family selection. The progenies are families, usually of half sibs, and selection is made between them on the basis of the family means in the manner described above. The only difference is that the selected families are increased in size by allowing their parents to go on breeding. The additional, younger, members of the families do not contribute to the estimates of the

family means and are therefore selected by sib selection. Increasing the size of the selected families by unmeasured individuals does not improve the accuracy of the selection, but it reduces the replacement rate and so increases the intensity of selection that can be achieved. This is the principal advantage of progeny testing, but it can only be realized in operations on a large scale, when the danger of inbreeding is not introduced by limitation of space.

Within-family selection The criterion of selection is the deviation of each individual from the mean value of the family to which it belongs, those that exceed their family mean by the greatest amount being regarded as the most desirable. This is the reverse of family selection, the family means being given zero weight. The chief condition under which this method has an advantage over the others is a large component of environmental variance common to members of a family. Pre-weaning growth of pigs or mice might be cited as examples of such a character. A large part of the variation of individuals' weaning weights is attributable to the mother and is therefore common to members of a family. Selection within families would eliminate this large non-genetic component from the variation operated on by selection. An important practical advantage of selection within families, especially in laboratory experiments, is that it economizes breeding space, for the same reason that family selection is costly of space. If single-pair matings are to be made, then two members of every family must be selected in order to replace the parents. This means that every family contributes equally to the parents of the next generation, a system that we saw in Chapter 4 renders the effective population size twice the actual. Thus when selection within families is practised, the breeding space required to keep the rate of inbreeding below a certain value is only half as great as would be required under individual selection.

Prediction of response

To evaluate the relative merits of the different methods of selection we have to deduce the response expected from each. There is nothing to be added here about individual selection to what was said in Chapter 11. The expected response was given in equation [11.3] as $R = i\sigma_P h^2$, where i is the intensity of selection (i.e. the selection differential in standard deviations), σ_P is the standard deviation and h^2 the heritability of the phenotypic values of individuals. The response expected under family selection or within-family selection is arrived at in an analogous manner. Under family selection, the criterion of selection is the mean phenotypic value of the members of a family, so the expected response to family selection is

$$R_f = i\sigma_f h_f^2 \quad \dots [13.2]$$

where i is the intensity of selection, σ_f is the observed standard deviation of family means, and h_f^2 is the heritability of family means. In the same way, the expected response to within-family selection is

$$R_w = i\sigma_w h_w^2 \quad \dots [13.3]$$

where σ_w is the standard deviation, and h_w^2 the heritability of within-family deviations.

Heritability The concept of heritability applied to family means or to within-family deviations introduces no new principle. It is simply the proportion of the phenotypic variance of these quantities that is made up of additive genetic variance. These heritabilities can be expressed in terms of the heritability of individual values (which we shall continue to refer to simply as the heritability, with symbol h^2), the phenotypic correlation between members of families, and the number of individuals in the families, all of which can be estimated by observation. To arrive at the appropriate expressions we have to consider again how the observational components of variance are made up of the causal components, as explained in Chapters 9 and 10 (see in particular Tables 9.5 and 10.4). First let us simplify matters by supposing that all families contain a large number of individuals, so that the means of all families are estimated without error. Consider first the phenotypic variance. The intraclass correlation t between members of families is the between-group component divided by the total variance: $t = \sigma_B^2/\sigma_T^2$. Therefore the between-group component can be expressed as $\sigma_B^2 = t\sigma_T^2$, and the within-group component as $\sigma_W^2 = (1 - t)\sigma_T^2$. This expresses the partitioning of the phenotypic variance into its observational components. The total variance, written here as σ_T^2 , is the phenotypic variance, which we shall write as V_P in the context of causal components. The partitioning of the additive variance between and within families can be expressed in the same way, in terms of the correlation of breeding values, r . Thus the additive variance between families is rV_A and the additive variance within families is $(1 - r)V_A$. The dual partitioning is summarized in Table 13.2.

Table 13.2 Partitioning of the variance between and within families of large size.

Observational component	Additive variance	Phenotypic variance
Between families, σ_B^2	rV_A	tV_P
Within families, σ_W^2	$(1 - r)V_A$	$(1 - t)V_P$

This partitioning of both the additive and the phenotypic variance leads at once to the heritabilities of family means and of within-family deviations, since these heritabilities are simply the ratios of the additive variance to the phenotypic variance. Thus, when the families are large, the heritability of family means is rV_A/tV_P , or $(r/t)h^2$, since V_A/V_P is the heritability of individual values, h^2 . The values of r for different relationships were given in Table 9.3; for full sibs it is $\frac{1}{2}$ and for half sibs it is $\frac{1}{4}$. In order to be able to discuss full-sib and half-sib families at the same time in what follows, we shall retain the symbol r in the formulae instead of inserting the appropriate values of $\frac{1}{2}$ or $\frac{1}{4}$.

The foregoing account of the heritabilities of family means and within-family deviations was simplified by the supposition of large families. The simplification is not justified in practice and we must now remove it by considering families of finite size. We shall, however, suppose that all families are of equal size. The number of individuals in a family has to be taken into consideration for the following reason. If selection is based on the family mean, or on the deviations from the family mean, then it is the observed mean that we are concerned with and not the true mean. In other words we are not concerned with the observational components of variance which we have hitherto discussed, but with the variance of the observed means and

Table 13.3 Composition of observed variances with families of size n.

<i>Observed variance</i>	<i>Causal components</i>		
	<i>Observational components</i>	<i>Additive</i>	<i>Phenotypic</i>
Of family means, σ_f^2	$\sigma_B^2 + \frac{1}{n}\sigma_w^2$	$\frac{1+(n-1)r}{n}V_A$	$\frac{1+(n-1)t}{n}V_P$
Of within-family deviations, σ_w^2	$\sigma_w^2 - \frac{1}{n}\sigma_w^2$	$\frac{(n-1)(1-r)}{n}V_A$	$\frac{(n-1)(1-t)}{n}V_P$

of the observed within-family deviations. The observed means of groups are subject to sampling variance which comes from the within-group variance. If there are n individuals in a group then the sampling variance of the group mean is $(1/n)\sigma_w^2$, where σ_w^2 is the component of variance within the group. Thus the variance of observed group means is augmented by $(1/n)\sigma_w^2$, and the variance of observed deviations within groups is correspondingly diminished by the same amount. The observed variances, with family size n , are therefore made up of the observational components as shown in Table 13.3. The causal components entering into the observed variances can now be found by translating the observational components into causal components from Table 13.2. They are shown in the two right-hand columns of Table 13.3.

To find the heritabilities of family means and of within-family deviations, we have only to divide the additive component by the phenotypic component of the observed variances. Thus the heritability of family means is

$$h_f^2 = \frac{1+(n-1)r}{1+(n-1)t} h^2 \quad \dots [13.4]$$

and the heritability of within-family deviations is

$$h_w^2 = \frac{1-r}{1-t} h^2 \quad \dots [13.5]$$

Sib selection has to be distinguished from family selection, from which it differs in that the selected individuals are not measured. The appropriate heritability is best deduced by considering it as a regression in the manner of equation [10.2]. In this case it is the regression of the breeding values of the unmeasured individuals on the mean phenotypic value of their measured sibs. The covariance of these is simply the covariance of full or half sibs, i.e., rV_A , and it is not affected by the numbers of either the measured or the unmeasured individuals for reasons explained in Chapter 9. The regression is therefore rV_A/σ_P^2 , where σ_P^2 is the observed variance of the family means of the measured individuals as given in Table 13.3. Substitution gives the heritability of family means appropriate to sib selection as

$$h_s^2 = \frac{nr}{1+(n-1)t} h^2 \quad \dots [13.6]$$

The heritabilities of the different methods of selection, whose derivations have now been explained, are listed in Table 13.4.

Expected responses To deduce the expected responses is now a simple matter. Family selection will be taken for illustration. The expected response was given in equation [13.2] as $R_f = i\sigma_f h_f^2$. This expression, however, is not much use as it stands, because it does not readily allow a comparison to be made with the other methods. It will be most convenient to cast it into a form that facilitates comparison with individual selection. This can be done by substituting the expression for the heritability of family means, h_f^2 , given in equation [13.4], and by putting the standard deviation of observed family means, σ_f , in terms of the standard deviation of individual phenotypic values, $\sigma_P (= \sqrt{V_p})$ from the right-hand column of Table 13.3. The expected response then becomes

$$R_f = i \sqrt{\left[\frac{1 + (n - 1)t}{n} \right]} \times \sigma_P \times \left[\frac{1 + (n - 1)r}{1 + (n - 1)t} \right] h^2$$

which reduces to

$$R_f = i\sigma_P h^2 \left[\frac{1 + (n - 1)r}{\sqrt{[n(1 + (n - 1)t)]}} \right]$$

The term $i\sigma_P h^2$ is equivalent to the expected response under individual selection, so the expression within the square brackets is the factor that compares family selection with individual selection. The expression looks very complicated but it contains only three simple quantities: n , which is the family size; r , which is $\frac{1}{2}$ for full-sib and $\frac{1}{4}$ for half-sib families; and t , which is the phenotypic intraclass correlation.

The expected responses under the different methods of selection are listed in Table 13.4, all expressed in this manner, which allows the comparisons to be made with individual selection.

Combined selection

Combined selection will be dealt with very briefly here because it will be more fully explained later. The appropriate weighting factors to be used in its application can be deduced as follows. We saw before that the phenotypic value of an individual is made up of two parts, the family mean and the within-family deviation, $P = P_f + P_w$, and that each part gives some information about the individual's breeding value. In Chapter 10 we saw that the heritability is equivalent to the regression of breeding value on phenotypic value (equation [10.2]), so that the best estimate of an individual's breeding value to be derived from its phenotypic value is $h^2 P$ (equation [10.4]). This idea can be applied separately to the two parts of the phenotypic value, since these are uncorrelated and supply independent information about the breeding value. Therefore, taking both parts of the phenotypic value into account, the best estimate of an individual's breeding value is given by the multiple regression equation

$$\text{expected breeding value} = h_f^2 P_f + h_w^2 P_w \quad \dots [13.7]$$

Table 13.4 Heritability and expected response under different methods of selection.

Method of selection	Heritability	Expected response
Individual	h^2	$R = i\sigma_p h^2$
Family	$h_f^2 = h^2 \frac{1+(n-1)r}{1+(n-1)t}$	$R_f = i\sigma_p h^2 \frac{1+(n-1)r}{\sqrt{n\{1+(n-1)t\}}}$
Sib	$h_s^2 = h^2 \frac{nr}{1+(n-1)t}$	$R_s = i\sigma_p h^2 \frac{nr}{\sqrt{n\{1+(n-1)t\}}}$
Within-family	$h_w^2 = h^2 \frac{(1-r)}{(1-t)}$	$R_w = i\sigma_p h^2 (1-r) \sqrt{\left[\frac{n-1}{n(1-t)} \right]}$
Combined	—	$R_c = i\sigma_p h^2 \sqrt{\left[1 + \frac{(r-t)^2}{(1-t)} \times \frac{(n-1)}{1+(n-1)t} \right]}$

i = intensity of selection (selection differential in standard measure): assumed to be equal for all methods, but not necessarily so.

σ_p = standard deviation of phenotypic values of individuals.

h^2 = heritability of individual values.

r with full-sib families, $r = \frac{1}{2}$.
with half-sib families, $r = \frac{1}{4}$.

t = correlation of phenotypic values of members of the families.

n = number of individuals in the families.

P_f being measured as a deviation from the population mean, and P_w as a deviation from the family mean. The weighting factors that make the most efficient use of the two sources of information are therefore the two heritabilities, which are the partial regression coefficients on family mean and within-family deviation respectively. If the values of the two heritabilities from Table 13.4 are inserted in equation [13.7], it will be seen that the term h^2 is common to both weighting factors, and this term may therefore be omitted without affecting the relative weighting. This gives the expected breeding value as

$$E(A) = \left[\frac{1-r}{1-t} \right] P_w + \left[\frac{1+(n-1)r}{1+(n-1)t} \right] P_f$$

In practice it is more convenient to work with the individual values in place of the within-family deviations, and to assign them a weight of 1. The family mean is thus used in the manner of a correction, supplementing the information provided by the individual itself. Rearrangement of the appropriate weighting factor for the family mean leads to an index of merit as follows (Lush, 1947):

$$I = P + \left[\frac{r-t}{1-r} \times \frac{n}{1+(n-1)t} \right] P_f \quad \dots [13.8]$$

In this equation, P is the individual value, and P_f is the deviation of the family mean from the population mean, the individual itself being included in the family mean. Note that the weighting of P_f is negative if t is greater than r . This can only

occur when there is a large environmental component in the correlation; the family mean is then an indicator of environment rather than of breeding value. The expected response to combined selection, cast in a form suitable for comparison with individual selection, is given in Table 13.4. For its derivation see Lush (1947).

Example 13.1

The operation of combined selection will be illustrated by application of equation [13.8] to the figures in Table 13.1, which are realistic values for litter sizes of mice. The phenotypic values are listed again here in table (i) with the family means as deviations from the overall mean. The full-sib correlation of litter size is about $t = 0.1$. Substituting this, with $r = 0.5$, $n = 4$, in equation [13.8] gives the index of merit as $I = P + 2.46P_f$. The index so calculated for each individual is given in table (ii). The only difference between the individuals selected by combined selection and those selected by individual selection is in the 4th-ranking individual, A3 being chosen instead of B2 or D1.

Table (i)

	A	B	C	D
1	13	11	7	9
2	10	9	7	5
3	8	6	6	3
4	5	6	4	3
P_f	+2	+1	-1	-2
Overall mean	7			

Table (ii)

A	B	C	D
17.9	13.5	4.5	4.1
14.9	11.5	4.5	0.1
12.9	8.5	3.5	-1.9
9.9	8.5	1.5	-1.9
		7	

Relative merits of the methods

The merit of any one method of selection relative to any of the others can be worked out from the expected responses given in Table 13.4. The formulae

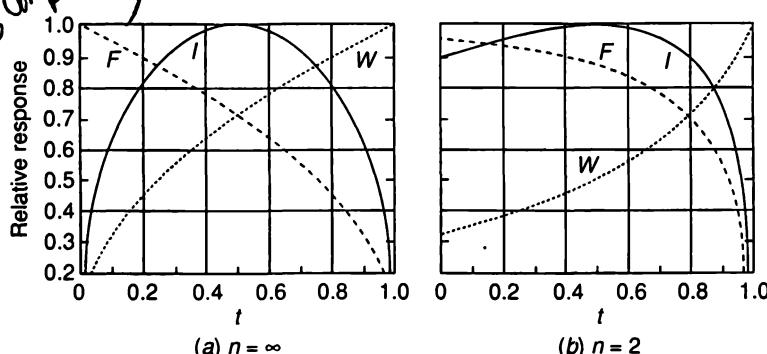


Fig. 13.1. Relative merits of the different methods of selection, with full-sib families. Responses relative to that for combined selection plotted against the phenotypic intraclass correlation, t . I = individual selection; F = family selection; W = within-family selection.

~~-LAB-~~

expressing relative merits, however, are very cumbersome, depending in a complicated way on the phenotypic correlation t , the family size n , and whether the families are full or half sibs, i.e., r . The relative merits are summarized graphically in Fig. 13.1. This shows the expected responses of the three simple methods relative to combined selection, which must always be the best method. The relative responses are plotted against the phenotypic correlation t with the two extremes of family size: very large families in (a) and families of size 2 in (b). The intensity of selection i is assumed to be the same for all methods. The following conclusions can be drawn from the graphs though, for reasons to be explained, they are not immediately applicable to practical breeding operations. First, comparing the three simple methods with combined selection, one or other of the simple methods is seldom more than 10 per cent, and never more than 20 per cent below combined selection in the expected response. Second, comparing the three simple methods, individual selection is best over much of the range of t . The reason for this is that individual selection operates on the whole of the additive genetic variance, whereas family selection operates only on the variance between family means, and within-family selection only on the variance within families. Family selection is better than individual selection when the phenotypic correlation t is low. Low sib-correlations imply a low heritability and little resemblance from common environment. These are the conditions that, in general, make family selection better than individual selection. Within-family selection is better than individual selection when the sib-correlation is very high. Very high correlations can only arise from a very large common environment component of variance V_{Ec} ; this is the condition that makes within-family selection better than individual selection, but it occurs only rarely. There are, however, other considerations. The first is inbreeding. Family selection is likely to result in fewer families being represented among the selected parents, unless the intensity of selection is correspondingly reduced. Consequently the rate of inbreeding is likely to be greater with family than with individual selection. Indeed, any use of family means, as with combined selection, tends to increase the rate of inbreeding. Conversely, within-family selection is likely to reduce the rate of inbreeding. The second consideration is the reduction of the additive variance explained in Chapter 11. As shown in Table 11.1, it is only the between-family variance that is reduced by the disequilibrium generated by selection. Consequently within-family selection has the advantage over between-family selection in that it operates on a larger amount of additive variance. The third consideration is economic, and this is what makes the comparisons in Fig. 13.1 not immediately relevant to practical breeding operations. The cost of obtaining both individual and family records may make combined selection uneconomic or impracticable. In animal breeding, individual records are easily obtainable but pedigree records, needed to apply combined selection, may be costly to obtain. The choice is between the less efficient individual selection and the more costly combined selection. In plant breeding, on the other hand, families may be easily identified but individual plant records may be difficult to obtain, or they may not be meaningful. In this case family selection may be the only practicable method. For details of family selection applied to plants, see England (1977).

Example 13.2

To illustrate how the different methods of selection are compared, their relative merits will be calculated for three characters in mice. The families are assumed to be single litters. Weaning weight has a very large common environment component giving a high full-sib correlation of 0.8. Six-week weight has a smaller, but still large, common environment component giving a correlation of 0.6 (see Example 10.5). Litter size, a character of the adult female, has a low heritability and a small amount of common environment, giving a low full-sib correlation of 0.1. The intensity of selection is assumed to be the same for all methods of selection, though this would not be true in practice. The family size is assumed to be $n = 4$. The families are full sibs, so $r = 0.5$. The expected responses relative to individual selection are calculated from Table 13.4, by entering these values of n and r and the appropriate value of t . The relative responses are given in the table. Combined selection would be nearly 20 per cent better than individual selection for weaning weight and litter size, but would have virtually no advantage for 6-week weight. Family selection would be 10 per cent better than individual selection for litter size. (If males were to be selected they would have to be selected by sib selection whatever method was applied to the females.) Within-family selection would not be better than individual selection for any of the characters, but it would be for weaning weight if the family size was more than 5.

	Weaning weight	6-week weight	Litter size
t	0.8	0.6	0.1
Weighting of P_f in eq. [13.8]	-0.71	-0.29	+2.46
Combined: R_c/R	1.18	1.01	1.19
Family: R_f/R	0.68	0.75	1.10
Within family: R_w/R	0.97	0.68	0.46

Example 13.3

A comparison of sib selection with individual selection has been made experimentally with *Drosophila* (Clayton and Robertson, 1957). Sib selection was made with both full-sib and half-sib families. The responses were compared with individual selection with intensity $i = 1.40$ as given in Example 11.2. The table gives the data needed to calculate the expected responses, relative to individual selection, from the formulae in Table 13.4. It will be seen that r for the half sibs was a little greater than 0.25. This was because the females mated to the same male were not entirely unrelated to each other. The relative responses expected and observed are given in the right-hand part of the table. The expectation is that sib selection should be less good than individual selection, and so it proved to be. There was, however, some discrepancy between the upward and downward responses, for which the reason is not known.

	Data		Relative response, R_j/R	
	Full sibs	Half sibs	Full sibs	Half sibs
i	1.33	1.27	Exp.	0.832
n	12	20	Obs. up	0.618
r	0.50	0.275	Obs. down	0.919
t	0.265	0.121		0.635

Index selection

* The optimal procedure for selection uses all the information available about each individual's breeding value, combined into an index of merit. The solution given above for combining the family mean and within-family deviation is not readily applicable to more complex situations when there may be more than two sources of information. There may, for example, be information from the individual, its parents, full sibs, half sibs, and other relatives. Or, if the character is limited to one sex, the information about individuals that cannot themselves be measured will come only from relatives of different sorts. The aim therefore is to combine all the information into an *index* on the basis of which the individuals will be selected. The construction of an index is not easy without the use of matrix methods, particularly if there are more than two sources of information. The technical details are beyond the scope of this book and only a brief account of the principles involved can be given. For more detailed accounts see Nordskog (1978), Lin (1978), Nicholas (1987) and Van Vleck (1993).

Construction of an index

The index is the best linear prediction of an individual's breeding value and it takes the form of a multiple regression of breeding value on all the sources of information. Consider first the simplest situation, where the only information we have is the individual's own phenotypic value P as a deviation from the population mean. Then the predicted, or expected, breeding value is $E(A) = b_{AP}P$, where b_{AP} is the regression of breeding value on phenotypic value. In this case $b_{AP} = h^2$ (equation [10.2]). Now suppose that there are several pieces of information, P_1, P_2, P_3 , etc., where each P is the phenotypic value of an individual or a group of relatives. These pieces of information in the form of phenotypic values will be referred to as 'measurements'; all are to be expressed as deviations from the population mean. The index of an individual is then

$$I = b_1P_1 + b_2P_2 + b_3P_3 + \dots \quad \dots [13.9]$$

in which the b 's are the factors by which each measurement is to be weighted. The problem is to find the best value for each weighting factor. This is done by finding what values will give the maximum correlation r_{IA} between the index and the breeding value. Maximizing r_{IA} is equivalent to minimizing the sum of squared deviations of index values from the linear regression of I on A , i.e., $\Sigma(I - A)^2$. The resulting values of the b 's are then the partial regression coefficients of the individual's breeding value on each measurement. The maximizing of r_{IA} is a standard procedure for calculating partial regressions and it need not be explained here. The maximization leads to a set of simultaneous equations, with as many equations as there are measurements, and the solution of these equations gives the values of the b 's to be used in equation [13.9]. These index equations for solution are given below (equations [13.10]). The equations for three measurements are given; it will easily be seen how they would be extended or reduced for more or fewer measurements. Each equation relates the phenotypic variances and covariances of the measurements, on the left, to the additive genetic variances and covariances of the

individuals measured, on the right. The notation is condensed as follows. P means the phenotypic variance or covariance of the measurements denoted by subscript numbers. For example, P_{11} is the phenotypic variance of measurement 1, and P_{12} is the phenotypic covariance of measurements 1 and 2. The variances and covariances of breeding values are similarly written as A . The equations are

$$\left. \begin{array}{l} b_1 P_{11} + b_2 P_{12} + b_3 P_{13} = A_{11} \\ b_1 P_{21} + b_2 P_{22} + b_3 P_{23} = A_{21} \\ b_1 P_{31} + b_2 P_{32} + b_3 P_{33} = A_{31} \end{array} \right\} \dots [13.10]$$

To solve these equations the numerical values of the P 's and A 's must of course be inserted. The P 's and A 's can all be expressed in terms of the following parameters: the phenotypic variance V_P , which will be denoted here by σ^2 ; the heritability of individual values, h^2 ; the phenotypic correlations between individuals, t ; and the coefficients of relationship, r as in Table 9.3. When 'measurements' are the means of groups of individuals, the number n in the group is also needed. There are standard computer programs for solving the equations. The indices obtained will be illustrated by reference to specific examples, simplified by considering only two measurements. Some other examples are dealt with by Becker (1984).

Individual and one relative Let measurement 1 be of the individual whose index is to be calculated, and measurement 2 be that of one relative. Then the phenotypic variances of the measurements are the same and $P_{11} = P_{22} = \sigma^2$. The phenotypic covariance is $P_{12} = P_{21} = t\sigma^2$. The additive variance is $A_{11} = h^2\sigma^2$ and the additive covariance is $A_{21} = rh^2\sigma^2$, where r is the coefficient of relationship between the relative and the individual. After dividing all through by σ^2 , the equations for solution become

$$\begin{aligned} b_1 + tb_2 &= h^2 \\ tb_1 + b_2 &= rh^2 \end{aligned}$$

and the solution, after some simplification, is

$$b_1 = \frac{h^2(1 - rt)}{1 - t^2}; \quad b_2 = \frac{h^2(r - t)}{1 - t^2}$$

The index is obtained by substituting the values b_1 and b_2 into equation [13.9].

For the practical purpose of choosing individuals it may be convenient to rescale the index so that the individuals' own measurements are given a weight of 1. The weight to be given to P_2 is then $b_2/b_1 = (r - t)/(1 - rt)$, and the rescaled index is

$$I' = P_1 + \left(\frac{r - t}{1 - rt} \right) P_2$$

With the index in this form the actual value of P_1 can be used, but P_2 must be a deviation from the population mean; the value of the index is then in the units of measurement. In its original form the index predicts the individual's breeding value; in the rescaled form it is a phenotypic value adjusted by the information on the relative. Any index can be similarly rescaled. It must be noted, however, that if

the response to index selection is to be predicted, allowance must be made for any rescaling of the index. The prediction of the response will be explained later.

Mother and one paternal half sister This exemplifies the selection of males for a female character, such as milk-yield or egg production. The individual whose index is to be calculated is not measured. To make the index equations comparable with those of equations [13.10] we shall regard measurement 1 as being absent, measurement 2 as that of the mother, and measurement 3 as the half sister. The relevant parts of equations [13.10] are therefore

$$\begin{aligned} b_2 P_{22} + b_3 P_{23} &= A_{21} \\ b_2 P_{32} + b_3 P_{33} &= A_{31} \end{aligned}$$

The phenotypic variances are again equal, and $P_{22} = P_{33} = \sigma^2$. The mother and half sister will be assumed to be unrelated and uncorrelated environmentally, so $P_{23} = P_{32} = 0$. A_{21} is the additive covariance of the individual with his mother, which is $\frac{1}{2} h^2 \sigma^2$. A_{31} is the additive covariance of the individual with his half sib, which is $\frac{1}{4} h^2 \sigma^2$. The index equations then reduce directly to the solutions

$$b_2 = \frac{1}{2} h^2; \quad b_3 = \frac{1}{4} h^2$$

giving the index

$$I = \frac{1}{2} h^2 P_1 + \frac{1}{4} h^2 P_2$$

Individual and mean of sibs This is the situation with which the problem was introduced at the beginning of this chapter, and described earlier as 'combined selection'. The individual is again measurement 1, so $P_{11} = \sigma^2$ and $A_{11} = h^2 \sigma^2$ as before. The variance of a family mean was given in Table 13.3, from which $P_{22} = [1 + (n - 1)t]\sigma^2/n$. It is usually convenient to include the individual in the family mean. The covariance of the individual with the family mean is then equal to the variance of family means. Thus $P_{12} = P_{21} = P_{22}$. In the same way the additive covariance is equal to the additive variance of family means. Taking the additive variance from Table 13.3 gives $A_{21} = [1 + (n - 1)r]h^2 \sigma^2/n$. The index equations are thus

$$\begin{aligned} b_1 + Kb_2 &= h^2 \\ Kb_1 + Kb_2 &= kh^2 \end{aligned}$$

$$\text{where } K = \frac{1 + (n - 1)t}{n} \text{ and } k = \frac{1 + (n - 1)r}{n}$$

Solving for b_1 and b_2 gives the index

$$I = \frac{h^2(1 - k)}{(1 - K)} P_1 + \frac{h^2(k - K)}{K(1 - K)} P_2$$

If different individuals have different numbers of sibs, k and K must be evaluated separately for each individual. If the number of sibs is constant, the index can be rescaled so as to become the same as equation [13.8].

The usefulness of the information obtainable from sibs depends on the family size n . Because there are usually many more half sibs than full sibs, half-sib families may give more information than full sibs, despite the less close genetic relationship. The relative merits of indices for application to poultry are examined by Osborne (1957).

Other 'measurements' involving means In applying the quantities denoted by K and k above in other situations, two points need to be noted. First, a group of relatives may be related to each other differently from the way that they are to the individual. Care must then be taken to use the appropriate values of t and r . For example, P_2 might be the mean of a group of full sibs that are half sibs to the individual. Then the t appropriate to P_{22} is the correlation of full sibs, but the t appropriate to P_{12} and P_{21} , and the r appropriate to A_{21} , are the correlations of half sibs. Second, the 'measurement' of an individual may be the mean of several repeated records. Then the repeatability must be used in place of t .

Accuracy

The correlation r_{IA} between index values and breeding values, which is maximized in the construction of an index, is known as the *accuracy* of the index. It provides a convenient way of comparing indices, or any criteria of selection, because the higher the correlation the better is the criterion as a predictor of breeding values. With individual selection the criterion is simply the individual's phenotypic value. The accuracy of individual selection is therefore the correlation of phenotypic values with breeding values, which is h , the square root of the heritability (equation [10.3]). The accuracy r_{IA} of an index is calculated as follows.

First, we need to know the variance of index values. From equation [13.9] this can be seen to be

$$\sigma_I^2 = b_1^2 P_{11} + b_2^2 P_{22} + \dots + 2b_1 b_2 P_{12} + \dots \quad \dots [13.11]$$

where variances and covariances are written in the notation of equations [13.10]. This expression can be put into a form that is easier to calculate. Rearranging the terms gives

$$\sigma_I^2 = b_1(b_1 P_{11} + b_2 P_{12} + \dots) + b_2(b_1 P_{21} + b_2 P_{22} + \dots) + \dots$$

Substituting for the terms in brackets from equations [13.10] leads to

$$\sigma_I^2 = b_1 A_{11} + b_2 A_{21} + b_3 A_{31} + \dots \quad \dots [13.12]$$

Next we need to know the covariance of index values with breeding values. This is $\text{cov}_{IA} = \sigma_I^2$ for the following reason. The construction of the index so that the weighting factors, the b 's, are partial regression coefficients results in the regression of breeding values on index values being unity; i.e., $b_{AI} = 1$. Another way of saying this is that the construction of the index results in 1 unit of the index being equivalent to 1 unit of predicted breeding value. Now, $\text{cov}_{AI}/\sigma_I^2 = b_{AI} = 1$, from which it follows that $\text{cov}_{AI} = \sigma_I^2$. Thus, provided the index has not been rescaled, the correlation is given by

$$r_{IA} = \frac{\text{cov}_{IA}}{\sigma_I \sigma_A} = \frac{\sigma_I}{\sigma_A} \quad \dots [13.13]$$

Here σ_I is obtained from equation [13.12] and σ_A is the square root of the additive genetic variance in the population.

The correlation r_{IA} is a multiple correlation, and its square expresses the fraction of the additive variance that is accounted for by the measurements combined in the index, i.e., $r_{IA}^2 = \sigma_I^2/\sigma_A^2$. Conversely, $(1 - r_{IA}^2)$ is the fraction of the additive variance that is not taken account of in the index. This shows how much room there is for improvement of the index by inclusion of additional measurements.

Response to selection

The response to selection is the mean breeding value of the selected parents, which is predicted from the regression of breeding values on index values as $R = b_{AI}S$, where S is the selection differential of index values. Putting $b_{AI} = r_{IA}\sigma_A/\sigma_I$ and $S = i\sigma_I$ gives the predicted response as

$$R = ir_{IA}\sigma_A \quad \dots [13.14]$$

This prediction applies to any index, however constructed and whether optimal or not, provided r_{IA} refers to the index actually used. If the index has not been rescaled, substitution for r_{IA} can be made from equation [13.13] to give

$$R = i\sigma_I \quad \dots [13.15]$$

Index selection is obviously much more laborious and costly to apply than simple individual selection. How much is to be gained by it? The relative merits can be easily seen by comparing the expected response to index selection in equation [13.14] with that to individual selection in equation [11.4] ($R = ih\sigma_A$). Provided the intensity of selection is the same, the improvement expected from index selection relative to that from individual selection is the ratio r_{IA}/h , which is the ratio of their respective accuracies.

Practice In practical animal breeding there are numerous complications to the estimation of breeding values: individuals whose breeding values are to be estimated may be related, some individuals may have repeated measurements and others only a single record, and, most seriously, there may be systematic environmental differences between groups of individuals. To give an example of the latter, dairy cows are raised in herds with different management practices, so the estimate of a bull's breeding value for milk yield must be adjusted for the herd effects of his daughters. If estimates of all the relevant fixed environmental factors are known, then the measurement of each individual can be adjusted and the selection index constructed using the adjusted values. However, estimates of the adjustment factors are usually not known in advance. The statistical procedure known as BLUP (best linear unbiased prediction) is used to estimate the fixed effects and breeding values simultaneously. The conventional selection index is thus a special case of BLUP with known fixed effects. BLUP can also accommodate other complications such as non-random mating and bias due to selection of individuals, provided the data on which selection was practised are included in the analysis. BLUP assumes genetic and phenotypic variances are known. If this is not true, genetic parameters can be simultaneously estimated from the data using REML. A version of BLUP called the

(individual) animal model is used extensively to evaluate animal breeding data. The animal model defines the breeding value for each individual measured, and accounts for all the genetic relationships among the individuals whose breeding values are to be estimated. Because the relationships among animals across generations can be included in the model, the animal model can account for changes in the genetic mean and variance and is the optimal way to analyse data from selection experiments. For excellent accounts and numerical examples see Nicholas (1987) and Van Vleck (1993), and for more detail see Henderson (1977, 1988), Thompson (1979, 1989) and Kennedy and Sorensen (1988).

Indices for predicting breeding values can be improved by the incorporation of data on other characters correlated with the one for which prediction is required, and which may themselves be objects of selection. This aspect of indices is dealt with in Chapter 19.

Actual achievements

Before leaving the subject of selection we should consider how much improvement of farm animals has actually been achieved by the application of selection in the recent past. This question has been reviewed by Smith (1984, 1988). Genetic improvement has been assessed in poultry for weight gain in broilers and egg number in layers, in pigs and sheep for aspects of body weight and for litter size, in cattle for weight and milk-yield. All of these show improvement. Expressed as percentages of the means, the rates are mostly in the range from 1 to 2 per cent per year (not per generation). Broiler poultry, however, showed 6 per cent improvement and beef cattle only 0.3 per cent. Except for the broilers these rates were somewhat below what should have been possible. The possible rates were calculated from the known heritabilities, the accuracies of the selection methods, and the intensities of selection. The possible rates of improvement ranged between 1.4 and 3.2 per cent per year. The conclusion is that substantial progress is undoubtedly being made, but it should be possible to increase the rates by improved procedures.

Problems

13.1 Calculate the heritability of family means, h_f^2 , and of within-family deviations, h_w^2 , for characters with the following parameters. Calculate also the expected responses to family selection and to within-family selection, relative in each case to the response to individual selection, i.e., R_f/R and R_w/R , assuming equal intensities of selection.

<i>Individual heritability</i>	<i>Type of family</i>	<i>Sib correlation</i>	<i>Family size</i>
(1) 0.1	Half sibs	0.025	10
(2) 0.1	Half sibs	0.025	20
(3) 0.1	Full sibs	0.5	4
(4) 0.2	Full sibs	0.8	4
(5) 0.2	Full sibs	0.8	8

13.2 Daily weight gain in British Large White pigs has a half-sib correlation of 0.10 and a full-sib correlation of 0.36. Compare the expected rates of progress, relative to that of individual selection, when selection is based on

- (1) The mean of 5 half sibs, all from different dams, the selected individual being one of the five.
- (2) The mean of 5 full sibs, which include the selected individual.
- (3) The mean of 5 full sibs, which exclude the selected individual.
- (4) The individual's deviation from the mean of its 5 full sibs, which includes itself.

Data from Smith, C. et al. (1962) *Anim. Prod.*, 4, 128–43.

[Solution 87]

13.3 What would be the appropriate index for selecting pigs for daily weight gain on the basis of the individual's gain and the family mean of 5 full sibs, the individual being included in the family mean? Take the full-sib correlation to be 0.36 as in Problem 13.2.

[Solution 97]

13.4 If the figures below were the daily weight gains of four individual pigs from different full-sib families, what would be their order of merit according to the index worked out in Problem 13.3 with any necessary modification for the numbers of sibs?

<i>Weight gain</i>			
<i>Pig</i>	<i>Individual</i>	<i>Family mean</i>	<i>Number in family</i>
A	1.6	1.3	5
B	1.5	1.6	5
C	1.5	1.6	8
D	1.3	1.7	8

Population mean = 1.5

[Solution 107]

13.5 If selection for daily weight gain in pigs were applied by the index calculated in Problem 13.3, how would the expected response compare with the response expected from individual selection?

[Solution 117]

13.6 Construct an index for selecting bulls for milk-yield on the basis of the yields of the mother and 10 paternal half sisters. Assume that the half sisters all have different mothers which are not related to the bull's mother. Assume also that there is no environmental correlation between half sibs. Take the heritability of milk-yield to be 0.35 (Table 10.1), though this is higher than most estimates.

[Solution 127]

13.7 Predict the rate of improvement of milk-yield per generation if 1 in 20 bulls were selected by the index of Problem 13.6, and 1 in 2 cows were selected on their own yield. Take the phenotypic standard deviation of milk-yield to be 696 kg (Example 8.7), and assume that the selection is made from a large number measured.

[Solution 137]

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 utilization 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.

In the treatment of inbreeding given in Chapter 3, the consequences were described in terms of the changes of gene frequencies and of genotype frequencies. Here we have to show how these changes of gene and genotypic frequencies affect metric characters, and how they can account for the observed effects of inbreeding and crossing. The effects on the mean value will be explained in this chapter and the effects on the variance in the next. In Chapter 16 we shall consider the use of inbreeding and crossing as a means of plant and animal improvement.

The effects of inbreeding to be described do not apply to naturally self-fertilizing plants. Since inbreeding is their normal mating system they cannot be further inbred. They can, however, be crossed and they do then often show hybrid vigour, though less than when inbred lines of outbreeding species are crossed. The improvement of self-fertilizing plants, for which crossing is the first step, will be described briefly in Chapter 16.

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 –

Table 14.1 Some examples of inbreeding depression. Approximate *decrease* of mean per 10 per cent increase of inbreeding coefficient: (1) in absolute units; (2) as percentage of non-inbred mean; and (3) as percentage of the original phenotypic standard deviation. The depression given is due only to inbreeding in the individuals on which the characters are measured, except where noted below.

	(1) Units	(2) % of M	(3) % of σ_P
<i>Man</i>			
Height (cm) at age 10; [Schull, 1962]	2.0	1.6	37
IQ score (percentage points); [Morton, 1978]	4.4	4.4	29
<i>Cattle</i>			
Milk-yield (kg); [Robertson, 1954]	135	3.2	17
<i>Sheep</i> [Morley, 1954]			
Fleece weight (kg)	0.29	5.5	51
Body weight at 1 yr (kg)	1.32	3.7	36
<i>Pigs</i> [Bereskin <i>et al.</i> , 1968]			
Litter size (no. born alive)	(a)	0.24	3.1
Body weight at 154-days (kg)		2.6	4.3
<i>Mice</i>			
Litter size; [Bowman and Falconer, 1960]	(b)	0.56	7.2
Body weight at 6 wks (g); [White, 1972]		0.19	0.6
<i>Maize</i> [Cornelius and Dudley, 1974]			
Plant height (cm)	(FS)	5.20	2.1
	(S)	5.65	2.3
Yield of seed (g/plant)	(FS)	7.92	5.6
	(S)	9.65	6.8
			30

(a) Inbreeding in the mothers; litters non-inbred.

(b) Depression related to inbreeding in the mothers under consecutive full-sib mating; litters one generation more inbred than mothers.

(c) Depression related to inbreeding in the plants measured; inbreeding by consecutive full-sib mating (FS) or selfing (S). Dr. J. W. Dudley kindly provided the values of σ_P for maize.

the magnitude of the effect. From the results of these and many other studies we can make the generalization 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 are not closely connected with fitness show little or no change. In *Drosophila*, for example, bristle number and body weight do not change (Kidwell and Kidwell, 1966) but fertility and viability do (Tantawy and Reeve, 1956).

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 emphasize 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. 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.

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 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:

$$M_F = a(\bar{p} - \bar{q}) + 2d\bar{p}\bar{q}(1 - F) \quad \dots [14.1]$$

$$= M_0 - 2d\bar{p}\bar{q}F \quad \dots [14.2]$$

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

Table 14.2

Genotype	Frequency	Value .	Frequency × Value
A ₁ A ₁	$\bar{p}^2 + \bar{p}\bar{q}F$	+ a	$\bar{p}^2a + \bar{p}\bar{q}aF$
A ₁ A 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 ₂ A ₂	$\bar{q}^2 + \bar{p}\bar{q}F$	- a	$-\bar{q}^2a - \bar{p}\bar{q}aF$
Sum			$a(\bar{p} - \bar{q}) + 2d\bar{p}\bar{q} - 2d\bar{p}\bar{q}F$
$= a(\bar{p} - \bar{q}) + 2d\bar{p}\bar{q}(1 - F)$			

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 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:

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

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

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 directional dominance, which means dominance of the genes concerned being preponderantly in one direction. 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.

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 . If there is epistatic interaction between loci, the relation between the mean and the inbreeding coefficient is not linear. The non-linearity is due to the interaction deviation of double, or multiple, heterozygotes. The frequency of double heterozygotes declines in proportion to F^2 . Therefore as F increases, the rate of depression of the mean increases if the interaction deviations are on average positive, i.e., favourable, and the rate decreases if they are negative. No other form of interaction affects the linearity, and epistasis without dominance cannot itself cause any inbreeding depression. For the details of how epistasis affects inbreeding depression, see Crow and Kimura (1970, p. 79).

Examples of experimentally observed inbreeding depression are illustrated in Figs 14.1 and 14.2. On the whole, the observed inbreeding depression, as in these examples, 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 some individuals and of some entire 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

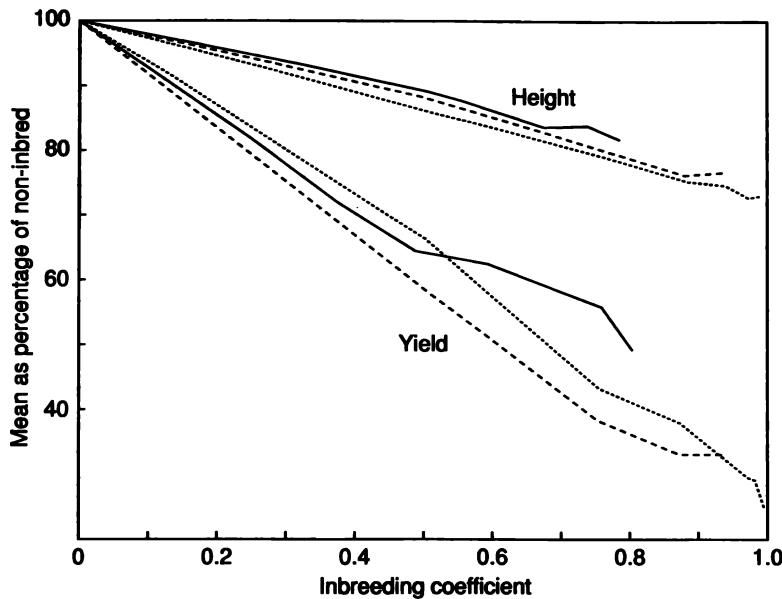


Fig. 14.1. Effects of inbreeding on plant height and yield of seed in maize (*Zea mays*). The dotted and dashed lines refer to consecutive selfing; the continuous lines refer to consecutive full-sib mating. No selection was practised. Data from Hallauer and Sears (1973) (dotted lines), and Cornelius and Dudley (1974) (continuous and dashed lines).

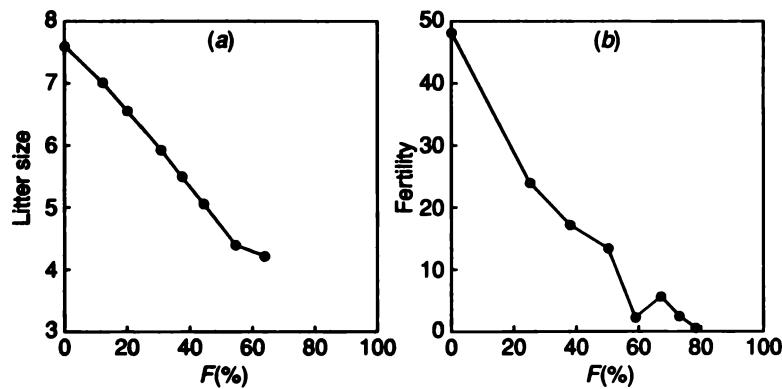


Fig. 14.2. Examples of inbreeding depression affecting fertility. (a) Litter size in mice (Data from Bowman and Falconer, 1960). Mean number born alive in 1st litters, plotted against the coefficient of inbreeding of the litters. The first generation was by double-first-cousin mating; thereafter by full-sib 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. (Based on Hollingsworth and Maynard Smith, 1955.)

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 twofold: part being attributable to the inbreeding of the individuals measured and part to the inbreeding in the mothers. When continuous breeding is practised, the mothers and the offspring have different coefficients of inbreeding in the early generations, so the relationship between the character measured and the coefficient of inbreeding cannot be expressed in any simple way. In consequence of these difficulties, reliable conclusions cannot easily be drawn from the exact form of the depression observed under continuous inbreeding.

✓ 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, and because deliberate inbreeding is usually accompanied by some artificial selection for characters subject to inbreeding depression. There are two effects of selection which must be distinguished: delay in the approach to fixation, and reduction in the inbreeding depression. Delay in the approach to fixation was discussed at the end of Chapter 5. It results in the actual proportion of homozygotes being less than would be predicted by the inbreeding coefficient calculated from the pedigree or the population size. Reduction of the inbreeding depression can occur, without a delay in the approach to homozygosity, if selection leads to the better allele being fixed at more of the loci than would occur by chance. To make effective use of selection in this way it is essential for a large number of lines to be inbred in parallel. Selection is then applied between the lines, so that the worst lines are eliminated and the best retained. The reason for this, which is explained in the next chapter, is that the genetic variation is progressively reduced within lines and increased between lines.

How effective can selection be in counteracting inbreeding depression? This is an important practical question because, if highly inbred lines are to be used for any practical purpose, the individuals must be reasonably viable and fertile. Selection has undoubtedly been successful in reducing, or even completely overcoming, the inbreeding depression of litter size in mice. If the graph in Fig. 14.2(a) is extrapolated to complete inbreeding at $F = 100$ per cent, the predicted litter size of highly inbred mice would be about 2. This is what would be expected of inbreeding without selection. In fact, most of the existing inbred strains have mean litter sizes well above 2, showing that selection in their development was successful in reducing the inbreeding depression. (Twenty strains listed by Green (1968) have a mean litter size of 5.7 with a range from 4.1 to 7.2.) Details of the making of one highly inbred strain with a mean better than the original population are given in the following example.

Example 14.1

The experiment on litter size illustrated in Fig. 14.2(a) was started with 20 lines. All females born in first litters were subsequently mated to provide the mean litter size.

Continued

Example 14.1 *continued*

Only first litters were reared, so lines became eliminated when they failed to produce one offspring of each sex in their first litters. No other selection between lines was applied. Selection within lines was applied in 10 of the lines (these are not included in Fig. 14.2). This selection had virtually no effect on the inbreeding depression. At generation 3 ($F = 55\%$), 1 of the 20 lines was lost, and at generation 6 ($F = 76\%$), only 3 lines remained. Over the next 5 generations, these 3 had a mean litter size of 6.6, an improvement of over 2 mice per litter attributable to selecting the best 3 out of 20 lines. One of the lines survived indefinitely and became a 'standard' inbred strain known as JU. Over the three years after it had had more than 20 generations of inbreeding, its mean litter size was 9.0 in first litters (McCarthy, 1965), which was better than the original population before inbreeding. The experiment is described by Bowman and Falconer (1960) and Falconer (1960a). Similar results have been obtained in two other experiments with mice (Falconer, 1971; Eklund and Bradford, 1977).

The three experiments cited in Example 14.1 prove that by selection it is possible to get highly inbred lines of mice that are at least as good as the original population in respect of the character selected. This provides strong, though not conclusive, evidence that overdominant loci are not an important cause of inbreeding depression of litter size in mice. If an overdominant locus is at its equilibrium gene frequency in the population before inbreeding, it is not possible to have a homozygous line that is as good as the non-inbred population. But if the frequency of the better homozygote is below its equilibrium value in the non-inbred population, fixing the better homozygote in an inbred line may increase the mean (Minvielle, 1979). The ways in which selection favouring heterozygotes affects the inbreeding depression are not straightforward. They depend on whether the gene frequencies start at their equilibrium values or not and, if they do, on whether the equilibrium frequency is intermediate or extreme, i.e., on whether the two homozygotes are nearly equal or very different in fitness (Hill and Robertson, 1968). When the initial frequency is the equilibrium value, selection reduces the inbreeding depression by delaying the approach to homozygosity if the two homozygotes are nearly equal in fitness; but it reduces the rate and the total amount of inbreeding depression if the two homozygotes are very different in fitness, because it then causes the better homozygote to be fixed preferentially.

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. The amount of heterosis is the difference between the crossbred and inbred means. 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 inbred without selection so that the mean gene frequencies are not changed. If the lines are crossed at random, the average

inbreeding coefficient in the crossbred progeny reverts to that of the base population and, if the gene frequencies have not changed, the frequencies of the genotypes are the same as in the base population. Thus if a number of crosses are made at random between the lines, the mean value of any character in the crossbred 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 crossbred 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 generalization 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 (Roberts, 1960) 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>F in</i>		<i>Mean litter size</i>
	<i>litters</i>	<i>mothers</i>	
Before inbreeding	0	0	8.1
Inbred	0.50	0.375	5.7
Crossbred litters	0	0.50	6.2
Crossbred litters and mothers	0	0	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 crossbred 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 crossbred generation', and the F_1 individuals are mated together at random to produce an F_2 or 'second crossbred 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

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

When the two populations are crossed to produce the F_1 , individuals taken at random from one population are mated to individuals 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 shown in Table 14.4. The mean genotypic value of the F_1 is

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

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]:

$$\begin{aligned} H_{F_1} &= M_{F_1} - M_{\bar{P}} \\ &= dy^2 \quad \dots [14.7] \end{aligned}$$

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

Table 14.3 Frequencies of zygotes in the F_1 .

		<i>Gametes from P₁</i>			
		A_1	A_2		
		p	q		
<i>Gametes</i>	A_1	$p - y$	$p(p - y)$	$q(p - y)$	
<i>from P₂</i>	A_2	$q + y$	$p(q + y)$	$q(q + y)$	

Table 14.4 Genotypes in the F_1 .

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

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

$$H_{F_1} = \Sigma dy^2 \quad \dots [14.8]$$

Three conclusions can be drawn from equation [14.8]:

(1) 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.

(2) The amount of heterosis is something specific to each particular cross. The genes by which two lines differ will not be the same for all pairs of lines, so different pairs of lines will have different values of Σdy^2 and will show different amounts of heterosis.

(3) If the lines crossed are highly inbred, and so completely homozygous, the difference of gene frequency between them can only be 0 or 1. The heterosis as shown by equation [14.8] is then the sum of the dominance deviations d of those loci that have different alleles in the two lines.

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 think of a population subdivided into many lines, and we suppose that pairs of lines are 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, i.e., $y^2 = 2\sigma_q^2$. The relationship between the variance of gene frequency and the coefficient of inbreeding was given in equation [3.14] as $\sigma_q^2 = \bar{p}\bar{q}F$. Therefore $y^2 = 2\bar{p}\bar{q}F$, showing that the mean amount of heterosis in crosses between random pairs of lines is equal to the inbreeding depression as given in equation [14.2], though of opposite sign.

Now 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

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

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],

$$\begin{aligned} H_{F_2} &= M_{F_2} - M_{F_1} \\ &= \frac{1}{2}dy^2 \\ &= \frac{1}{2}H_{F_1} \end{aligned} \quad \dots [14.10]$$

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 Chapter 5, 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. This, however, is not true with respect to genotypes at more than one locus

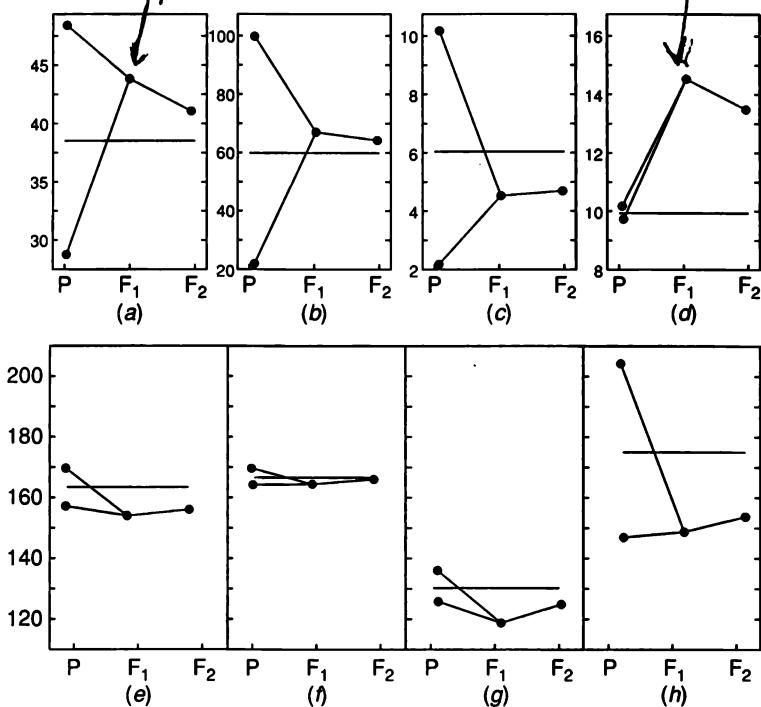


Fig. 14.3. Some illustrations of heterosis observed in crosses between pairs of highly inbred strains of plants. The points show the mean values of the two parent strains, the F_1 and the F_2 generations. The mid-parent values are shown by horizontal lines. Graph (a) refers to tobacco, *Nicotiana rustica*. (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 (g).
 (c) Number of locules per fruit.
 (d) Mean weight per locule (g).
 (e)-(h) Mean time in days between the planting of the seed and the ripening of the first fruit, in 4 different crosses.

considered jointly, for reasons that were explained in Chapter 1. Therefore if there is epistatic interaction, the population mean will not reach its equilibrium value in the F_2 , but will approach it in subsequent generations more or less rapidly according to the closeness of the linkage between the interacting loci. 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. 14.3. 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 graphs (e) to (h), 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. Not all the crosses in Fig. 14.3 provide heterosis that would be useful to a breeder. If the mean of the character is the only criterion of value, a cross is of no use unless the F_1 is better than both of the two parental lines. The term heterosis is sometimes used to mean useful heterosis, that is to say the amount by which the F_1 exceeds the better parent line.

Maternal effects The relative amount of heterosis observed in the F_1 and F_2 generations may be complicated by maternal effects. A character subject to a maternal effect, such as litter size, has two components belonging to different generations. Each component is expected to follow the general pattern of heterosis in the F_1 and F_2 described above, but the two components are one generation out of step with each other. 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 readily grasped from the diagrammatic representation in Fig. 14.4. This shows how the heterosis appears in two steps, the first due to the non-maternal component and the second due to the maternal component. These two steps were illustrated in Example 14.2.

Epistasis 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

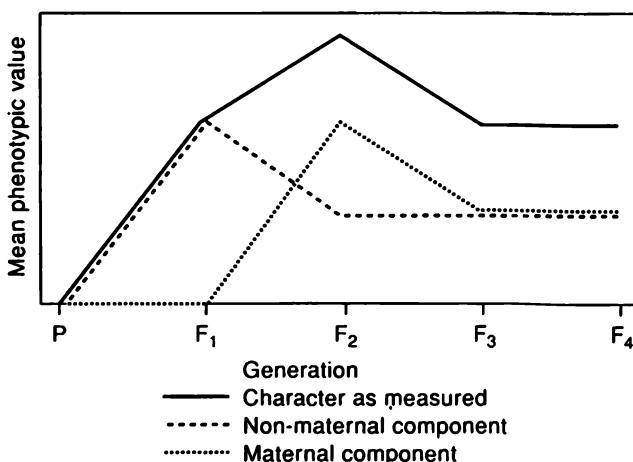


Fig. 14.4. Diagram of the heterosis expected in a character subject to a maternal effect, when two lines are crossed and the F_2 and subsequent generations are made by random mating. The maternal and non-maternal components of the character separately are here supposed to show equal amounts of heterosis, and to combine by simple addition to give the character as it is measured.

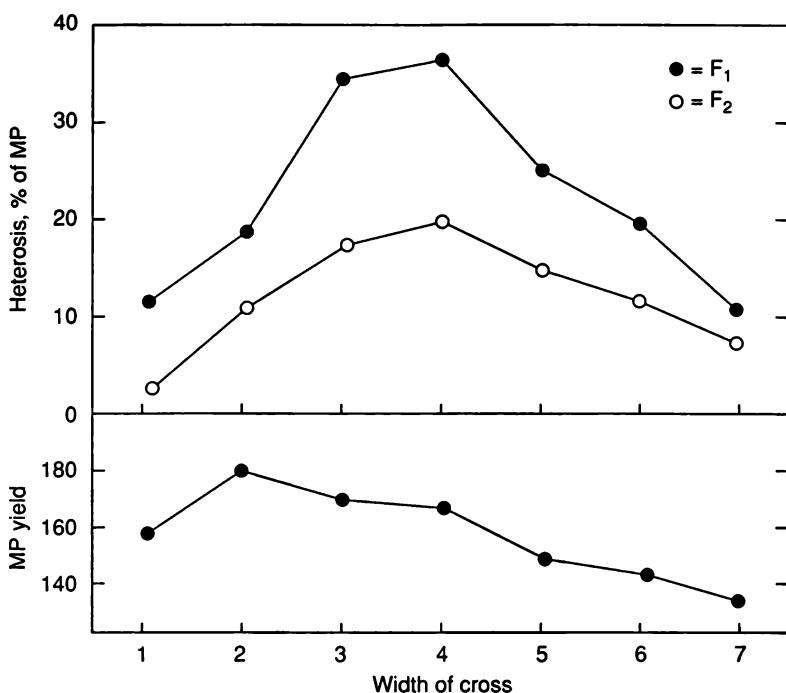


Fig. 14.5. Relationship between heterosis and width of cross as shown by yield of maize, as explained in Example 14.3. The heterosis is expressed as the percentage difference from the mid-parent. The mid-parent yields in g per plant are shown in the lower graph. (Data from Moll *et al.*, 1965.)

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. Populations that are widely differentiated through adaptations to local conditions may fail to show heterosis and may suffer a reduction of fitness in the F_2 generation, as has been shown by studies of *Drosophila* populations (Wallace and Vetukhiv, 1955). The failure of wide crosses to show the heterosis that might have been expected can be attributed to epistatic interaction, which we have so far assumed to be absent. Adaptation to widely different local conditions involves many different characters because the fitness of an organism depends on the harmonious interrelations of all its functions. Genes at many loci are therefore selected for their joint effects on fitness; the combinations of genes selected in this way are said to be 'coadapted'. In other words, some of the adaptation comes from epistatic interactions. When two populations adapted to different conditions are crossed, the hybrids are adapted to neither. Furthermore, the favourable epistatic combinations of genes are lost by segregation in the F_2 . The role of epistasis in relation to heterosis is summarized by Mayo (1987, p. 148) and is reviewed by Geiger (1988). Figure 14.5 and Example 14.3 show how heterosis for yield in maize is related to the width of the cross.

Example 14.3

(Data from Moll *et al.*, 1965). Varieties, or populations, of maize are adapted to different geographical regions. Two varieties from each of four regions were chosen and all of the 28 possible crosses were made. F_2 generations were made by random mating among the individuals of each F_1 . The varieties and the crosses were grown in each of the four regions of origin. The degree of diversity in the crosses was assessed in seven grades according to the known ancestral relationships of the varieties and the climatic conditions of the regions. Grade 1 was crosses between the varieties of the same region. Figure 14.5 shows the heterosis in the F_1 's and F_2 's as percentages of the mean of the parental varieties, plotted against the degree of diversity. The mean parental yields are also shown. Heterosis was greatest in the crosses of intermediate 'width'. The widest crosses gave much less heterosis though it was still positive even in the F_2 generations. There is, however, no evidence from these crosses that epistatic interaction contributed to coadaptation. If epistatic interactions contributed to the yields of the parent populations, the heterosis in the F_2 generations would be less than half the heterosis in the F_1 's; but in all except the Grade 1 crosses it was more than half. (See Lynch, 1991, for an analysis of these crosses.)

Problems

- 14.1** Suppose that a random-bred population of maize had a mean yield of 140 g per plant, and that four loci with known effects on yield were segregating. What would be the inbreeding depression caused by these loci after one generation of self-pollination, if the gene effects were as given below? The gene effects in each case are the differences in yield (g per plant) between the genotype listed and the 'AA' homozygote; the gene frequency is that of the 'a' allele.

<i>Difference from AA</i>			
<i>Locus</i>	<i>Aa</i>	<i>aa</i>	<i>q_a</i>
(1)	-10	-20	0.5
(2)	+ 5	-30	0.5
(3)	-20	-30	0.2
(4)	0	-60	0.1

[Solution 69]

- 14.2** If inbreeding with selection in the maize population specified in Problem 14.1 succeeded in fixing the more favourable allele at each of the four loci, by how much would the yield be increased?

[Solution 79]

- 14.3** From the data on mouse litter size in Example 14.2 calculate how much inbreeding depression of litter size results from inbreeding in the mother and how much from inbreeding in the litter. Assume that both are linear with respect to F , and that the maternal and litter effects combine additively. What would be the predicted litter size if mice could be inbred to $F = 100$ per cent without any selection operating?

[Solution 89]

- 14.4** Use the results of Problem 14.3 to predict the total inbreeding depression of litter size when the inbreeding coefficient of the mothers is 0.56 and that of the litters is 0.64. These

were the inbreeding coefficients in the last generation of the experiment depicted in Fig. 14.2(a). This was a different experiment from that of Example 14.2 used in Problem 14.3. How well do the two experiments agree? [Solution 99]

14.5 A control line of mice was kept for 30 generations and its litter size showed no evidence of inbreeding depression in spite of its effective population size being not greater than 40. One possible reason for the absence of inbreeding depression is that there may have been some inadvertent selection for litter size. The mating system was intended to be minimal inbreeding, one young female being taken at random from each family. In theory no selection was possible, but minimal inbreeding cannot be applied strictly in practice because some families contain no surviving female. Replacements have then to be taken from other families, and some selection can be caused by these replacements. How much selection would have been needed to counteract inbreeding depression at the rate expected from the solution of Problem 14.3? The selection resulting from replacements would have been individual selection, and the realized heritability appropriate to individual selection was estimated in the same strain to be 0.22.

Data from Falconer, D. S. (1960) *J. Cell. Comp. Physiol.*, **56** (Suppl. 1), 153–67.

[Solution 109]

14.6 Crosses were made between varieties of cultivated tomatoes, which are normally self-fertilizing. The mean weights (kg) of fruit produced per plant in a three-week period by the parental varieties and the F₁ in two crosses were as follows.

Cross	P ₁	P ₂	F ₁
(1)	1.44	1.36	1.41
(2)	1.28	0.88	1.42

What would be the predicted yields of the F₂ generations, and of the F₃ generations produced by selfing the F₂?

Data from Williams, W. (1960) *Genetics*, **45**, 1457–65.

[Solution 119]

14.7 In Problem 6.1 the mean leaf numbers in the F₁ and F₂ generations of a cross of two varieties of tobacco were calculated. The mean of the F₁ was 15.72 ± 0.24 and the mean of the F₂ was 15.84 ± 0.49. Without knowing the leaf numbers in the parental varieties, what can you conclude about the heterosis shown by the F₁? [Solution 129]

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 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. Only a brief description of the main outlines will be given here. For detailed treatment see Wright (1969), and Weir and Cockerham (1977). Similarly, when lines are crossed, the variance can be partitioned into components between and within crosses. The variance of crosses will be described at the end of this chapter. The redistribution of genetic variance is not the only effect of inbreeding; experiments have shown that the environmental variance is sometimes also affected. 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 expectations concerning the genetic variance being manifest in the observed phenotypic variance. Another matter concerning inbreeding to be considered is the genetic stability of highly inbred lines, which is important in connection with the use of 'standard' inbred strains for experimental purposes.

Inbreeding

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 proportion 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 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.

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 with 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 that show little non-additive genetic variance. The description to be given refers to slow inbreeding, which means that the inbreeding coefficient can be taken, without too much error, to be the same in two consecutive generations. 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 [8.5], is

$$V_G = V_A = 2p_0q_0a^2$$

The variance within any one line is $V_{Gw} = 2pq_0a^2$, 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 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 frequencies p and q is obtained from equation [7.2] as

Table 15.1 Partitioning of the variance in a population with inbreeding coefficient F , when the genetic variance V_G in the base population is due to genes with no dominance; f is the coancestry of individuals in the same line. (1) Slow inbreeding, when $F_{t+1} = F_t$ approximately. (2) Rapid inbreeding.

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

$M = a(p - q) = a(1 - 2q)$. Thus we want to find the variance of $(a - 2qa)$. Epistasis is assumed to be absent, so a is constant, i.e., the same in all lines. Therefore

$$\sigma_M^2 = \sigma_{(2aq)}^2 = 4a^2\sigma_q^2 = 4a^2p_0q_0F$$

(from equation [3.14]), which equals $2FV_G$. This 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 summarized in Table 15.1, column (1). When inbreeding is rapid the components are as in column (2) for reasons explained by Crow and Kimura (1970, p. 138). Here f is the coancestry of individuals of the same line, and this is equal to the inbreeding coefficient in the next generation if individuals are mated at random within lines. From Table 15.1 we see that the total genetic 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. 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 increasing variance between lines is illustrated from experimental data in Fig. 15.1.

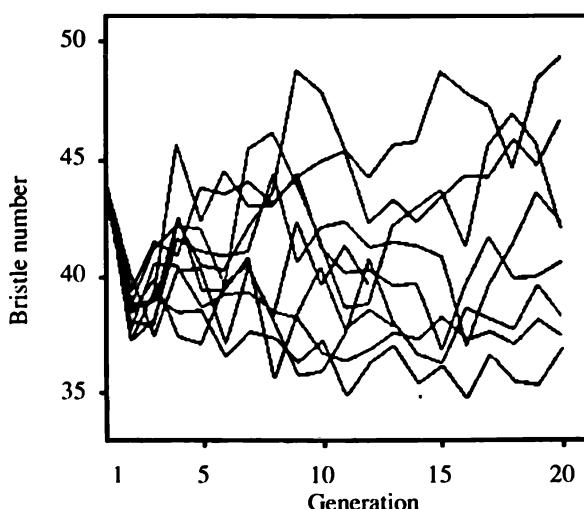


Fig. 15.1. Differentiation between lines by random drift, shown by abdominal bristle number in *Drosophila melanogaster*. The graphs show the mean bristle number in each of 10 lines during full-sib inbreeding without artificial selection. (After Rasmuson, 1952.)

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

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

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 changes in 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 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. Figure 15.2 shows the redistribution of variance arising from recessive genes at a frequency of $q = 0.1$ in the base population. Figure 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 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 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.

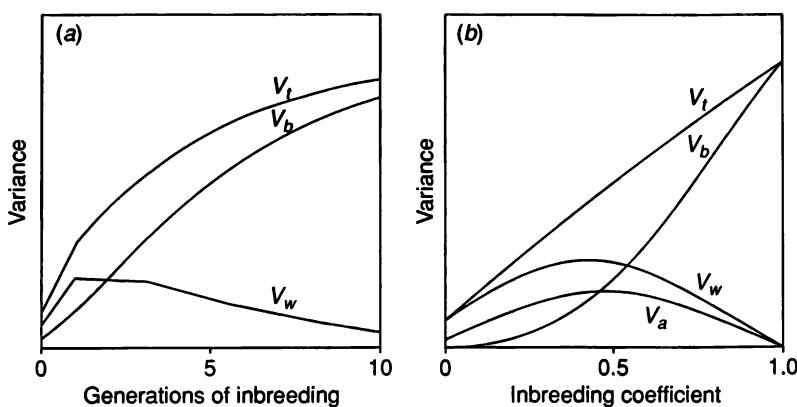


Fig. 15.2. Redistribution of variance arising from a single fully recessive gene with initial frequency $q_0 = 0.1$. (a) with full-sib mating, (b) with slow inbreeding. (After Robertson, 1952.)

V_t = total genetic variance.

V_b = between-line component.

V_w = within-line component.

V_a = additive genetic variance within lines.

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 variance than non-inbred individuals. This fact has been revealed by many experiments in which the variances of inbreds and of hybrids have been compared. If highly inbred lines are more variable than the F_1 cross between them (i.e., the 'hybrid') this difference must be attributed to the environmental component of variance, 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 is not a universal phenomenon, but it has been observed in a wide variety of characters and organisms. Some examples are cited in Table 15.2; others are given by Lerner (1954) and Wright (1977). The phenomenon has been extensively studied in behavioural characters of rats and mice; these have been reviewed by Hyde (1973), who found that 14 out of 19 behavioural characters showed the phenomenon.

Before we consider the possible reasons for the differences of environmental variance, there are two points in connection with the phenomenon that should be mentioned. The first is a technical matter. If the mean 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 be sure that any difference of variance found is not simply a reflection of the difference of mean. In other words, a measure of variation must be found that is uncorrelated with the mean. The coefficient of variation is often, though not always, an appropriate measure. The problem is basically a matter of the choice of scale, and will be considered 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 variation induced by the environment and adaptive responses by the

Table 15.2 Examples of characters with phenotypic variance greater in inbreds than in hybrids. The values are phenotypic variances averaged over the inbred lines and over the F_1 's where more than one cross was made. $(C.V.)^2 = \text{variance}/\text{mean}$

	Inbreds	Hybrids
<i>Drosophila melanogaster</i> (Robertson and Reeve, 1952)		
Wing length: 6 inbreds, 6 F_1 's.	2.35	1.24
<i>Mice</i> (McLaren and Michie, 1956)		
Duration of 'Nembutal' anaesthesia (log minutes).		
2 inbreds, 1 F_1	0.0665	0.0165
<i>Mice</i> (Yoon, 1955)		
Age at opening of vagina (days).		
3 inbreds, 2 F_1 's	51.7	17.4
<i>Mice</i> (Chai, 1957)		
Weight (g) at ages given ($C.V.$) ²	Birth	119
2 inbreds, 1 F_1	21 days	98
	60 days	24
		59
		47
		19
<i>Rats</i> (Livesay, 1930)		
Weight at 90 days ($C.V.$) ² , 3 inbreds, 2 F_1 's	522	170
<i>Maize</i> (Shank and Adams, 1960)		
Plant height ($C.V.$) ²	44	30
Ear weight ($C.V.$) ²	412	198
10 inbreds, 5 F_1 's		

organism to the particular environmental circumstances. The distinction is necessary when one considers the possible relation of variation to fitness. In the first case, the presumption is that there is an optimal phenotype that is the same for all the environmental circumstances under consideration. The body temperature of mammals is an obvious example. Insensitivity to environmental variables is then an aspect of fitness: the fittest individuals are those that can regulate their development, or their physiological processes, so as to achieve the optimal phenotype despite sub-optimal values of the environmental variables. The restriction of variation in this way is called *homeostasis*. The environmental factors causing the variation are not necessarily external, but include also internal causes of developmental variation. In the second case, when the organism responds adaptively, the character has different optima in different environments. The output of sweat in relation to variation of ambient temperature is an example. With characters of this sort the relation with fitness is reversed: individuals with the ability to vary are fitter than those without the ability.

What then is the cause of some characters being more variable in inbreds than in hybrids? The phenomenon can be looked on as a manifestation of inbreeding depression or heterosis (Mather, 1953). On this view, a character showing the phenomenon is one for which homeostasis is beneficial, and inbreeding has reduced this component of fitness, causing environmental variance to be increased in inbreds and correspondingly reduced when hybrids are compared with inbreds. This interpretation implies that there are genes that affect variability, i.e., homeostasis, independently of any effect they may have on the mean of the character, and that

these genes must have some degree of directional dominance for increased homeostasis. Another interpretation of the phenomenon is in biochemical terms. Different allelic forms of enzymes often have their maximal enzymic activity at different values of environmental variables such as temperature or pH. Heterozygotes, with both forms of the enzyme, may therefore maintain an adequate level of enzyme activity over a wider range of environmental variation than homozygotes, with only one form of the enzyme, can do. In so far as the enzyme activity is reflected in a measured character, then, heterozygotes are less sensitive to environmental variables than are homozygotes. On this view, the stability is not necessarily related to fitness, but is simply a biochemical consequence of heterozygosity at some loci that affect the mean of the character. These loci are consequently overdominant with respect to their effect on variability, though not necessarily in their effect on the mean of the character or on fitness.

Uniformity of inbred strains

Inbred strains of laboratory animals, particularly mice, are widely used as experimental material in testing and assay, and in many other areas of biological research. The inbred strains are single lines and are used because uniformity is desired. For some purposes, when for example the absence of antigenic differences is necessary, it is genetic uniformity that is required. Abundant experience has shown that the highly inbred strains of laboratory mice fully satisfy this requirement of genetic uniformity. For other purposes, however, it is not genetic uniformity alone that matters, but phenotypic uniformity. The less variable the animals, the smaller the number that need be used to attain a given degree of precision in measuring their response to a treatment. The value of inbred animals in this respect therefore depends on how much of the variance of the character is genetic in origin, because only the genetic variance is removed by inbreeding. It depends also on how much the environmental variance is affected by inbreeding; the increased environmental variance, as exemplified in Table 15.2, may sometimes offset the reduced genetic variance so that an inbred strain is more variable phenotypically than a non-inbred stock. The way to obtain genetic uniformity without increased environmental variation is, of course, to use the F_1 of a cross between two inbred strains. This has the added advantage that the F_1 individuals are usually healthier, more viable and more fertile than the inbreds, though it does not reduce the cost of production since the inbreds have to be maintained as parents. Another point in connection with the use of inbred or F_1 animals may be mentioned. 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. There may be appreciable differences of response between genotypes, and consequently results obtained with one strain or cross cannot be relied on to be applicable to other strains.

Mutation

We saw in Chapter 12 that mutation generates new variation of metric characters that is not negligible in the context of long-term selection. How much does

mutation affect the conclusions reached about the consequences of inbreeding? Consider first selectively neutral mutants at individual loci. The rate of origin of allelic differences was shown in Chapter 4 to be equal simply to the mutation rate to neutral alleles, irrespective of the population size. To repeat the argument in the present context: in a sib-mated line there are four representatives of each autosomal locus, so the rate of occurrence of mutations at a particular locus is $4u$, where u is the mutation rate per gamete per generation. But a mutation that has occurred has a one in four chance of becoming fixed. So the rate of allelic substitution per generation is equal to the mutation rate. Mutants that are not strictly neutral can become fixed, especially in very small populations. In Chapter 4 it was stated that a mutant is ‘effectively neutral’ if the coefficient of selection against it is less than $1/2N_e$, which is about 0.2 in a sib-mated line (see Chapter 5). Thus if, for example, the rate of mutation to alleles with coefficients of selection against them of less than about 20 per cent were 10^{-5} , and if the total number of loci were 10,000, then in any one subline there would be, on average, 1 allelic substitution every 10 generations ($10^{-5} \times 10^4 \times t = 1$; $t = 10$). With sib mating a new mutant is very soon fixed or lost, so the number of loci segregating at any one time is very small. Thus the conclusion drawn about the genetic uniformity of sib-mated lines is very little affected by mutation. The long-term constancy of inbred lines is, however, not absolute and mutation is not negligible when we consider metric characters, as we shall now see.

We cannot extend the foregoing argument to metric characters without knowing the number of loci affecting the character and the magnitude of their effects, neither of which is well enough known. What matters, however, is the rate at which new variance is generated by mutation at all relevant loci, and some estimates of this rate are available. The variance generated by mutation in one generation may be called the mutational variance, symbolized by V_M . This is most conveniently expressed as a proportion of the environmental variance V_E . Estimates from various characters in several species show that on average V_M is of the order of $V_E \times 10^{-3}$. (These estimates are reviewed by Lynch, 1988, and are considered again in Chapter 20.) This new variation arising in each generation by mutation accumulates until the gain in each generation is balanced by the loss from fixation due to the inbreeding. The genetic variance thereafter remains constant. With close inbreeding this constant state is attained after only a few generations (see Lynch and Hill, 1986).

The amount of genetic variance lost in each generation can be deduced as follows. The proportion of the original variance remaining within lines is $(1 - F)$ as given in Table 15.1. If we write F in terms of ΔF by equation [3.12] and ΔF in terms of N_e by equation [4.1], and if we put $t = 1$, we obtain $1 - (1/2N_e)$ as the proportion remaining after one generation. If we let V_G be the existing variance in any generation then the amount lost in the next generation is $V_G/2N_e$. When this is equated to the new mutational variance, V_M , we find

$$V_G = 2N_e V_M$$

This is the constant amount of genetic variance within an inbred line. It refers to neutral genes with additive effects on the character, though non-additivity makes

little difference (see Lynch and Hill, 1986). With sib mating $N_e = 2.6$ (see Chapter 5), and if we substitute this and the estimate given above for V_M , we find $V_G = (5 \times 10^{-3})V_E$ (approx.). This may be more meaningful if expressed as the heritability, which is $V_G/(V_G + V_E) = 0.5$ per cent. Again, therefore, mutation does not affect the conclusion that sib-mated lines are for most practical purposes genetically uniform.

Subline divergence

In contrast to its negligible effect on the variance within sib-mated lines, mutation does have important consequences if an inbred strain is split into sublines. The use of standard inbred strains facilitates the comparison of results from different laboratories. Dispersion to different laboratories inevitably leads to the strain being split into sublines and it is important to know the extent to which the sublines become differentiated by random drift acting on the mutational variance.

If the strain was highly inbred before separation into sublines none of the original variance in the base population will be left and, furthermore, the variance originating from mutation will have reached its stable level of $2N_e V_M$, and this will also be the stable level within sublines after their separation. The amount by which the variance between sublines increases in each generation is as follows. The variance between sublines is $2FV_G$ (by Table 15.1). Putting F in terms of N_e as was done above for the within-line variance gives the rate at which the variance between sublines increases per generation as V_G/N_e . Substituting $V_G = 2N_e V_M$ we find that the between-line variance increases by $2V_M$ in each generation. (This rate is independent of the population size because larger populations have more within-line variance but differentiate more slowly by random drift.) If the sublines were separated t generations previously then the variance of subline means will be $2tV_M$ because $2V_M$ is the rate of differentiation per generation. This, of course, assumes that there are no environmental differences between the sublines. To appreciate the practical importance of this differentiation we may express the variance between sublines, σ_b^2 , as a proportion of the phenotypic variance within sublines, σ_w^2 . We then have

$$\frac{\sigma_b^2}{\sigma_w^2} = \frac{2tV_M}{2N_e V_M + V_E}$$

If we substitute $V_M = 10^{-3}V_E$ and $N_e = 2.6$ we get

$$\sigma_b^2/\sigma_w^2 = (1.63 \times 10^{-3})t$$

Thus the variance between the means of sib-mated sublines separated, for example, 25 generations previously will be about 5 per cent of the phenotypic variance within the sublines. Detectable, and even quite large, differences between sublines are therefore to be expected, and have in fact been found in several experiments, for example McLaren and Michie (1954), Grewal (1962), Festing (1973), and the experiment described in Example 15.1 below. For further details about mutation and subline divergence see Lynch and Hill (1986) and Lynch (1988).

Example 15.1

This is a brief description of a study of two inbred mouse strains by Bailey (1959). Six measurements of various skeletal dimensions were studied in two sublines of the C57BL/6 strain and two sublines of the BALB/cAn strain. The strains had been separated into sublines after 30 and 78 generations respectively of full-sib mating, so differentiation by residual segregation was not a serious possibility. The average number of generations since the separation of the sublines was 46.5 in C57BL and 9 in BALB. The sublines of both strains had by then diverged a great deal in respect of some characters and in both strains the sublines differed significantly in four of the six characters. The ratio σ_b^2/σ_w^2 for the six characters in C57BL ranged from 0 to 1.27 with a mean of 0.41, and in BALB the ratio ranged from 0.08 to 0.52 with a mean of 0.23. By substituting the appropriate values into the expression given above for σ_e^2/σ_w^2 and rearranging, we can arrive at estimates of the mutational variance. The values of $(V_M/V_E) \times 10^{-3}$ ranged from 0 to 15 with a mean of 5 in C57BL and from 4 to 34 with a mean of 14 in BALB. These estimates, however, are very imprecise because they are based on only two sublines in each strain.

Crossing

In the first part of this chapter we saw how the genetic variance of a metric character is distributed between and within inbred lines. We now have to consider the complementary problem of how the variance is distributed between and within crosses. The variance between crosses is important in predicting what improvement can be expected from inbreeding and crossing; this will be explained in the next chapter. The variance after crossing presents a simpler problem than the variance after inbreeding for the following reason. The gametes produced by inbred lines are not different from the gametes produced by a non-inbred population, provided selection has not changed gene frequencies. This means that any F_1 individual has a genotype that could, in principle, be found in a random-breeding population; and, conversely, any genotype in the original random-breeding population could be found among the crosses. Consequently the total genetic variance after crossing is the same as that in the base population. The F_1 individuals of the same cross can be regarded as a 'family' with a degree of relationship dependent on the inbreeding coefficient of the parental lines. The covariance of these 'families' is the variance between crosses. If the parental lines are fully inbred, all members of the same F_1 have identical genotypes and the variance between crosses is equal to the total genetic variance in the base population. If the parental lines are not fully inbred, the covariance of the 'families' can be worked out from the coefficients of relationship derived from coancestries. This will now be explained by consideration of random crosses.

Variance between crosses

Assume that a large number of lines have been inbred without selection from the same base population and all to the same inbreeding coefficient. Crosses are then made at random between the lines. Assume further that each cross is made from many individuals of the parent lines, these parental individuals not being related to each other within their lines. This means that the genetic variance within the lines is fully represented in the crosses. Each cross, then, is to be regarded as a family with

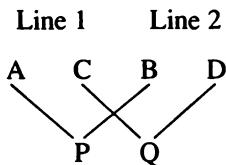


Fig. 15.3.

a certain degree of relationship between its members. The component of variance between crosses is the covariance of these related individuals. The composition of the covariance of relatives was given in equation [9.13] in terms of the genetic components and the coefficients of relationship, r and u . The coefficient r concerns the additive variance and u the dominance variance. The coefficients r and u can be derived from the coancestries as shown by equations [9.11] and [9.12]. The coancestries concerned in a cross are as follows. The relevant individuals are shown in Fig. 15.3, where they are given letters to correspond with those in Fig. 5.4. A and C are two individuals of one parental line; B and D two individuals of the other parental line. P and Q are two F_1 individuals produced by crossing A with B, and C with D, respectively. There are many other crosses producing other F_1 's with pedigree relationships like P and Q. We need the covariance appropriate to the relationship of P with Q expressed in the coancestry f_{PQ} . First, by equation [9.11], $r = 2f_{PQ}$, and by equation [5.2], $f_{PQ} = \frac{1}{2}(f_{AC} + f_{AD} + f_{BC} + f_{BD})$. The two parental lines are unrelated, so $f_{AD} = f_{BC} = 0$. The two lines have the same inbreeding coefficient, so $f_{AC} = f_{BD} = F$, where F is the inbreeding coefficient of the next generation of the lines, i.e., the generation contemporaneous in terms of generations with the F_1 . Thus $f_{PQ} = \frac{1}{2}F$, and this gives

$$r = F \quad \dots [15.2]$$

Next, by equation [9.12], $u = f_{AC}f_{BD} + f_{AD}f_{BC}$, which reduces to

$$u = F^2 \quad \dots [15.3]$$

The covariance can now be expressed in terms of the inbreeding coefficient by substituting equations [15.2] and [15.3] into equation [9.13]. This gives the variance between crosses as

$$\sigma_X^2 = FV_A + F^2V_D + F^2V_{AA} + F^3V_{AD} + F^4V_{DD} + \dots \quad \dots [15.4]$$

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, not of the parents used in the crosses, but of the next generation of the lines. The remainder of the genetic variance appears within lines, i.e., $(1 - F)V_A + (1 - F^2)V_D$, etc. The variance between crosses is the variance of the true means, which would be estimated as the component of variance from an analysis of variance. Equation [15.4] gives the genetic content of this component. It corresponds to what would be estimated experimentally only if there are no environmental differences between the crosses. If the variance of the observed means of crosses were to be calculated, this would be increased by a fraction of the within-cross variance depending on the number of

individuals measured in each cross for the reasons explained in connection with family selection in Chapter 13 (see Table 13.3).

The main point of interest in equation [15.4] is that the contributions of the different components of genetic variance are differently related to the inbreeding coefficient. The contribution of the additive variance increases linearly with F , but those of the dominance and interaction components increase in proportion to the square or higher powers of F . The consequence is that if the character is one with much non-additive variance, the crosses become differentiated much more rapidly in the late stages of inbreeding, as F approaches 1, than they do in the early stages. When $F = 0.5$, each cross is genetically equivalent to a full-sib family in the base population; when $F = 1$, the whole of the genetic variance appears between crosses. The practical importance of the way in which the between-cross variance is related to F will be considered in the next chapter.

Combining ability

The variance between crosses was derived above on the assumption that a large number of lines were crossed at random. The 'large number' implies that each line was used in only one cross. If, in contrast, each line is crossed with several others, the variance between crosses can be partitioned in a way that has great importance for understanding the use of crossbreeding for improvement. We shall assume, for the sake of explanation, that large numbers of lines, crosses, and individuals are used, so that all means are estimated without error. Crossing a line to several others provides an additional measure of the line, i.e., the mean performance of the line in all its crosses. This mean performance, when expressed as a deviation from the mean of all crosses, is called the *general combining ability* of the line. It is the average value of all F_1 's having this line as one parent, the value being expressed as a deviation from the overall mean of crosses. Any particular cross, then, has an 'expected' value which is the sum of the general combining abilities of its two parental lines. The cross may, however, deviate from this expected value to a greater or lesser extent. This deviation is called the *specific combining ability* of the two lines in combination. In statistical terms, the general combining abilities are main effects and the specific combining ability is an interaction. The true mean X of a cross between lines P and Q can thus be expressed as

$$X - \bar{X} = GCA_P + GCA_Q + SCA_{PQ} \quad \dots [15.5]$$

where \bar{X} is the mean of all crosses, and GCA and SCA are the general and specific combining abilities respectively. In practice, another term, E , must be added to the right-hand side to represent sampling error in estimating X .

The terms on the right-hand side of equation [15.5] are uncorrelated with each other, so the total between-cross variance (excluding error variance) is made up as follows:

$$\sigma_X^2 = \sigma_{GCA(M)}^2 + \sigma_{GCA(F)}^2 + \sigma_{SCA}^2 \quad \dots [15.6]$$

where (M) and (F) refer to the general combining abilities of lines used as male and as female parents respectively. If the lines are not distinguished by sex or in any other way, then equation [15.6] becomes

$$\sigma_X^2 = 2\sigma_{GCA}^2 + \sigma_{SCA}^2 \quad \dots [15.7]$$

The two components into which the total between-cross variance can be partitioned are the variance of general combining ability and the variance of specific combining ability. These are observational components of variance in the sense explained in Chapter 9, and are estimated from an analysis of variance. Their importance lies in the fact that the causal components of genetic variance contribute to them differently, as we shall now see.

A set of crosses with one line as common male parent can be regarded as a family analogous to a paternal half-sib family. The covariance of these families is the variance of general combining abilities of male lines, $\sigma_{GCA}^2(M)$. This covariance is found from the coefficients of relationship in the same way as before. Figure 15.3 will serve to illustrate the relevant pedigree. Individuals A and C are two members of the common male line, but B and D are now members of two different lines to which A and C are crossed, producing the two F_1 s, P and Q. The coancestries are now all zero except $f_{AC} = F$. This gives $r = \frac{1}{2}F$ and $u = 0$. Substitution into equation [9.13] as before gives

$$\sigma_{GCA}^2(M) = \frac{1}{2}FV_A + \frac{1}{4}F^2V_{AA} + \dots$$

The same argument applies to lines used as female parents and therefore, provided there are no maternal or sex-linked effects, $\sigma_{GCA}^2(F) = \sigma_{GCA}^2(M)$. The variance of specific combining ability is what is left of the total variance between crosses as given in equation [15.4]. We thus arrive at the following composition of the components of variance of crosses:

General combining ability

of male parents:	$\sigma_{GCA}^2(M) = \frac{1}{2}FV_A + \frac{1}{4}F^2V_{AA} + \dots$	}
of female parents:	$\sigma_{GCA}^2(F) = \frac{1}{2}FV_A + \frac{1}{4}F^2V_{AA} + \dots$	
Specific comb. ability:	$\sigma_{SCA}^2 = \frac{1}{2}F^2V_{AA} + F^2V_D + F^3V_{AD} + F^4V_{DD} + \dots$	

... [15.8]

From this it can be seen that differences of general combining ability are due to the additive variance and $A \times A$ interactions in the base population; and differences of specific 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 specific combining ability increases with higher powers of F . It is therefore the specific, and not the general, combining ability that is expected to increase in variance more rapidly as the inbreeding reaches high levels.

The components of genetic variance in equation [15.8] are those of a random-breeding population with all gene frequencies equal to those in the lines crossed and with coupling and repulsion linkages in equilibrium. This random-breeding population can be regarded as being the base population, real or hypothetical, from which the lines were derived without selection. Or, alternatively, it can be regarded as a synthetic population made by random mating among the crosses and then bred by random mating for long enough to reach linkage equilibrium. Which of these viewpoints is to be adopted affects the details of the analysis of variance. In the first case the lines are regarded as a sample of the population and are therefore random

factors: in the second case the lines are the whole population and are fixed factors (see Griffing, 1956b, for details).

Estimation of combining abilities A method of estimating general combining abilities that is 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. The general combining abilities measured are those of lines used as female parents. If the variances of general combining ability are assumed to be the same for male and female parents, the variances of general and specific combining ability can be estimated and interpreted as in equation [15.8].

The general combining ability of a line can be estimated by crossing it with individuals from the base population instead of with other inbred lines. This method is known as *top-crossing*. It is equivalent to crossing with a random set of lines inbred from the base population without selection because, as noted earlier, the gametes from inbred lines are not different in genetic content from those of the base population.

A commonly used experimental design for crossing inbred lines is the diallel cross, in which each line is crossed with every other line. The estimation of the general combining abilities of the lines is explained and illustrated in Example 15.2 below. The analysis of a diallel cross for the purpose of estimating variances is complicated because it depends on whether reciprocal crosses are included, and on the assumption made about the population to which the genetic components of variance refer. The theory and analytical procedures are explained by Griffing (1956a, b) and are evaluated by Pooni, Jinks, and Singh (1984) and A. J. Wright (1985).

Example 15.2

The calculation of general and specific combining abilities will be illustrated by data from Sprague and Tatum (1942) on crosses between inbred lines of maize. Ten lines were used and each was crossed with each of the other nine, but reciprocal crosses were not made. There were therefore $\frac{1}{2} n(n - 1) = 45$ crosses, n being the number of lines. The yields, in bushels per acre, are given in table (i); these are the mean yields of each cross. (100 bushels per acre of maize = 6.725 tonnes per hectare.) The column headed T gives the total yield of each line in all nine crosses, obtained by summing down the appropriate column and along the row as indicated by the arrows. Note that each cross contributes to two totals, so $\Sigma T = 2\Sigma X$, where X is the yield of a cross.

If there were a very large number of lines, the general combining ability of a line would be calculated simply as the deviation of its mean, $T/(n - 1)$, from the overall mean, \bar{X} . With a small number of lines, however, this is not valid, because each of the other lines contributes a fraction, $1/(n - 1)$, of its general combining ability to the mean of the line in question. Thus, for example, the mean \bar{A} of line A in all its crosses is

Continued

Example 15.2 continued

$$\bar{A} - \bar{X} = G_A + \frac{1}{n-1}(G_B + G_C + \dots + G_N)$$

where the G 's are the general combining abilities of the lines A to N as indicated by the subscripts. Now, $\Sigma G = 0$, so $(G_B + G_C + \dots + G_N) = -G_A$, and so

$$\bar{A} - \bar{X} = \left(\frac{n-2}{n-1}\right)G_A$$

from which

$$G_A = \left(\frac{n-1}{n-2}\right)(\bar{A} - \bar{X})$$

It is more convenient to work with the totals than with the means. Substituting $\bar{A} = T_A/(n-1)$ and $\bar{X} = \Sigma T/(n-1)$ leads to

$$G_A = \frac{T_A}{n-2} - \frac{\Sigma T}{n(n-2)}$$

The general combining abilities of the lines in the table are entered in the column headed GCA. Formulae appropriate to other designs of diallel cross are given by Simmonds (1979, p. 112).

Table (i)

	B	C	D	E	F	G	H	I	J	T	GCA
A	86	84	98	98	92	92	97	81	88	816	3.75
B	91	105	102	86	92	79	80	90	811	3.125	
C	.	87	80	65	84	93	77	83	744	-5.25	
D	.	.	97	100	101	97	91	80	856	8.75	
E	.	.	.	97	83	93	78	83	811	3.125	
F	80	93	76	70	759	-3.375	
G	90	74	72	768	-2.25	
H	91	96	829	5.375	
I	78	726	-7.50	
J	740	-5.75	
Sums									$2\Sigma X = \Sigma T = 7860$	0.000	
Overall mean									$\bar{X} = 87.333$		

The 'expected' value of each cross can now be calculated, 'expected' meaning the value that would be predicted from the two general combining abilities, in the absence of any knowledge about the specific combining ability. To take the best cross, BD, as an example, $E(X_{BD}) = 3.125 + 8.75 + 87.333 = 99.21$. The difference between the observed and expected values estimates the specific combining ability of the two lines in combination: $SCA_{BD} = 105 - 99.21 = +5.79$. The value of the specific combining ability so obtained is subject to the sampling error in estimating X_{BD} . Figure 15.4 shows a plot of the observed yields against the expected yields. If there were no deviations from expectation, the points would lie on the diagonal line with a slope of 1. The vertical distance of any point from the diagonal is the specific combining ability together with the sampling error of the yield of the cross. (If the lines were not highly inbred, there would also be error in estimating the specific combining abilities, this error being due to the sampling of genotypes from the lines.)

Continued

Example 15.2 continued**Table (ii)**

Source	d.f.	SS	MS	Expectation of MS
GCA	9	2,179	242.11	$\sigma_E^2 + \sigma_{SCA}^2 + 8\sigma_{GCA}^2$
SCA	35	1,617	46.20	$\sigma_E^2 + \sigma_{SCA}^2$
Error			5.36	σ_E^2
		$2\sigma_{GCA}^2 = 48.98 = 54.5\%$		
		$\sigma_{SCA}^2 = 40.84 = 45.5\%$		

For the purpose of illustration, the variances of general and specific combining ability will be calculated on the supposition that the lines were a random sample from a population of lines, though in fact they were not randomly selected. The analysis of variance for estimating the components is given in table (ii). The sums of squares for GCA and SCA were calculated from the data in table (i); the mean square for error is the value stated in the paper. The variance of the true means of crosses, i.e., after deducting the variance due to error, is made up of 54.5 per cent due to general combining ability and 45.5 per cent due to specific combining ability. The proportion attributed to specific combining ability is large because these lines were a selected group, and the variation in general combining ability among them was consequently less than would be expected in a random sample.

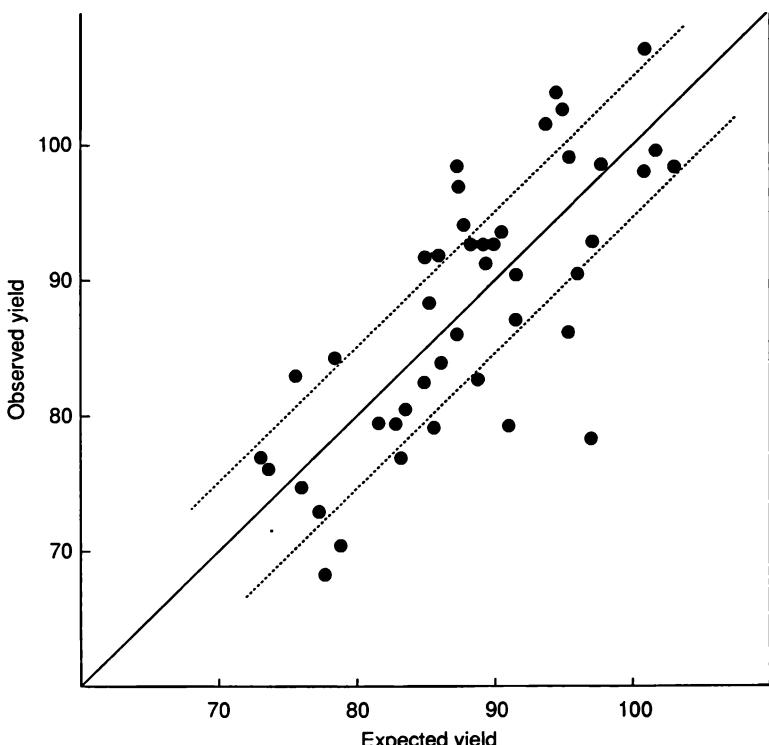


Fig. 15.4. Observed and expected yield (bushels per acre) in crosses between ten lines of maize. The expected yield of each cross is the sum of the general combining abilities of the two parental lines. Deviations from the regression line are due to specific combining ability and error in estimating the mean yield of the cross. The two dotted lines show the positions of deviations from the regression of ± 2 standard errors of cross means. (Data from Sprague and Tatum, 1942.)

Problems

15.1 The genetic variance of abdominal bristle number in *Drosophila* is predominantly additive (see Table 8.2). Suppose that a large population is subdivided into replicate lines each bred from 20 parents, and that these lines are continued until the calculated inbreeding coefficient is 50 per cent. If the phenotypic variance in the base population was 4.0 and the heritability 52 per cent, what would be the components of the phenotypic variance between lines and within lines? What would be the heritability (1) within lines and (2) overall, disregarding the subdivision into lines?

[Solution 75]

15.2 Suppose that the base population of *Drosophila* in Problem 15.1 is inbred for three generations by full-sib mating. What would be the expected response to selection carried out in the following manner? There are many lines, each consisting of a single full-sib family. Four flies, two of each sex, are taken at random from each line; the best 5 per cent of the lines are selected on the basis of the mean of the 4 flies sampled from them; the 4 flies from each of the selected lines are then mated with their sibs and the progeny are measured.

[Solution 85]

15.3 The body size of *Drosophila*, measured as thorax length, has little non-additive genetic variance (Table 8.2). Suppose that the heritability of thorax length was found to be 0.34 in a stock that was maintained by random mating among large numbers but had recently been started from a single pair of flies. What would be the estimate of the heritability in the population from which the original pair was taken?

[Solution 95]

15.4 Minor differences in the skeleton are common in mice. Twenty-seven characters of which variants occur were studied in sublines of the C57BL inbred strain. Two particular sublines were found to differ in respect of 5 of the 27 characters, and each difference was attributed to one mutational step. The strain had been inbred by full-sib mating for 40 or more generations before separation of the sublines. After separation, one of the sublines had a further 21 generations, and the other had 29 generations, of full-sib mating at the time of the study. If the differences did arise from mutation, how would these results be interpreted in terms of the number of loci at which mutations can affect the characters and their mutation rates?

Data from Deol, M.S. *et al.* (1975) *J. Morph.*, **100**, 345–76.

[Solution 105]

15.5 The following estimates of the parameters of individual plant yield were made in an open-pollinated variety of maize.

$$\text{Mean} = 308 \text{ g}; \quad V_P = 5,798; \quad V_A = 864; \quad V_D = 188$$

If this population were inbred without any selection and the lines were crossed (1) when the inbreeding coefficient was 50 per cent, and (2) when the inbreeding coefficient was virtually 100 per cent, what would be the phenotypic components of variance between crosses and within crosses? Assume that $V_I = 0$, and that environmental differences between crosses were eliminated by the experimental design.

If each cross mean were estimated from measurements of 20 individual plants, what would be the variance of the observed means of crosses?

Data from Gardner, C.O. (1977) pp. 475–89 in Pollak, E. *et al.* (eds), *Proc. Int. Conf. Quantitative Genetics*. Iowa State Univ., Ames, Iowa, USA.

[Solution 115]

15.6 Consider again the crosses in Problem 15.5. If 50 crosses were made at each stage, what would you predict the highest observed mean yield among the 50 crosses to be? If this best cross were then repeated, and a new set of plants from it were grown and measured, what would you predict the mean yield to be, assuming that there was no environmental difference between the first and second determinations of its yield? [Solution 125]

15.7 A diallel cross, without reciprocals, was made between five varieties of the bean *Phaseolus aureus*, which is normally self-pollinating. The mean yields in grams per plant of the crosses are given below. The varieties are designated A to E and their yields are also given (on the diagonal), although these are not needed for this problem. Calculate (1) the general combining ability of each variety, and (2) the deviation from expectation of each cross, i.e., the specific combining ability + error. Plot a scatter diagram like Fig. 15.4.

	A	B	C	D	E
A	9.7	14.1	22.8	16.9	31.8
B	—	3.3	16.5	6.2	12.4
C	—	—	9.0	8.3	9.2
D	—	—	—	6.8	13.1
E	—	—	—	—	12.5

Data from Singh, K.B. & Jain, R.P. (1971) *Theor. Appl. Genet.*, **41**, 279–81.

[Solution 135]

16 Inbreeding and Crossbreeding

III. Applications

The crossing of inbred lines to produce hybrids plays a major role in the improvement of some plants, most notably maize. Crossing is also widely used in animal breeding, though highly inbred lines of farm animals are not available because of the severe loss of fertility from inbreeding depression. Animal crosses are therefore made between mildly inbred lines or between different breeds. The principles underlying the use of inbreeding and crossing for improvement will be explained in this chapter. We shall be concerned mainly with outbreeding plants, but animals and naturally self-fertilizing plants will be considered briefly in separate sections. Technical details will not be given; for these the reader should consult a textbook of plant breeding, e.g., Simmonds (1979). Two simplifications will be made. First, it will be assumed that the only criterion of merit in plant breeding is yield, though in practice other characters have to be taken into consideration as well as yield. Second, the complications arising from genotype \times environment interactions will not be discussed. Obviously an improved hybrid must perform well in a range of different environments associated with different years and different localities. It will be assumed that this requirement is included in the assessment of merit. Crossing highly inbred lines is used also as a method of genetic analysis both with plants and laboratory animals. These analyses of crosses and the later generations derived from them are fully described by Mather and Jinks (1977, 1982) and will not be dealt with here.

Applied to outbreeding organisms, the purpose of crossing is, of course, to produce superior crossbred, or F_1 , individuals. Consider first a set of lines all derived from the same random-breeding base population. The crosses must then be superior not only to the inbred lines but to the outbred population from which the lines were derived. Something more than heterosis is therefore sought, since heterosis is the superiority over the inbred lines. It was shown in Chapter 14 that when lines are inbred without selection the mean of all their crosses is expected to be equal to the mean of the outbred population from which they were derived. Therefore inbreeding and crossing alone cannot produce any improvement; there must be selection at some stage if any improvement is to be made.

The lines that are crossed are, however, usually derived from different base populations. Some of the superiority of the crosses then comes from heterosis. If the two base populations differ in gene frequencies, a cross between them will show heterosis, as explained in Chapter 14. In the same way, the mean of crosses between sets of inbred lines derived without selection from the two base populations will be

superior to the mean of the two base populations. Some improvement would therefore be achieved even without any selection. With animals, the lines crossed already exist and there is no existing base population from which they were derived. All the gain from crossing is therefore heterosis, and the only selection is in the choice of which lines or breeds to cross. There is nothing to add here to the account of heterosis given in Chapter 14. We are concerned therefore with the selection by which most of the improvement is achieved in plants. It will be assumed for simplicity that all the lines to be crossed are derived from the same base population.

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 crossbred 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). Most of the improvement, therefore, must come from artificial selection applied to the economically desirable characters. The methods of applying this artificial selection are the main topic for consideration. There is, however, another question that must be considered at the same time. Developing inbred lines and evaluating their crosses is a long and costly process. What are the advantages of this method over straightforward selection applied to the original outbreeding population? This question can be partly answered now.

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.

When a good cross has been found, its genotype can be produced in any required number of individuals and, by repeating the cross, in successive generations. Furthermore, the genetic identity of the F_1 individuals gives them a phenotypic uniformity which is an economic benefit, particularly for mechanical harvesting. For example, uniformity of ripening time means that all individuals are ready for harvesting at the same time. Though the genotype of a cross might be found in an individual of the base population, the replication of the genotype in the 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.

Selection for combining ability

Ultimately the breeder is looking for the pair of inbred lines among all those available that will give the best cross. In other words, the selection is ultimately to be applied to the crosses. The amount of improvement that can be made by selection among a number of crosses depends on the amount of variation between the crosses, and on the intensity of selection as described in Chapter 11. To get a high intensity of selection requires a large number of crosses, and to get the maximum amount of variation between the crosses requires the lines to be inbred to a high level, as was shown in the previous chapter. Time and space can, however, be saved by applying some preliminary selection to the lines. This can be done in two ways. First, the lines to be used for the cross finally selected must themselves be reasonably productive as inbreds. Lines are therefore selected first for their own performance. A line's inbred performance is correlated, with its performance in crosses to some extent depending on how much of the variance is due to additive genes. The correlation, however, is rather small – about 0.1 for yield in maize (Gama and Hallauer, 1977) – so the improvement of the crosses expected from selection of the lines for their performance as inbreds is not very great. Second, the value of a cross is made up of two parts, as explained in the previous chapter: the general and specific combining abilities of the two parent lines. The general combining abilities of the lines can be tested in a variety of ways, outlined in the previous chapter, without the necessity of making all possible crosses. Furthermore, a useful guide to the general combining ability can be obtained from lines that are not yet fully inbred.

The improvement made by the preliminary selection of the lines for their general combining ability comes from the additive variance in the base population. Any further improvement, making use of the non-additive genetic variance, must come from selection for specific combining ability. Here there is no way of selecting the lines by preliminary tests; the crosses must be made, from which to select the best. Since the variance of specific combining abilities is proportional to the square or higher powers of the inbreeding coefficient (equation [15.8]), the lines must have reached a high level of inbreeding before much can be gained from selection for specific combining ability.

Relative importance of general and specific combining abilities How much of the improvement is expected to come from general combining ability and how much from specific combining ability? If the intensity of selection applied to each is the same, the relative amount of improvement due to each will be proportional to their variances. If the lines are fully inbred, the variance of general combining ability is equal to the additive variance in the base population and the variance of specific combining ability is equal to the non-additive variance (equation [15.8]). So if the variance components in the base population are known, the relative amount of improvement from the two combining abilities can be predicted. In an open-pollinated variety of maize the additive variance of yield as a proportion of the total was 0.149, and the non-additive variance was 0.032 (Gardner, 1977). The proportion of additive variance in the total genetic variance was thus $0.149/0.181 =$

0.823. Therefore if inbreeding and crossing were applied to this population, and selection was applied to the crosses, about 80 per cent of the improvement would be expected to come from general combining ability and only about 20 per cent from specific combining ability. If these variance components are characteristic of maize populations, it seems that by far the largest part of the improvement in hybrid maize comes from general combining ability and ultimately from additive variance in the base populations. This raises the question of how far yield could be improved by selection in a random-breeding population without inbreeding. Several experiments have shown that selection in open-pollinated varieties is effective. In one, the population responded for 14 generations with a total improvement of 40 per cent in yield (Gardner, 1977). An improved open-pollinated variety does not have the uniformity which is an important feature of inbred-crosses, but prior selection in the base populations is an effective way of increasing the general combining abilities of inbred lines subsequently made from them.

Synthetic populations When inbred lines have been made and selected for their combining abilities, no further improvement can be made to the crosses of those lines. To achieve further improvement a new set of inbred lines must be made from an improved base population. The new base population may have been improved by selection without inbreeding, or it can be constructed from the selected inbred lines. Crossing a number of selected inbred lines and allowing the F_1 and later generations to cross-pollinate at random creates a new *synthetic* population. The improved general combining ability of the lines, being based on additive variance, is retained in the synthetic population. Segregation in the F_2 and later generations then allows a new set of inbred lines to be made with gene combinations different from those of the lines used to construct the population. In this way, further improvement of combining abilities can be achieved. The hybrid maize currently in use is the product of two or more such cycles of inbreeding and crossing. In addition to the improvement of the hybrids, the yield of the lines as inbreds is also improved, which is important economically because the hybrid seed sold for commercial growing must be produced by an inbred parent.

Three-way and four-way crosses; backcrosses

The practical difficulties associated with the low productivity of inbred lines can be overcome by the use of 3-way and 4-way crosses, though with some loss of performance and of uniformity in the crosses. These crosses were widely used for the production of hybrid maize until the improved inbreds mentioned above were available. In a 3-way cross the F_1 of two lines is used as female or seed parent, in which high productivity is required, and the F_1 is then crossed with a third line. In a 4-way cross, or *double-cross*, two F_1 s of different pairs of lines are crossed. If lines derived from different base populations are available, then in order to make use of the inter-population heterosis the final cross is made between lines of different origin. For example, if lines A and B are from one origin and lines P and Q from another origin, a 4-way cross is made as A \times B and P \times Q, followed by AB \times PQ. The performance of 3-way and 4-way crosses can be reliably predicted from the performances of single crosses of the constituent lines, provided there is no

epistatic interaction. Consider for example the 3-way cross $(A \times B) \times P$. Let these letters represent alleles at a single locus carried by the corresponding lines. The F_1 of $A \times B$ then has the genotype AB, which when crossed with line P gives two genotypes, AP and BP, in equal proportions. These are the genotypes of crosses of lines $A \times P$ and $B \times P$ respectively. Therefore the mean performance of these two crosses predicts the performance of the 3-way cross. In the same way, the performance of the 4-way cross $(A \times B) \times (P \times Q)$ is predicted by the mean of $A \times P$, $A \times Q$, $B \times P$, and $B \times Q$. If more than one locus is considered, however, segregation in the F_1 parents produces genotypes in the final cross that could not appear in any single cross of the lines used. Therefore if there is epistatic interaction, the single crosses will not predict the final cross accurately.

The population produced by any particular 3- and 4-way cross is a mixture of genotypes, all of which could in principle have been produced by single crosses, but 3- and 4-way crosses are expected to differ from single crosses in the following ways: (1) If the lines crossed have been selected, and if any of the consequent superiority of their single crosses is due to epistatic interactions, some of this superiority will be lost in the 3- and 4-way crosses. (2) There is genetic variation within crosses and a consequent loss of phenotypic uniformity. (3) The variance between crosses is reduced and the best 3- or 4-way cross is consequently not as good as the best single cross. For experimental comparisons of 3- and 4-way crosses with single crosses, illustrating these consequences in maize, see Weatherspoon (1970), and Otsuka, Eberhart, and Russell (1972).

Another way of avoiding the low productivity of inbred lines is by a *backcross*. Here only two lines are involved, the F_1 being mated to one of the lines used in the first cross, i.e., $(A \times B) \times B$. The genotypes in the progeny of the backcross are AB and BB in equal proportions. Therefore, in the absence of epistatic interactions, the mean of the backcross is equal to the mean of the F_1 and the line used in the second cross. Consequently there is less heterosis in backcrosses than in 3-way or 4-way crosses.

Crosses in animals Crossing is widely used in animal production, most of the animals produced for meat being the progeny of either a 3-way cross or a back-cross. As was noted earlier, the lines crossed are not deliberately inbred. They have, however, been previously selected for desirable characters and have become mildly inbred with a consequent reduction of some desirable characters, particularly fertility. The purpose of the crossing is partly to make use of heterosis to improve fertility and partly to combine the different characteristics for which the lines were previously selected. For meat production a desirable quality in the final product is rapid growth and what is desired of the final cross is to produce large numbers of rapidly growing individuals. This requires good fertility in the mother coupled with good growth rate in the progeny. Accordingly, the first cross $(A \times B)$ is made to produce F_1 's with good fertility, which comes from heterosis. These F_1 (AB) individuals are used as mothers and crossed to a third line (C) with good growth rate to produce the $(A \times B) \times C$ progeny. Or if no suitable third line is available, the F_1 is backcrossed to one of the lines used in the first cross. The improved growth of the final progeny comes partly from heterosis and partly from the additive effects of the

sire line. Their growth rate may not always be as good as the best of the lines, but the increased numbers produced by the fertile AB mothers makes the crossing economically advantageous. The gains from different types of cross are reviewed by Dickerson (1969) and by Sheridan (1981).

Example 16.1

A 3-way cross of sheep breeds will serve to illustrate the gain from combining the heterosis of fertility with the superior growth of the sire-line. The data come from Sidwell, Everson, and Terrill (1962, 1964). The table gives the pure-bred and 3-way cross performances of the three characters: (a) fertility as the number of lambs weaned per ewe mated; (b) growth rate as the weight per lamb at weaning; and (c) the economically important character, total weight of lamb weaned per ewe mated, which is the product of (a) \times (b). The weaning weight of the cross was not as good as the sire-line itself, but the larger number of lambs weaned by the F_1 females made the 3-way cross superior to the best pure breed in respect of the total weight of the weaned lambs.

	<i>Production per ewe mated</i>		
	(a) No. of lambs weaned	(b) Weaning wt. (kg) per lamb	(c) Total wt. (kg) weaned
<i>Pure breeds</i>			
A = Shropshire	0.80	23.0	18.4
B = Southdown	0.79	19.1	15.1
C = Hampshire	1.00	29.2	29.2
Mid-parent ($\frac{1}{4}$ A + $\frac{1}{4}$ B + $\frac{1}{2}$ C)	0.90	25.1	22.6
3-way cross (A \times B) \times C	1.25	27.5	34.4
Heterosis, % above mid-parent	39	10	52
Superiority over best breed (%)	+25	- 6	+18

Reciprocal recurrent selection (RRS)

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 a pair of 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. Furthermore, both general and specific combining ability would be selected for simultaneously. Selection for combining ability in this way is known as reciprocal

recurrent selection. Its theoretical basis has been examined by Comstock, Robinson, and Harvey (1949) and Dickerson (1952). In outline, the procedure is as follows.

The start is made from two populations, preferably two already known to give some heterosis when crossed. These two populations, whose combining ability is to be improved, will be referred to as lines A and B. Crosses are made reciprocally, a number of A ♂♂ being mated to B ♀♀, and a number of B ♂♂ to A ♀♀. The crossbred 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 crossbred 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. Deliberate inbreeding is avoided because random changes of gene frequencies are not desired.

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.

Evidence about the practical value of reciprocal recurrent selection is conflicting. It is used by some commercial breeders of poultry for egg production (see Krosigk *et al.*, 1973), and has given promising results with maize (Eberhart, 1977). On the other hand, direct comparisons with other methods of selection in poultry and in laboratory animals have not been encouraging (see Calhoon and Bohren, 1974; McNew and Bell, 1976).

Overdominance

The question of whether inbreeding and crossing is a better method of improvement than selection without inbreeding hinges on overdominance as a property of the genes concerned. Overdominance for fitness was discussed in Chapter 2 as a mechanism for the maintenance of polymorphism, and the different ways in which true overdominance and pseudo-overdominance due to linkage can arise were explained. Here we are concerned with overdominance for the character to be improved and in practice it matters little how the overdominance arises. Both methods of improvement involve selection, as we have already seen, so the essential distinction is in the crossing. Crossing two lines in which different alleles are fixed gives an F₁ 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, in theory, 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 theory, and leaving all practical considerations aside, inbreeding and crossing can surpass selection without inbreeding only when there is at least some degree of overdominance of the genes concerned.

A variety of experimental work on both plants and animals, some of which has been mentioned in earlier chapters, suggests that overdominance for the characters studied is not an important property of the genes. This is true even of yield in maize, for which inbreeding and crossing has been so successful (Eberhart, 1977). There seems, therefore, to be little theoretical justification for believing that inbreeding and crossing is a better way of increasing the mean of the desired character. Its advantages are mainly in the uniformity rather than in the improved mean.

Naturally self-fertilizing plants

Self-fertilizing plants usually show a small amount of heterosis when crosses are made. The reason for this is presumably that a few deleterious mutant genes have been fixed by the inbreeding despite the selection against them. The heterosis, however, is much less than is shown by outbreeding plants. For example, the heterosis in crosses between varieties of wheat and of barley (inbreeders) amounts to about 10 per cent (Geiger, 1988), whereas in crosses between inbred lines of maize (an outbreeder) the heterosis is commonly about 150 per cent. To make use of the heterosis for commercial growing is, however, not easy because making the crosses is usually difficult technically, and to produce hybrid seed requires crossing on a large scale in every generation. There are several ways of overcoming the technical difficulties of crossing but these have been successful with only a few crops (see Simmonds, 1979, p. 231). The purpose of the crossing is therefore usually to generate segregation. After a cross has been made, the F_1 and subsequent generations are allowed to self-fertilize, producing a new set of inbred lines which become differentiated by recombination and random drift. The aim is to find one or more of these recombinant lines that is better than either of the parental lines. The amount of improvement to be expected from any particular cross can be predicted from the additive genetic variance in the F_2 and the intensity of selection that will be applied to the recombinant lines (see Jinks and Pooni, 1976; Pooni and Jinks, 1979).

Problems

- 16.1 If you were to make a three-way cross and a four-way cross of the varieties in Problem 15.7, which varieties would you choose, and how would you make the crosses, in order to get the highest predicted yields? What would the predicted yields be? [Solution 96]

16.2 A 'rotational cross' with two breeds or lines, A and B, is made as follows, where X always refers to the crossbred generation.

- (1) $A \times B$
- (2) $X_1 \times A$
- (3) $X_2 \times B$
- (4) $X_3 \times A$

Calculate the expected performance of the crossbred progeny in each generation up to (4), in terms of the purebred and single-cross performances, assuming no epistatic interaction and no maternal effects.

[Solution 106]

16.3 A rotational cross with 3 breeds, A, B, C, is made as follows, where X again represents the crossbred progeny.

- (1) $A \times B$
- (2) $X_1 \times C$
- (3) $X_2 \times A$
- (4) $X_3 \times B$
- (5) $X_4 \times C$

Calculate the expected performance of each generation in terms of the purebred and single-cross performances, assuming the absence of epistasis and maternal effects.

[Solution 116]

16.4 Suppose that all the single crosses of the lines used in rotational crossing show the same amount of heterosis. What proportion of this single-cross heterosis will be attained in successive generations of the rotational cross? Work this out for the four generations of the two-line rotational cross in Problem 16.2 and for the five generations of the three-line rotational cross in Problem 16.3.

[Solution 126]

16.5 When rotational crossbreeding is applied to animals the females used for crossing are always crossbred and the males always purebred. The system then has the useful feature that the pure breeds themselves need produce no more females than are required for replacements. The data below are the mean weights of individual pigs at 154 days (W) and the mean number of pigs per litter at 154 days (N), in three breeds, Chester White (C), Duroc (D) and Yorkshire (Y), and their single crosses. From the solution of Problem 16.3 calculate the expected mean total weight per litter in each of the 5 generations of rotational crossing, starting with $(Y\varnothing \times C\delta)\varnothing \times D\delta$. Make the simplifying assumptions that the number in the litter depends only on the mother's genotype and the weight depends only on the individual's genotype, and that epistasis is negligible.

	C	D	Y	CD	CY	DY
W (kg)	78	88	84	92	90	96
N	6.6	6.3	7.9	7.4	8.2	7.3

Data from Schneider, J.F. (1978) Ph.D. Thesis, Iowa State Univ., Ames, Iowa, USA.

[Solution 136]

17 Scale

The choice of a suitable scale for the measurement of a metric character has been mentioned several times in the foregoing chapters. The explanation of what is involved in the choice of a scale and a discussion of the criteria of suitability have, however, been deferred till this point because these are matters that cannot be properly appreciated until the nature of the deductions to be made from the data are understood. In other words, the choice of a scale has to be made in relation to the object for which the data are to be used. The data from any experimental or practical study are obtained in the form most convenient for the measurement of the character. That is to say, the phenotypic values are recorded in grams, centimetres, days, numbers, or whatever unit of measurement is most convenient. The point at issue is whether these raw data should be transformed to another scale before they are subjected to analysis or interpretation. A transformation of scale means the conversion of the original units to logarithms, reciprocals, or some other function, according to what is most appropriate for the purpose for which the data are to be used.

It is tempting to suppose that each character has its 'natural' scale, the scale on which the biological process expressed in the character works. Thus, growth is a geometrical rather than an arithmetical process, and a geometric scale would appear to be the most 'natural'. For example, an increase of 1 g in a mouse weighing 20 g has not the same biological significance as an increase of 1 g in a mouse weighing 2 g; but an increase of 10 per cent has approximately the same significance in both. For this reason a transformation to logarithms would seem appropriate for measurements of weight. This, however, is largely a subjective judgement, and some objective criterion for the choice of a scale is needed. Different criteria, however, are often inconsistent in the scale they indicate and, moreover, the same criterion applied to the same character may indicate different scales in different populations. Therefore the idea that every character must have its 'natural' and correct scale is largely illusory.

There are, broadly speaking, three main reasons for making a scale transformation: (1) to make the distribution normal; (2) to make the variance independent of the mean; and (3) to remove or reduce non-additive interactions. The criterion for the choice of a scale is in each case the empirical one of achieving the particular objective. When a scale transformation is called for but is not made, certain phenomena arise, called *scale effects*, which disappear when the appropriate transformation is made. The objectives noted above might equally well be stated as being the removal of these scale effects. We shall discuss in particular the logarithmic transformation which converts an arithmetic to a geometric scale. This is

probably the commonest and most useful transformation. Other transformations are described by Wright (1968, Ch. 10). The general principles, outlined by reference to the log transformation, apply equally to other transformations.

Distribution and variance

Consider first the distribution of phenotypic values. Figure 17.1 shows three distributions plotted as if from the original data on an arithmetic scale. They would all three be symmetrical and normal if the data were first transformed to logarithms. There are two points of importance to notice. First, the degree of departure from normality depends on the amount of variation in relation to the mean. This may be seen from a comparison of the two upper graphs, (a) and (b), which are not very noticeably asymmetrical, with the lower graph, (c), which is. The relationship between the amount of variation and the mean, which determines the degree of departure from normality, is best expressed as the coefficient of variation, i.e., the ratio of standard deviation to mean, often multiplied by 100 to bring it to a percentage. The coefficient of variation of the two upper graphs is 20 per cent, while that of the lower graph is 50 per cent. Thus, a transformation to logarithms does not make an appreciable difference to the shape of the distribution unless the coefficient of variation is fairly high – that is, above about 20 per cent or so. Consequently, statistical procedures which do not rely on a strictly normal distribution, such as the analysis of variance, can be carried out on the untransformed data when the coefficient of variation is not above about 20 per cent. Transformations to other scales are also less necessary when the coefficient of variation is low than when it is high.

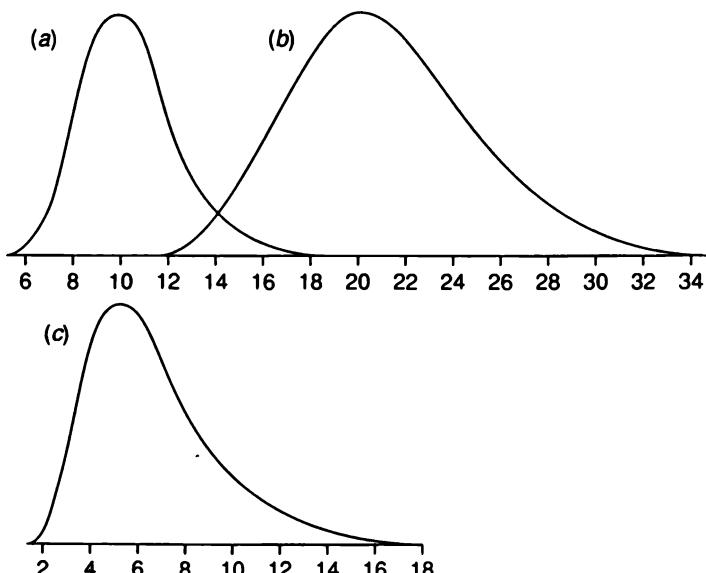


Fig. 17.1. Distributions that are symmetrical and normal on a logarithmic scale shown plotted on an arithmetic scale. Explanation in text.

The second point to notice in Fig. 17.1 is that the variance, when computed in arithmetic units, increases when the mean increases. This may be seen in graphs (a) and (b). These both have the same variance in logarithmic units, but different means. The mean – or strictly speaking the mode – of (b) is double that of (a) and the standard deviation in arithmetic units is correspondingly doubled. Though the distributions are not very noticeably skewed and a transformation does not seem to be very strongly indicated, yet in consequence of the difference of mean the variances differ very greatly. Here, then, is one of the commonest scale effects, namely a change of variance following a change of the population mean. The two graphs (a) and (b) in Fig. 17.1 might well represent two populations which have diverged by some generations of two-way selection, if the character were something like body size measured in units of weight. Such characters are commonly found to increase in variance when the mean increases, and to decrease in variance when the mean decreases. Figure 17.2 shows an example from an experiment with mice, the character being weight at 60 days. Note that none of the three distributions considered separately seems to be sufficiently asymmetrical or non-normal to need a scale transformation on this criterion; but to make the variance independent of the mean, a transformation is very obviously required.

Phenomena such as the change of variance discussed above are called scale effects if they disappear when the measurements are appropriately transformed: in

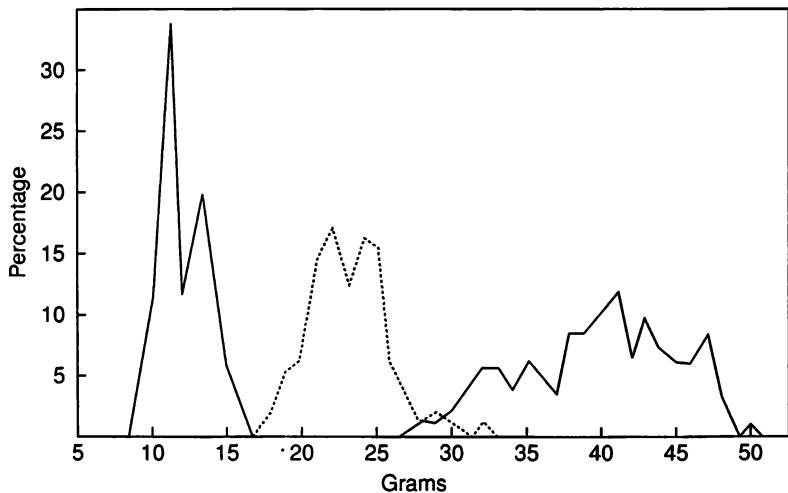


Fig. 17.2. Distributions of body weight of male mice at 60 days. Centre: base population before selection. Left and right: small and large strains after 21 generations of two-way selection. (Based on MacArthur, 1949.)

	<i>Small</i>	<i>Unselected</i>	<i>Large</i>
Mean	11.97	23.16	39.85
Standard deviation	1.71	2.56	5.10
Coeff. of variation, %	14.3	11.1	12.8

other words, if their cause can be attributed to the scale of measurement. But they are none the less real, though labelled as a scale effect or removed by transformation. The large mice, for example, are really more variable than the small when their weights are measured in grams. What is gained by recognizing this as a scale effect is that there is no need to look deeper into the genetic properties of the character for an explanation.

A convenient test for the appropriateness of a logarithmic transformation is provided by the proportionality of standard deviation and mean, which we noted in connection with graphs (a) and (b) in Fig. 17.1. If two distributions have the same variance on a logarithmic scale then the coefficients of variation in arithmetic units will be the same. Thus, constancy of the coefficient of variation indicates constancy of variance on a logarithmic scale. And, if variances are to be compared, we may simply compare the coefficients of variation instead of expressing the variances in logarithmic units. The standard deviations and coefficients of variation of the distributions shown in Fig. 17.2 are given in the legend to the figure. The coefficients of variation, though not identical, are much more alike than the standard deviations, and this shows that the changes of variance that have resulted from the selection can be attributed, in large part at least, to the scale of measurement.

When a logarithmic transformation is required, it is not always necessary to convert each individual measurement. Conversion of the mean and of the variance can conveniently be made by the following formulae (Wright, 1968, p. 229):

$$(\overline{\log x}) = \log \bar{x} - \frac{1}{2} \log(1 + C^2) \quad \dots [17.1]$$

$$\sigma_{(\log x)}^2 = 0.4343 \log(1 + C^2) \quad \dots [17.2]$$

The first converts the mean of arithmetic values to the mean of logarithmic values, and the second converts the variance as computed from the arithmetic values to the variance as it would be computed from logarithmic values. In these formulae C is the coefficient of variation in the form σ/\bar{x} computed from arithmetic values, and the logarithms are to the base 10. The formulae are accurate only if the distribution really is normal on the logarithmic scale.

When conclusions about variances depend critically on eliminating any scale effect, it may be necessary to find the empirical relationship between variance or standard deviation and mean. This can be done if several populations with different means are available, and if there are no reasons other than the scale effect for thinking that their variances would differ. Then the regression equation relating the standard deviation to the mean gives the expected standard deviation in another population with a particular mean. If the regression is linear the regression equation is $\sigma = a + b\bar{x}$, where σ is the expected standard deviation in a population with a mean of \bar{x} , a is the intercept and b is the regression coefficient. A scale on which the variance would be independent of the mean would be $X = \log(x + a/b)$, where x is the original measurement and X its transformed value (Wright, 1968, p. 232).

Let us return to the consequences of selection and pursue them a little further. If the variance changes with the change of mean as a result of selection, so also will the selection differential and the response. The response per generation of a

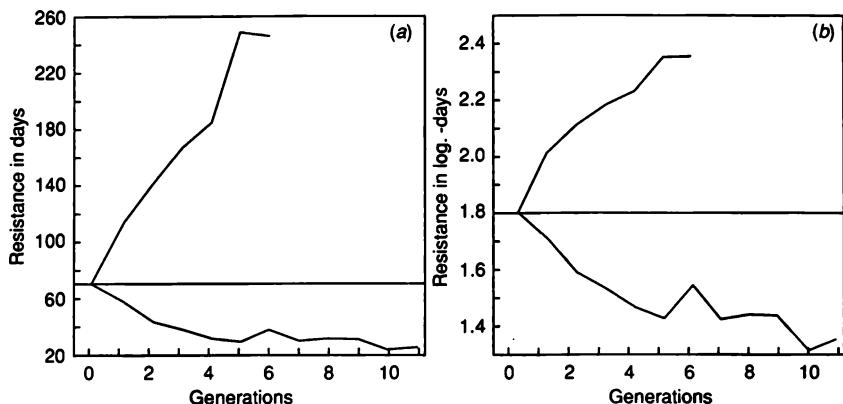


Fig. 17.3. Response to two-way selection for resistance to dental caries in rats. Resistance is measured in days and plotted on an arithmetic scale in (a), and on a logarithmic scale in (b). The arithmetic means were converted to logarithmic means by formula [17.1]. The coefficient of variation was high – about 50 per cent – and was approximately constant. The reason why the upward selection has not covered so many generations as the downward is simply that the increased resistance lengthened the generation interval. (*Data from Hunt, Hoppert, and Erwin, 1944.*)

character such as we have been considering would therefore be expected to increase with the progress of selection in the upward direction, and to decrease correspondingly in the downward direction. The response to two-way selection would then be asymmetrical. An example of an asymmetrical response which can most probably be attributed to a scale effect in this way is shown in Fig. 17.3. Plotted in arithmetic units, as in (a), the response is much greater in the upward than in the downward direction. A transformation to logarithms, shown in (b), renders the response much more nearly symmetrical. This does not do away with the fact that the character as measured increased much more than it decreased under selection. But it accounts for the asymmetry without the need for more elaborate hypotheses. A convenient way of eliminating scale effects from the graphical presentation of a response to selection is to plot the response in the form of the realized heritability, as explained in Chapter 11 and illustrated in Fig. 11.5. The realized heritability, which is the ratio of response to selection differential, is very little influenced by scale effects (Falconer, 1954).

Interactions

We turn now to what is perhaps a more fundamental effect of a scale transformation – its effect on the apparent nature of the genetic variance. To understand this we must go back to a single locus and consider the effect, or mode of action, of the genes. Imagine a locus with two alleles whose mode of action is geometric, the genotypic value of A_2A_2 being 50 per cent greater than A_1A_2 , and that of A_1A_2 being also 50 per cent greater than A_1A_1 . Thus on the logarithmic scale there is no dominance, the heterozygote being exactly mid-way between the two homozygotes. Now suppose the genotypic values are measured in arithmetic units, such as

grams, and that A_1A_1 has a value of 10 units. Then A_1A_2 will be 15 units and A_2A_2 22.5 units. On the arithmetic scale, therefore, A_1 is partially dominant to A_2 , the heterozygote no longer falling mid-way between the homozygotes. Thus the degree of dominance is influenced by the scale of measurement, and so also is the proportionate amount of dominance variance. This effect of a scale transformation, however, is normally rather small. A gene that causes a 50 per cent difference between the genotypic values, such as we have considered, would be a major gene, easily recognizable individually. But even so, the degree of dominance on the arithmetic scale is not very great. Minor genes with effects of perhaps 1 per cent or 10 per cent would be scarcely influenced in their dominance.

In the same way that the dominance is affected by the scale, so also is the epistatic interaction between different loci. Loci with geometric effects would combine without interaction if the genotypic values were measured in logarithmic units. But when measured in arithmetic units there would be interaction deviations due to epistasis. Thus the amount of interaction variance is also influenced by the scale of measurement. The following example illustrates the dependence of interaction on scale.

Example 17.1

The pygmy gene in mice is a major gene affecting body size, homozygotes being much reduced in size. The effect of this gene was studied in different genetic backgrounds (King, 1955). The gene was transferred from the strain selected for small size where it arose, to a strain selected for large size, by repeated backcrosses. The mean difference between pygmy homozygotes and normals (i.e., heterozygotes and normal homozygotes together) was measured in the two strains and during the transference, the comparisons being made between pygmies and normals in the same litters. The results are shown in Fig. 17.4. The difference between pygmies and normals increases with the weight of the normals. In the background of the small strain the pygmies were about 7 g smaller than normals, but in the background of the large strain they were about 14 g smaller. Thus the pygmy gene shows epistatic interaction with the other genes that affect body size. But if the effect of the gene is expressed as a proportion, it is constant and independent of the other genes present. Pygmies are about half the weight of their normal litter-mates, no matter what the actual weights are. Thus if the comparisons are made in logarithmic units there is no epistatic interaction.

In general, therefore, a scale transformation may remove or reduce the variance attributable to epistatic interaction, and this variance might then be labelled as a scale effect. A transformation which removes or reduces interaction variance may be useful if conclusions are to be drawn from an analysis that depends for its validity on the absence of interaction. Interactions between genotype and environment may also arise from a scale effect, and a transformation may be useful for removing or reducing them. Interactions, whether epistatic or genotype \times environment, however, cannot always be removed or even reduced by a transformation of scale. For example, no meaningful transformation can remove an interaction that causes a reversal of order, such as was illustrated in Fig. 8.2.

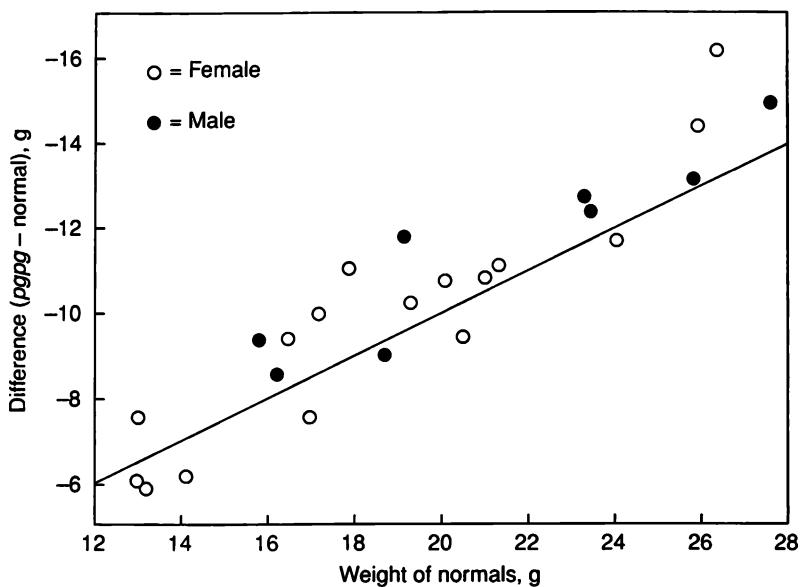


Fig. 17.4. Effect of the pygmy gene in mice of different body weights. Difference of 6-week weight between pygmies and their normal litter-mates plotted against the weight of the normals in the same litter. The straight line is not a fitted regression, but shows the relationship: weight of pygmy = 0.5 × weight of normal. See Example 17.1. (Data from King, 1955.)

There are two ways by which a suitable scale for removing interactions can be found. The first is by comparing the effects of a specific factor and finding a scale that makes the effect additive. This was illustrated in Example 17.1 above. The effects of a single gene were compared in different genetic backgrounds, and it was found that on a logarithmic scale the gene added the same amount on all genetic backgrounds. The specific factor whose effects are to be made additive can be environmental rather than genetic. The second test of a suitable scale for removing epistatic interaction can be applied when two populations with different means are available and can be crossed. It was shown in chapters 14 and 16 that in the absence of epistatic interaction the means of the F_2 and backcross generations were expected to be as follows:

$$\left. \begin{aligned} F_2 &= \frac{1}{2}(F_1 + \bar{P}) \\ B_1 &= \frac{1}{2}(F_1 + P_1) \\ B_2 &= \frac{1}{2}(F_1 + P_2) \end{aligned} \right\} \quad \dots [17.3]$$

where \bar{P} is the mean of the two parental populations and all the other symbols are the means of the corresponding generations. A scale is chosen which brings the observed means closest to their expectations. For details, see Mather and Jinks (1982, p. 71).

Conclusions

In this chapter we have outlined some of the scale effects most commonly met with, and have indicated the circumstances under which a transformation of scale

may be helpful to the interpretation of results and the drawing of conclusions. Transformations of scale, however, should not be made without good reason. The first purpose of experimental observations is the description of the genetic properties of the population, and a scale transformation obscures rather than illuminates the description. If epistasis, for example, is found, this is an essential part of the description, and it is better labelled as epistasis than as a scale effect. The transformation of scale is essentially a statistical device to be employed for the purpose of simplifying the analysis of the data, or to make possible the drawing of valid conclusions from the analysis. It is sometimes helpful also in the interpretation of results. If epistasis, for example, were found to disappear on transformation to a logarithmic scale we could conclude that the effects of different loci combined by multiplication rather than by addition. Or, if there were good reasons for attributing a difference of variance to a scale effect we should not need to invoke more complicated genetic explanations. The choice of scale, however, raises troublesome problems in connection with the interpretation of results. Logical justification of a scale transformation can only come from some criterion other than the property about which the conclusions are to be drawn. If there is no independent criterion the argument becomes circular, and the distinction between a scale effect and some other interpretation becomes meaningless. There is also a more fundamental difficulty: the scale appropriate for one population may not be appropriate for another, and the scale appropriate to the genetic and environmental components of the variation may be different. This difficulty is strikingly illustrated by an analysis of the character 'weight per locule' in a number of crosses between varieties of tomato (Powers, 1950). By the same criterion – normality of the distribution – this character was found to require an arithmetic scale in some crosses and a geometric scale in others; and, moreover, in the F_2 generations of some crosses the genetic variation required one scale while the environmental variance required another.

Problems

17.1 Figure 17.2 shows data where a transformation to logarithms is indicated if equality of the variances of the three lines is desired. What would be the standard deviations of log-weights? The data show a large amount of asymmetry in the responses to selection. Would this asymmetry be removed by transformation to logs? [Solution 10]

17.2 The data below are the 6-week weights (g) of mice from selected strains of different body weights and crosses of these strains. There were three 'size groups', large, control and small. In each size group there were six replicate lines. (Figure 12.1 refers to these lines.) Crosses were made between lines of the same size group and between lines of different size groups. The object was to find out if the heterosis would be greater in crosses between lines of different size than in crosses within size groups. The first row of the table gives the mean weights of the replicates in each size group and the rest of the table gives the mean weights of the crosses, reciprocals averaged. How would the conclusions about the heterosis be altered by transformation of the means to logarithms?

	<i>Large</i>	<i>Control</i>	<i>Small</i>
<i>Line means</i>	28.74	20.99	14.91
Large	30.68	26.00	21.85
Control	—	21.91	18.48
Small	—	—	14.84

Data from Kumar, C.K.B. (1980) Ph.D. Thesis, University of Edinburgh.

[Solution 20]

17.3 The table shows the mean number of sternopleural bristles in *Drosophila* males with different combinations of *X* chromosome and autosomes. There were two *X* chromosomes, one from a high bristle-number line and the other from a low bristle-number line. These two *X* chromosomes were put into the background of autosomes from lines at different levels of bristle number. There is a strong epistatic interaction between the *X* chromosomes and the autosomes. Can you find a scale transformation that will remove the interaction and make the *X* chromosome effect the same in all backgrounds? This is not straightforward. It is helpful to know that four of the bristles, two on each side, are larger than the others, different in structure, and never absent except when the mean is very low.

<i>Autosomal background</i>	<i>Source of X chromosome</i>		<i>Difference H-L</i>
	<i>High</i>	<i>Low</i>	
A	9.49	7.75	1.74
B	13.34	10.84	2.50
C	22.72	16.36	6.36
D	34.87	24.84	10.03
E	47.80	32.80	15.00

Data from McPhee, C.P. & Robertson, A. (1970) *Genet. Res.*, 16, 1–16.

[Solution 30]

18 Threshold Characters

There are many characters of biological interest or economic importance which vary in a discontinuous manner but are not inherited in a simple Mendelian manner. Familiar examples are susceptibility to disease, where there are two phenotypic classes – affected or not-affected – and litter size of the larger mammals that usually bear one young at a time but sometimes two or three. There are also discontinuous anatomical differences, such as the number of vertebrae of mice, whose genetics has been extensively studied. Characters of this sort appear at first sight to be outside the realm of quantitative genetics; yet when they are subjected to genetic analysis they are found to be inherited in the same way as continuously varying characters.

Liability and threshold

The clue to understanding the inheritance of such characters lies in the idea that the character has an underlying continuity with a *threshold*, which imposes a discontinuity on the visible expression, as depicted in Fig. 18.1. When the underlying variable is below this threshold level the individual has one form of phenotypic expression, e.g., is ‘normal’; when it is above the threshold the individual has the other phenotypic expression, e.g., is ‘affected’. The underlying continuous variable has been called the *liability* in the context of human diseases as threshold characters, and this term will be used here. The continuous variation of liability is both genetic and environmental in origin, and may be thought of as the concentration of some substance, or the rate of some developmental process – of something, that is to say, that could in principle be measured and studied as a metric character in the ordinary way. It may be a compound of several different physiological or developmental processes but it is not necessary to know how these are combined to give the liability, or even to know what they really are.

That the idea of an underlying variable is a realistic one can be appreciated by thinking of litter size. The litter size of mice or pigs, though in reality obviously discontinuous, can be treated as a continuous variable because there are a large enough number of classes. The litter size of cows has only two classes, single and twin births, more than two calves being exceedingly rare. But there is no reason to think that the physiological causes of twinning in cattle are different from those of litter size in mice or pigs. The underlying variable in both cases is made up mainly of the levels of circulating gonadotrophic hormones, which determine the number of eggs shed, the intra-uterine factors that affect embryonic survival and, in the case of cattle, the factors determining monozygotic twinning.

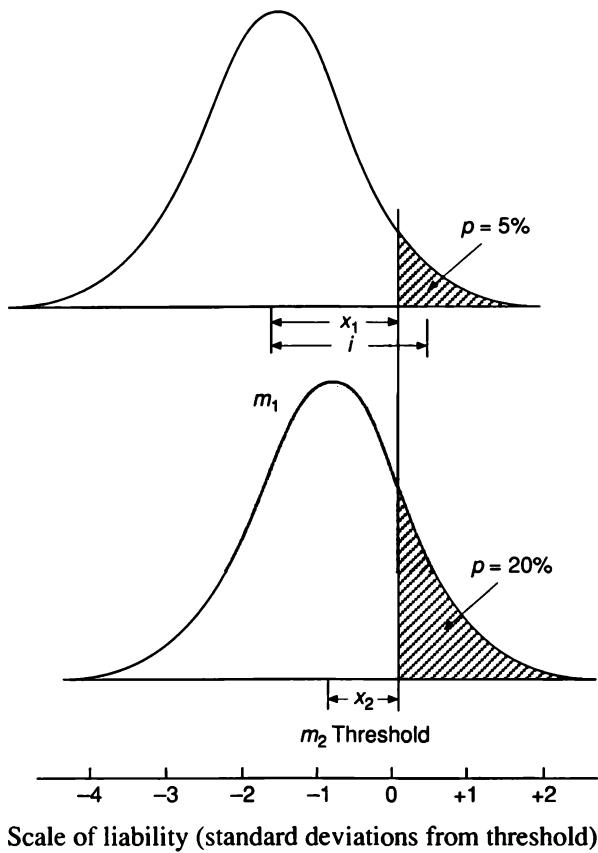


Fig. 18.1. Two populations or groups with different incidences, p , of a threshold character and consequently different mean liabilities. The variance of liability is the same in the two groups and the means differ by 0.8 standard deviations of liability. x is the normal deviate of the threshold from the mean; i is the mean deviation of affected individuals from their group mean.

Two classes, one threshold

Let us first consider characters which have only two phenotypic classes with a single threshold separating them. The two classes will be referred to as normal and affected. On the phenotypic level; or visible scale, individuals can have only two possible values, which might be designated 0 for normal and 1 for affected. Groups of individuals, however, such as families or the population as a whole, can have any value, in the form of the proportion or percentage of individuals that are affected. This is referred to as the *incidence* or, in the context of human diseases, the *prevalence*. The incidence is quite adequate as a simple description of the population or group, but the percentage scale in which the incidence is expressed is inappropriate for many purposes, because on a percentage scale variances differ according to the mean. For genetic analyses, therefore, incidences must be converted to mean liabilities. In order to make this transformation it is necessary to define the liability as being normally distributed. This definition carries with it the requirement that if we could measure the liability directly, it would be possible to

render its distribution normal by some scale transformation. We shall return to this requirement later; meantime we assume that it can be met. With liability being normally distributed, then, the unit of liability is its standard deviation σ . The mean liability is then related to the incidence by the (single-tailed) normal deviate x , which is the deviation of the threshold from the mean in standard-deviation units of liability. Values of x for different incidences are tabulated in Appendix Table A.

Comparison of means Consider two populations or groups with different incidences, as shown in Fig. 18.1. By how much do they differ in mean liability? For comparing different groups, the threshold must be defined as being fixed; that is to say, it is the same level of liability in all groups. The mean of any group is then expressed as a deviation in σ units from the threshold. In other words, the threshold is taken as the origin or zero-point on the scale of liability. The upper group in Fig. 18.1 has an incidence $p_1 = 0.05$, which gives $x_1 = 1.6\sigma_1$. The mean liability is thus $m_1 = -1.6\sigma_1$. (Care must be taken with the signs of mean liabilities. If the threshold is above the mean, the mean is below the threshold and therefore negative.) Similarly, the lower group in Fig. 18.1, with an incidence of 0.20, has a mean of $m_2 = -0.8\sigma_2$. Note that the means are expressed in units of their own population's standard deviation. We can go no further with the comparison of the means unless we assume that the two standard deviations are the same. If this can be accepted as a reasonable assumption then $\sigma_1 = \sigma_2 = \sigma$, and $m_2 - m_1 = 0.8\sigma$; the means of the two groups differ by 0.8 standard deviations of liability.

Heritability of liability Suppose that the upper distribution in Fig. 18.1 represents a parental generation from which affected individuals are selected as parents. When these parents are bred they produce offspring with the lower distribution. Knowing the incidence in the parental generation and in the progeny, we have all that is needed to calculate the regression of offspring on mid-parent values of liability, and from this the heritability of liability. Consider first the response to the selection. This is the difference in mean between the parental and progeny generations, which was given above as 0.8σ assuming the variances of the two generations to be equal. In fact the variances will not be quite the same, but the small error introduced will be neglected for the moment. Now consider the selection differential. This is the mean liability of the affected individuals in the parent generation as a deviation from their population mean. The proportion of individuals used as parents may be less than the incidence: in other words, not all affected individuals may be used as parents. But so long as all parents are affected, the mean of those used is expected to be the same as the mean of all affected individuals. The mean of the affected individuals in standard deviation units is equivalent to the intensity of selection, i , corresponding to the incidence as the proportion selected. Values of i are tabulated in Appendix Table A. With the incidence of $p = 0.05$ the intensity of selection is $i = 2.1$, and the selection differential is therefore $S = 2.1\sigma$ (see equation [11.5]). The regression of offspring on mid-parent values is the ratio of response to selection differential (equation [11.1]) and is $R/S = 0.8\sigma/2.1\sigma = 0.38$. Finally, provided there is no environmental resemblance between offspring and their parents, the heritability of liability is equal to the regression of offspring on mid-parent values.

The calculation of the regression and heritability explained above by reference to parents and offspring can be applied to any sort of relationship. Suppose that the upper distribution in Fig. 18.1 represents a population, and the lower distribution represents any specified sort of relatives, e.g., full sibs, of affected individuals. Then the regression calculated is that of an individual on his relative. Since the variances of the two groups – the population and the relatives – are approximately equal, the regression is approximately equal to the correlation. Thus, with the incidences in Fig. 18.1 the correlation of full sibs in respect of liability would be 0.38. In the absence of resemblance due to common environment and of dominance, the heritability would be estimated as twice the correlation of full sibs, or 0.76.

The calculations explained above can be summarized in the following formulae. The correlation of liability between relatives of any specified sort is given by

$$t = \frac{m_R - m_P}{i} = \frac{x_P - x_R}{i} \quad \dots [18.1]$$

where the subscripts P and R refer to the population and the relatives respectively, m is the mean as a deviation from the threshold, x is the normal deviate of the threshold from the mean, and i is the mean deviation of affected individuals from the population mean. The signs are appropriate to a scale that assigns a higher liability to affected than to normal individuals. The heritability is then obtained from the correlation as

$$h^2 = t/r \quad \dots [18.2]$$

as in equation [10.5], r being the coefficient of relationship as given in Table 9.3. For 1st, 2nd, and 3rd degree relatives r is $\frac{1}{2}$, $\frac{1}{4}$, and $\frac{1}{8}$ respectively. When the relatives are offspring of two affected parents, the appropriate ' r ' is the regression on mid-parent, which is 1.

The sampling variance of the mean liability, i.e., the normal deviate x , is

$$\sigma_x^2 = (1 - p)/i^2 A$$

where A is the number affected and p is the incidence. The sampling variance of the correlation estimated by equation [18.1] is rather complex (see Falconer, 1965a), but if the population incidence can be assumed to have negligible error it is given by

$$\sigma_t^2 = (1 - p_R)/i_P^2 i_R^2 A_R \quad (\text{approx.})$$

where subscripts P and R refer to the population and the relatives respectively and A is the number affected.

The error introduced by assuming the variance to be the same in the relatives of affected individuals as it is in the population as a whole leads to the correlation estimated by equation [18.1] being too low by a factor of 5 or 10 per cent. A modified formula that takes account of the unequal variances is the following (Reich, James, and Morris, 1972):

$$t = \frac{x - x_R \sqrt{[1 - (x^2 - x_R^2)(1 - (x/i))]} }{i + x_R^2(i - x)} \quad \dots [18.3]$$

where x and i without subscript refer to the population, and x_R refers to the relatives; the sign of the square root is taken to make t between 0 and 1.

Example 18.1

Cryptorchidism is a congenital defect of males that occurs in some herds of pigs. The data in the table refer to one herd reported by Mikami and Fredeen (1979). The incidence in the herd, i.e., the population, was 3.9 per cent and the incidence among the full sibs of affected males was 11.6 per cent. The corresponding values of x and i taken from Appendix Table A are given in the table. The full-sib correlation is calculated by equation [18.1] as follows:

$$t = \frac{1.762 - 1.195}{2.165} = 0.26$$

Assuming no common environment and no dominance, the heritability of liability, by equation [18.2], is

$$h^2 = 2t = 0.52$$

Calculated by the more accurate formula in equation [18.3], the correlation is $t = 0.28$ giving $h^2 = 0.56$.

	<i>Numbers</i>		<i>Incidence</i>		
	<i>Affected</i>	<i>Total</i>	<i>p%</i>	<i>x</i>	<i>i</i>
Population (P)	44	1,129	3.9	1.762	2.165
Full sibs (R)	25	215	11.6	1.195	

The calculation of the heritability of liability has been widely applied in the study of the inheritance of human diseases. The data are collected by questioning patients with a particular disease about the disease status of their relatives. The correlation in respect of liability can then be calculated as above. The interpretation of the correlation in terms of the heritability, however, is subject to the uncertainties about resemblances due to common environment that were emphasized in Chapter 10. Estimates obtained for the heritability of liability, assuming no environmental resemblance, range from 85 per cent for schizophrenia to 35 per cent for congenital heart diseases (Emery, 1976, p. 54). Knowledge of the heritability is useful in genetic counselling for calculating recurrence risks in families because it allows all the information about the family to be combined correctly. For further details about the application to human diseases, see Falconer (1965a, 1967), and Curnow and Smith (1975).

Adequacy of the liability model

The definition of liability as a normally distributed continuous variable must be examined more closely. It implies, as noted earlier, the assumption that the underlying variables that combine to give the liability could be made normal by a scale transformation. This in turn implies that the distribution of liability is unimodal. If in reality it is bimodal or multimodal, no reasonable scale transformation could

make its distribution normal. The calculations of correlations and heritabilities would then be invalid. A bimodal or trimodal distribution could arise in two main ways; first, if there was a single gene whose effect on liability was fairly large in relation to the residual variation, and second, if there was an environmental factor with an effect large in relation to the other variation. Such an environmental factor affecting liability to a disease might be exposure to a pathogen. Thus the genetic analyses in terms of liability are valid only if liability is multifactorial, which means that there are many causes of variation, all with relatively small effects, and the genetic control is by genes at more than one or a few loci.

There is no means of knowing in advance whether these requirements for valid analyses are met, because liability cannot be measured to see if its distribution is unimodal. One can, however, see whether the results obtained are reasonable and consistent. For example, a heritability in excess of 100 per cent would obviously be unacceptable, and would suggest a single major gene. Also, in the absence of resemblance due to common environment, the heritability estimated from different sorts of relatives should be the same. On the whole, the results obtained have been reasonably consistent and have given no strong reason to doubt the adequacy of the liability model. A method of analysis which tests the consistency of different sorts of relatives, and at the same time detects a single major gene, and environmental resemblance if present, is known as complex segregation analysis (see Morton and MacLean, 1974; Lalouel *et al.*, 1977), but it is too complicated for description here. A different test of adequacy can be made with characters that have two thresholds, which will be described below.

Scale relationships

It is possible to assign arbitrary values, 0 and 1, to the two phenotypic classes of a threshold character and to calculate the correlation between relatives in respect of these values. To do this is like using the phenotypic expression as a very coarsely graduated instrument for measuring the liability; an instrument, in fact, with only one graduation mark. This introduces a large amount of measurement error which appears as environmental variance if components of variance are estimated. The amount of variance due to measurement error on the (0, 1) scale depends on the incidence; it is least with an incidence of 0.5 and becomes larger with lower or higher incidences. In consequence, a correlation calculated on the (0, 1) scale varies with the incidence, becoming reduced as the incidence decreases or increases from 0.5. Transformation to the liability scale as described above removes this variance due to measurement error and renders correlations, and heritabilities derived from them, independent of the incidence. There is a simple relationship by which correlations or heritabilities can be converted from one scale to the other (Dempster and Lerner, 1950). If t_c is a correlation on the continuous scale of liability and t_{01} the same correlation calculated on the (0, 1) scale, the two are related by

$$t_c = t_{01} \left(\frac{1-p}{i^2 p} \right) \quad \dots [18.4]$$

where p is the incidence and i the mean liability of affected individuals in the population. The two heritabilities are related in the same way. Estimates of heritabilities

obtained in the above manner have been shown to be generally less accurate than estimates obtained by equation [18.3] (Mercer and Hill, 1984).

Three classes, two thresholds

Genetic analysis of threshold characters can be taken further if there are three phenotypic classes, provided the classes can be logically ordered with respect to liability. That is to say, provided there are biological reasons for believing that one class is intermediate in liability between the other two. An example would be single, twin and triplet births. Then the two thresholds separating the three classes are at different levels of liability. The two thresholds mark fixed points on the liability scale, which are the same in all groups. The difference in liability between the two thresholds therefore provides a fixed unit of liability which is independent of the standard deviation. This makes it possible to compare the standard deviations or variances of different groups, and to compare the means of groups that are expected to have different variances. The idea is most easily explained by a numerical example.

Consider the two populations illustrated in Fig. 18.2. They have different means and different variances. The thresholds T_1 and T_2 are fixed points on the liability scale and the difference between them is 1 threshold unit (t.u.) of liability. The

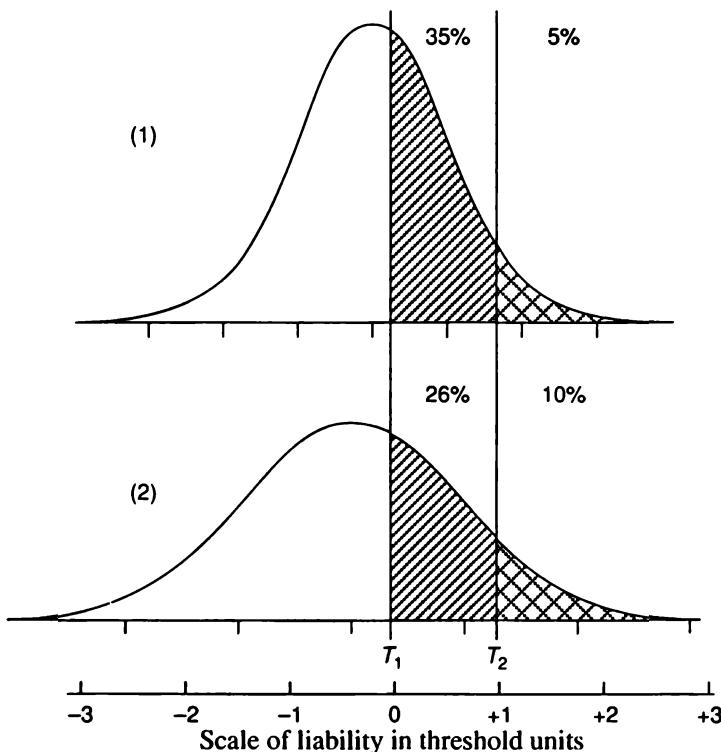


Fig. 18.2. A threshold character with three phenotypic classes and two thresholds. Distributions of liability in two populations with different means and different variances.

scale of liability is shown at the bottom with the zero at the position of T_1 . The first step is to express each standard deviation in terms of threshold units. This is done from the incidences as follows. Let p' be the proportion of individuals above T_1 , i.e., the incidence of the intermediate and extreme classes together, and let p'' be the proportion of individuals above T_2 , i.e., the incidence of the extreme class. Let x' and x'' be the deviations of T_1 and T_2 from the population mean in standard deviations. Then the difference between the thresholds, for any population, is $(x'' - x')\sigma$, where σ is the standard deviation of the population. The difference between the thresholds is by definition 1 t.u., so $(x'' - x')\sigma = 1$ t.u., and the standard deviation in threshold units is given by

$$\sigma = \frac{1}{x'' - x'} \text{ t.u.} \quad \dots [18.5]$$

The calculation of the standard deviations of the populations in Fig. 18.2 is as follows, where the values of x are found from Appendix Table A:

Population	$p'(\%)$	$p''(\%)$	x'	x''	1 t.u.	σ
(1)	40	5	0.25	1.64	$1.39\sigma_1$	0.72 t.u.
(2)	36	10	0.36	1.28	$0.92\sigma_2$	1.09 t.u.

Thus the standard deviation of population (2) is found to be 1.5 times that of population (1). The means as deviations from T_1 in threshold units are found as follows:

$$m_1 = -x'_1\sigma_1 = -0.25 \times 0.72 \text{ t.u.} = -0.18 \text{ t.u.}$$

$$m_2 = -x'_2\sigma_2 = -0.36 \times 1.09 \text{ t.u.} = -0.39 \text{ t.u.}$$

Thus the mean liability of population (2) is 0.21 threshold units below that of population (1).

When the variance can be estimated in the manner described above, it becomes possible to study crosses between lines with different incidences and to compare the variances of F_1 and F_2 generations. This provides another test of the adequacy of the liability model, and in particular of the interpretation of one class as being intermediate in liability between the other two. The following example illustrates such a study of a cross of inbred lines of mice. The means and variances of the parental lines, F_1 , F_2 , and the two backcrosses agree very well with what would be expected of a metric character; in this case there is no reason to doubt the validity of the threshold model.

Example 18.2

The number of presacral vertebrae in mice varies between 25 and 27, presacral being defined as being anterior to the first vertebra that is fused to the sacrum. The character therefore reflects the longitudinal position at which the sacrum is fused to the vertebral column. Usually only two numbers are present in any one inbred strain, and we consider here two inbred strains with 25 and 26 but in very different proportions.

Continued

Example 18.2 *continued*

A third phenotypic class is provided by the few individuals which are asymmetrical, having 25 on one side and 26 on the other, through having the last vertebra fused to the sacrum on one side only. There is clearly some doubt about the asymmetrical mice being intermediate in liability; they might, instead, be less well regulated in development. But treating them as intermediate seems to be justified by the genetic analysis of crosses. The data here refer to one of several crosses described by Green (1962). The strains were C3H having 13 per cent of individuals with 26 vertebrae, and C57BL having 90 per cent. The incidences of the different generations are given in the table with the means and standard deviations calculated as above. The means are deviations in threshold units from the threshold separating '25' from 'asymmetrical'. The mid-parent value, and the expected means of the F_2 and backcross generations calculated from equations [17.3], are also shown in the table. On the whole, the results agree well with expectations: the F_1 is intermediate between P_1 and P_2 ; the F_2 has its mean near the F_1 but has a greatly increased variance; the backcross means are between the F_1 and parental means and have variances between those of the F_1 and F_2 . The only disturbing anomaly is the very greatly different variances of the two parental lines.

	No. of mice	p' %	p'' %	m	\bar{P}	σ	$\sigma^2 = V_P$
					$E(m)$		
P_1	282	12.8	8.5	-4.8	-0.7	4.2	18.0
P_2	619	96.4	89.8	+3.4		1.9	3.6
F_1	532	50.0	31.8	0.0	—	2.1	4.5
F_2	206	56.8	46.1	+0.6	-0.3	3.7	13.8
B_1	205	33.7	21.5	-1.1	-2.4	2.7	7.4
B_2	194	75.3	60.8	+1.7	+1.7	2.4	5.9

The degree of genetic determination, V_G/V_P , in the F_2 can be estimated from the difference of variance between the F_2 and the F_1 as follows:

$$\begin{aligned} F_2: V_G + V_E &= 13.8 \\ F_1: V_E &= 4.5 \\ F_2 - F_1: V_G &= 9.3 \\ V_G/(V_G + V_E) &= 0.68 \end{aligned}$$

Thus 68 per cent of the variation of liability in the F_2 was genetic. This, again, is a very reasonable result.

From what has been said in this chapter it will be clear that threshold characters do not provide ideal material for the study of quantitative genetics, because the genetic analyses to which they can be subjected are limited in scope and subject to assumptions that one would be unwilling to make except under the force of necessity. If a continuously varying character that is closely correlated with liability can be found, it would clearly be better to analyse this as a metric character instead of the threshold character. For example, 'time of survival' might be used instead of 'resistant versus susceptible'; or an abnormality might be graded in degrees of severity.

Selection for threshold characters

The application of selection to a threshold character does not involve the theoretical difficulties of genetic analyses. It has some practical importance in connection with reducing the incidence of abnormalities and with changing the response of experimental animals to treatments such as, for example, increasing or decreasing drug resistance. We shall consider a character with two visible classes and refer first to individual selection.

The response to selection depends in the usual way on the selection differential. But the selection differential does not depend primarily on the proportion selected, as with a continuously varying character, but on the incidence, for the following reason. We may breed exclusively from those individuals in the desired phenotypic class, but we cannot discriminate between those with high and those with low liabilities. The selected individuals are therefore a random sample from the desired class and their mean is the mean of the desired class, irrespective of whether we select all of the desired class or only a portion of it. Thus selecting a smaller proportion than the incidence gives no advantage. If, on the other hand, the proportion that has to be selected is greater than the incidence, we shall be forced to use some individuals of the undesired class. Their mean liability will be below the population mean, so the use of undesired individuals as parents will apply some negative selection. (The mean of the undesired class is easily calculated as $-ip/(1-p)$, where i is the mean of the desired class whose incidence is p). These considerations make it clear that the maximal selection differential is obtained when the incidence of the desired class is equal to the proportion that must be selected for replacement. The greater the difference between the two, the less effective is the selection. For this reason individual selection against a rare abnormality is very ineffective. As an example, consider an abnormality that has an incidence of 5 per cent. Then 95 per cent of individuals are normal and a random sample of them has a mean liability of 0.1σ below the population mean, giving a very small selection differential. If we select in the other direction, for the abnormality, and have to select, for example, 20 per cent of the population as parents, then of these 20 individuals selected out of 100, only 5 will be abnormal, the remaining 15 being of necessity normal. The abnormals will each contribute a differential of $+2.1\sigma$ and the normals each -0.1σ , making the net selection differential 0.4σ . In contrast, selection of 20 per cent for a continuously varying character gives a differential of 1.4σ .

Family selection for a threshold character is much more effective than individual selection, particularly when the incidence is low. An individual's phenotype on the liability scale is very imprecisely known from its status as affected or normal. The mean liability of a family, however, is much more precisely known from the proportion of affected members. The precision depends of course on the number in the family, but also on the incidence in the family because the family represents a sample from a binomial distribution. An incidence of 50 per cent gives the best discrimination between families. The study quoted in Example 18.1 was made in order to assess the efficacy of different methods of selection. Individual selection was found to require 50 generations to reduce the incidence of cryptorchidism from 5 to 1 per cent, whereas half-sib family selection was predicted to do the same in 3

generations. Progeny testing is a form of family selection; for an assessment of its efficacy under various circumstances see Curnow (1984).

The selection differential under individual selection is maximal, as we have seen, when the incidence of the desired class is equal to the proportion selected. In some circumstances it is possible to control the incidence by external means and to make it more nearly optimal. If, for example, the character being selected is a reaction to some treatment, the treatment can be intensified or reduced so that the incidence is altered. This changed incidence is best regarded as a shift in the threshold relative to the mean liability of the population. If the treatment can be further changed as the selection proceeds so as to keep the incidence as nearly as possible equal to the proportion selected, the maximal response to individual selection will be obtained. The progress made can be assessed by subjecting the population, or part of it, to the original treatment.

Genetic assimilation A very interesting result of the application of this principle of changing the threshold by environmental means is the phenomenon known as 'genetic assimilation' (Waddington, 1953). If a threshold character appears as a result of an environmental stimulus, and selection is applied for this character, it may eventually be made to appear spontaneously, without the necessity of the environmental stimulus. In this way, what was originally an 'acquired character' becomes by perfectly orthodox principles of selection an 'inherited character' (Waddington, 1942). In such a situation there are two thresholds, one spontaneous and the other induced, as shown in Fig. 18.3. The spontaneous threshold is at first outside the range of variation of the population, so that there is no variation of phenotype and no selection can be applied (Fig. 18.3(a)). The induced threshold, however, is within the range of liability covered by the population, and it allows individuals toward one end of the distribution to be picked out by selection. In this

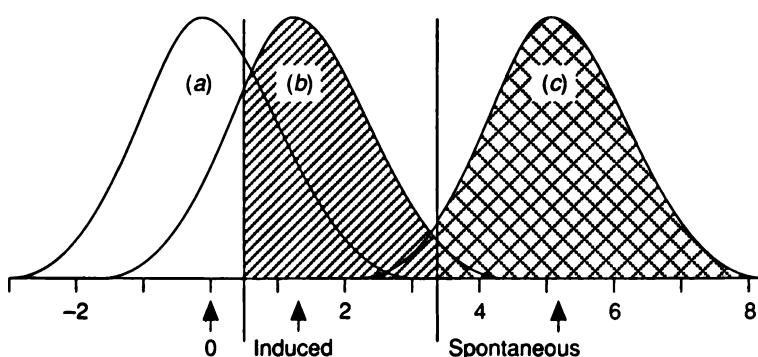


Fig. 18.3. Diagram illustrating the genetic assimilation described in Example 18.3. The distributions of liability are marked in standard deviations from the original population mean. The vertical lines show the positions of the induced and spontaneous thresholds, and the arrows mark the population means at the following three stages of selection.

- (a) before selection: incidence – induced = 30%, spontaneous = 0%
- (b) after some selection: incidence – induced = 80%, spontaneous = 2%
- (c) after further selection: incidence – induced = 100%, spontaneous = 95%

way the mean genotypic value of the population is changed. If this change goes far enough, some individuals will eventually cross the spontaneous threshold and appear as spontaneous variants (Fig. 18.3(b)). When the spontaneous incidence becomes high enough, selection may be continued without the aid of the environmental stimulus, and the spontaneous incidence may be further increased (Fig. 18.3(c)).

Example 18.3

An experimental demonstration of genetic assimilation in *Drosophila melanogaster* is described by Waddington (1953). The character was the absence of the posterior cross-vein of the wing. In the base population no flies with this abnormality were present, but treatment of the puparium by heat shock caused about 30 per cent of cross-veinless individuals to appear. Selection in both directions was applied to the treated flies, and after 14 generations the incidence of the induced character had risen to 80 per cent in the upward selected line, and fallen to 8 per cent in the downward selected line. At this time cross-veinless flies began to appear in small numbers among untreated flies of the upward-selected line, and by generation 16 the spontaneous incidence was between 1 and 2 per cent. Selection was then continued without treatment, the population being subdivided into a number of lines. The best four of the lines, selected without further treatment, reached spontaneous incidences ranging from 67 per cent to 95 per cent. The distributions in Fig. 18.3 illustrate the progress of the upward selection. Graph (b) shows a spontaneous incidence of 2 per cent and an induced incidence of 80 per cent and thus corresponds approximately with generation 16. On the assumption of constant variance, the change of mean at this stage amounted to 1.36 standard deviations. Graph (c) shows a spontaneous incidence of 95 per cent and represents the line that finally showed the greatest progress. Its mean liability is 5.15 standard deviations above that of the initial population.

Problems

18.1 A family study of congenital dislocation of the hip (human) gave the following results. There were altogether 397 'index patients' whose relatives were studied. The first-degree relatives were mostly parents and full sibs, the second-degree mostly grand-parents, uncles, aunts, nephews and nieces, and the third-degree were all first cousins. The numbers of relatives examined and the numbers affected with the malformation were as follows.

	Affected	Total
1st degree	35	1,777
2nd degree	16	4,746
3rd degree	8	4,220

The incidence in the population as a whole was about 1 per 1,000. From these data evaluate (approximately) the correlation of relatives of the three sorts with respect to liability, and estimate the heritability of liability. Which estimate of the heritability would you think likely to be the most reliable?

Data from Wynne-Davies (1970) pp. 316–38 in Emery, A.E.H. (ed.), *Modern Trends in Human Genetics – 1*. Butterworth, London.

[Solution 94]

18.2 The data below come, somewhat simplified, from an analysis of twinning in Swedish Friesian cattle. Cows (or heifers) which had one twin birth were picked at random from the records. The proportions of their mothers and of their daughters that had twins in their fourth, fifth, or sixth calvings were then found. These incidences and the incidence in the breed as a whole are given below. Of those cows which had twins at their first calving, the proportion that had twins in a later calving is given in the last line of the table. Calculate approximately the heritability and the repeatability of liability to produce twins.

Population	3.5%
Mothers	4.6%
Daughters	4.8%
Repeat calvings	10.0%

Data from Johansson, I. et al. (1974) *Hereditas*, **78**, 201–34.

[Solution 104]

18.3 An alternative way of analysing twinning is to treat it as ‘litter size’, individuals having a value of 1 if they have single calves or 2 if they have twins. When analysed in this way the correlation of half sibs in the Swedish Friesians was found to be 0.0058. Is this consistent with the heritability of liability calculated in Problem 18.2?

[Solution 114]

18.4 Fleece-rot is a damaging condition in Australian Merino sheep, associated with wet weather. There is, however, genetic variation in susceptibility. The heritability of liability was estimated as 0.3 in a flock where the incidence was 23 per cent. Reducing the incidence is obviously desirable; increasing the incidence might be useful in an experimental flock. What would be the incidences after two generations of two-way selection, for reduced and for increased incidence, if 10 per cent of males and 50 per cent of females were selected on an individual basis?

Data kindly supplied by Kevin D. Atkins.

[Solution 124]

18.5 A form of polydactyly (extra fingers and toes) appeared in a strain of mice under selection for large size. At first it was at low frequency and only the hind feet were affected. Breeding from the affected individuals over a few generations increased the frequency and resulted in the appearance of individuals with hind and fore feet affected. There were thus three phenotypic classes: normal (*N*), hind feet only affected (*H*), and both hind and fore feet affected (*F*). The frequencies after 5 generations of selection were

<i>N</i>	<i>H</i>	<i>F</i>
20%	50%	30%

The progeny of different types of mating provided good evidence that *H* was intermediate in liability between *N* and *F*.

Calculate (1) the difference in liability between the two thresholds, in standard deviation units, (2) the mean of the population in threshold units, as a deviation from the threshold separating *N* from *H*, (3) the mean liability of each of the three phenotypes in threshold units as deviations from the population mean.

Data from Roberts, R.C. & Mendell, N.R. (1975) *Genet. Res.*, **191**, 427–44. [Solution 134]

19 Correlated Characters

This chapter deals with the relationships between two metric characters, in particular with characters whose values are correlated – either positively or negatively – in the individuals of a population. Correlated characters are of interest for three chief reasons. Firstly, in connection with the genetic causes of correlation through the pleiotropic action of genes: pleiotropy is a common property of major genes, but we have as yet had little occasion to consider its effects in quantitative genetics. Secondly, in connection with the changes brought about by selection: it is important to know how the improvement of one character will cause simultaneous changes in other characters. And thirdly, in connection with natural selection: the relationship between a metric character and fitness is the primary agent that determines the genetic properties of that character in a natural population. This last point, however, will be discussed in the next chapter.

Genetic and environmental correlations

In genetic studies it is necessary to distinguish two causes of correlation between characters, genetic and environmental. The genetic cause of correlation is chiefly pleiotropy, though linkage is a cause of transient correlation, particularly in populations derived from crosses between divergent strains. Pleiotropy is simply the property of a gene whereby it affects two or more characters, so that if the gene is segregating it causes simultaneous variation in the characters it affects. For example, genes that increase growth rate increase both stature and weight, so that they tend to cause correlation between these two characters. Genes that increase fatness, however, influence weight without affecting stature, and are therefore not a cause of correlation. The degree of correlation arising from pleiotropy expresses the extent to which two characters are influenced by the same genes. But the correlation resulting from pleiotropy is the overall, or net, effect of all the segregating genes that affect both characters. Some genes may increase both characters, while others increase one and reduce the other; the former tend to cause a positive correlation, the latter a negative one. So pleiotropy does not necessarily cause a detectable correlation. The environment is a cause of correlation in so far as two characters are influenced by the same differences of environmental conditions. Again, the correlation resulting from environmental causes is the overall effect of all the environmental factors that vary; some may tend to cause a positive correlation, others a negative one.

The association between two characters that can be directly observed is the correlation of phenotypic values, or the *phenotypic correlation*. This is determined from

measurements of the two characters in a number of individuals of the population. Suppose, however, that we knew not only the phenotypic values of the individuals measured, but also their genotypic values and their environmental deviations for both characters. We could then compute the correlation between the genotypic values of the two characters and the correlation between the environmental deviations, and so assess independently the genetic and environmental causes of correlation. And if, in addition, we knew the breeding values of the individuals, we could determine also the correlation of breeding values. In principle there are also correlations between dominance deviations, and between the various interaction deviations. To deal with all these correlations would be unmanageably complex but fortunately is not necessary since the practical problems can be quite adequately dealt with in terms of two correlations. These are the *genetic correlation*, which is the correlation of breeding values, and the *environmental correlation*, which is not strictly speaking the correlation of environmental deviations, but the correlation of environmental deviations together with non-additive genetic deviations. In other words, just as the partitioning of the variance of one character into two components, additive genetic versus all the rest, was adequate for many purposes, so now the covariance of two characters need only be partitioned into these same two components. The 'genetic' and 'environmental' correlations thus correspond to the partitioning of the covariance into the additive genetic component versus all the rest. The methods of estimating these two correlations will be explained later. The first problem to be considered is how the genetic and environmental correlations combine together to give the directly observable phenotypic correlation.

The following symbols will be used throughout this chapter:

- X and Y: the two characters under consideration.
- r_P : the phenotypic correlation between the two characters X and Y.
- r_A : the genetic correlation between X and Y (i.e., the correlation of breeding values).
- r_E : the environmental correlation between X and Y (including non-additive genetic effects).
- cov: the covariance of the two characters X and Y, with subscripts P, A, or E, having the same meaning as for the correlations.
- σ^2 and σ : variance and standard deviation, with subscripts P, A, or E, as above, and X or Y according to the character referred to; e.g., σ_{PX}^2 = phenotypic variance of character X.
- h^2 : the heritability, with subscript X or Y, according to the character.
- e^2 : $= 1 - h^2$.

(The symbol r_G is often used for the genetic correlation but, since the correlation referred to is almost always the correlation of breeding values, the symbol r_A will be used here for the sake of consistency with previous chapters.)

| A correlation, whatever its nature, is the ratio of the appropriate covariance to the product of the two standard deviations. For example, the phenotypic correlation is

$$r_P = \frac{\text{cov}_P}{\sigma_{PX}\sigma_{PY}}$$



and the phenotypic covariance can be written as

$$\text{cov}_P = r_P \sigma_{PX} \sigma_{PY}$$

The phenotypic covariance is the sum of the genetic and environmental covariances, i.e.,

$$\text{cov}_P = \text{cov}_A + \text{cov}_E$$

Writing these covariances in terms of the correlations and standard deviations as above gives

$$r_P \sigma_{PX} \sigma_{PY} = r_A \sigma_{AX} \sigma_{AY} + r_E \sigma_{EX} \sigma_{EY}$$

Now note that $\sigma_A = h\sigma_p$ and $\sigma_E = e\sigma_p$. Substituting these gives

$$r_P \sigma_{PX} \sigma_{PY} = r_A h_X \sigma_{PX} h_Y \sigma_{PY} + r_E e_X \sigma_{PX} e_Y \sigma_{PY}$$

Dividing through by $\sigma_{PX} \sigma_{PY}$ leads to

$$r_P = h_X h_Y r_A + e_X e_Y r_E \quad \dots [19.1]$$

This shows how the genetic and environmental causes of correlation combine together to give the phenotypic correlation. If both characters have low heritabilities, then the phenotypic correlation is determined chiefly by the environmental correlation; if they have high heritabilities, then the genetic correlation is the more important. The dual nature of the phenotypic correlation makes it clear that the magnitude and even the sign of the genetic correlation cannot be determined from the phenotypic correlation alone.

A few examples of genetic and environmental correlations are given in Table 19.1. In some cases the genetic and environmental correlations are different in magnitude, or even in sign. In other cases the two correlations are of the same sign and

Table 19.1 Some examples of phenotypic, genetic, and environmental correlations. The estimates quoted refer to particular populations in particular circumstances; they should not be taken as generally applicable.

	r_P	r_A	r_E
<i>Man</i> (Grundbacher, 1974)			
Serum immunoglobulin levels, IgG: IgM	0.20	0.07	0.31
<i>Cattle</i> (Barker and Robertson, 1966)			
Milk-yield: butterfat % (1st lactation)	-0.26	-0.38	-0.18
Milk-yield in 1st: 2nd lactations	0.40	0.75	0.26
<i>Pigs</i> (Smith, King, and Gilbert, 1962)			
Weight gain: backfat thickness	0.00	0.13	-0.18
Weight gain: efficiency	0.66	0.69	0.64
<i>Poultry</i> (Emsley, Dickerson, and Kashyap, 1977)			
Body weight: egg weight	0.33	0.42	0.23
Body weight: egg production	0.01	-0.17	0.08
Egg weight: egg production	-0.05	-0.31	0.02
<i>Mice</i> (Rutledge, Eisen, and Legates, 1973)			
Body weight: tail length	0.45	0.29	0.56
<i>Drosophila melanogaster</i> (Sheridan <i>et al.</i> , 1968)			
Bristle number, abdominal: sternopleural	0.14	0.41	0.06

not very different magnitude, and this is the more usual situation. A large difference, and particularly a difference of sign, shows that genetic and environmental sources of variation affect the characters through different physiological mechanisms.

The genetic correlation expresses the extent to which two measurements reflect what is genetically the same character. For example, the length of the two wings of *Drosophila* must obviously be measures of the same character, wing length. But wing length and thorax length, though both measures of body size, are not quite the same character; the genetic correlation between them is about 0.75 (Reeve and Robertson, 1953). In this connection the genetic correlation has a bearing on the interpretation of the repeatability of multiple measurements. In Chapter 8 it was said, without explanation, that the repeatability has a precise genetic interpretation only if the different measurements are of the same genetic character. The meaning of this requirement can now be seen to be that the genetic correlation between the measurements must be 1. If the two characters X and Y in equation [19.1] are the same, the expression for the phenotypic correlation reduces to $r_P = h^2 + e^2$, which is equivalent to the repeatability in equation [8.12], since here e^2 is the proportion of variance due to the general environment (V_{Eg}) and the non-additive genetic variance. The repeatability nevertheless remains a useful concept even though the genetic correlation may often be somewhat less than 1.

There are some pairs of characters for which no phenotypic correlation exists. These are characters that cannot both be measured on the same individual. The age at sexual maturity in males and in females is an example of two such characters. Though no phenotypic correlation can be measured, the two characters may nevertheless be correlated genetically and environmentally, and both these correlations can be estimated.

Estimation of the genetic correlation

The estimation of genetic correlations rests on the resemblance between relatives in a manner analogous to the estimation of heritabilities described in Chapter 10. Therefore only the principle and not the details of the procedure need be described here. Instead of computing the components of variance of one character from an analysis of variance, we compute the components of covariance of the two characters from an analysis of covariance, which takes exactly the same form as the analysis of variance. Instead of starting from the squares of the individual values and partitioning the sums of squares according to the source of variation, we start from the product of the values of the two characters in each individual and partition the sums of products according to the source of variation. This leads to estimates of the observational components of covariance, whose interpretation in terms of causal components of covariance is exactly the same as that of the components of variance given in Table 10.4. Thus, in an analysis of half-sib families the component of covariance between sires estimates $\frac{1}{4} \text{cov}_A$, i.e., one-quarter of the covariance of breeding values of the two characters. For the estimation of the correlation, the components of variance of each character are also needed. Thus the between-sire components of variance estimate $\frac{1}{4} \sigma_{AX}^2$ and $\frac{1}{4} \sigma_{AY}^2$. Therefore the genetic correlation is obtained as

$$r_A = \frac{\text{cov}_{XY}}{\sqrt{(\text{var}_X \text{var}_Y)}} \quad \dots [19.2]$$

where var and cov refer to the components of variance and covariance.

The offspring-parent relationship can also be used for estimating the genetic correlation. To estimate the heritability of one character from the resemblance between offspring and parents, we compute the covariance of offspring and parent for the one character by taking the product of the parent or mid-parent value and the mean value of the offspring. To estimate the genetic correlation between two characters we compute what might be called the 'cross-variance', obtained from the product of the value of X in parents and the value of Y in offspring. This 'cross-variance' is half the genetic covariance of the two characters, i.e., $\frac{1}{2} \text{cov}_A$. The covariances of offspring and parents for each of the characters separately are also needed, and then the genetic correlation is given by

$$r_A = \frac{\text{cov}_{XY}}{\sqrt{(\text{cov}_{XX} \text{cov}_{YY})}} \quad \dots [19.3]$$

where cov_{XY} is the 'cross-variance', and cov_{XX} and cov_{YY} are the offspring-parent covariances of each character separately. The cross-variance can be calculated from X in parents and Y in offspring or from Y in parents and X in offspring. If both are available the arithmetic mean should be used. The genetic correlation can also be estimated from responses to selection in a manner analogous to the estimation of realized heritability. This will be explained in the next section.

Data that provide estimates of genetic correlations provide also estimates of the heritabilities of the correlated characters, and of the phenotypic correlations. The environmental correlation can then be found from equation [19.1]. If highly inbred lines are available, the environmental correlations can be estimated directly from the phenotypic correlation within the lines, or preferably within the F_1 's of crosses between the lines.

Estimates of genetic correlations are usually subject to rather large sampling errors and are therefore seldom very precise. Furthermore, genetic correlations are strongly influenced by gene frequencies (Bohren, Hill, and Robertson, 1966), so they may differ markedly in different populations. For these reasons the examples quoted in Table 19.1 must be regarded as approximate values and not necessarily valid for other populations. The sampling variance of a genetic correlation is a complicated matter. (For details see Van Vleck and Henderson, 1961; Hammond and Nicholas, 1972.) An approximate formula for the standard error, derived from Reeve (1955b) and Robertson (1959b) is

$$\sigma_{(r_A)} = \frac{1 - r_A^2}{\sqrt{2}} \sqrt{\left[\frac{\sigma_{(h_X^2)} \sigma_{(h_Y^2)}}{h_X^2 h_Y^2} \right]} \quad \dots [19.4]$$

where σ denotes standard error. This refers to an estimate based on both cross-covariances; if only one is used the $\sqrt{2}$ is to be omitted. Since the standard errors of the two heritabilities appear in the numerator, an experiment designed to minimize the sampling variance of an estimate of heritability, in the manner described in Chapter 10, will also have the optimal design for the estimation of a genetic correlation.

Correlated response to selection

The next problem for consideration concerns the response to selection: if we select for character X, what will be the change of the correlated character Y? The expected response of a character Y, when selection is applied to another character X, may be deduced in the following way. The response of character X – i.e., the character directly selected – is equivalent to the mean breeding value of the selected individuals. This was explained in Chapter 11. The consequent change of character Y is therefore given by the regression of the breeding value of Y on the breeding value of X. This regression is

$$b_{(A)YX} = \frac{\text{cov}_A}{\sigma_{AX}^2} = r_A \frac{\sigma_{AY}}{\sigma_{AX}}$$

The response of character X, directly selected, by equation [11.4], is

$$R_X = ih_X \sigma_{AX}$$

Therefore the correlated response of character Y is

$$CR_Y = b_{(A)YX} R_X \quad \dots [19.5a]$$

$$= ih_X \sigma_{AX} r_A \frac{\sigma_{AY}}{\sigma_{AX}}$$

$$= ih_X r_A \sigma_{AY} \quad \dots [19.5b]$$

Or, by putting $\sigma_{AY} = h_Y \sigma_{PY}$, the correlated response becomes

$$CR_Y = ih_X h_Y r_A \sigma_{PY} \quad \dots [19.6]$$

The term $h_X h_Y r_A$ is called the *coheritability* because it is equivalent to h^2 in the response to direct selection, which is $R = ih_X^2 \sigma_{PX}$ (equation [11.3]).

Thus the response of a correlated character can be predicted if the genetic correlation and the heritabilities of the two characters are known. And, conversely, if the correlated response is measured by experiment, and the two heritabilities are known, the genetic correlation can be estimated. If the heritability of character Y is to be estimated as the realized heritability from the response to selection, then it is necessary to do a double selection experiment. Character X is selected in one line and character Y in another. Then both the direct and the correlated responses of each character can be measured. This type of experiment provides two estimates of the genetic correlation (by equation [19.6]), one from the correlated response of each character; and the two estimates should agree if the theory of correlated responses expressed in equation [19.6] adequately describes the observed responses. A joint estimate of the genetic correlation can be obtained from such double selection experiments, without the need for estimates of the heritabilities, from the following formula, which may be easily derived from equations [11.4] and [19.5b]:

$$r_A^2 = \frac{CR_X}{R_X} \frac{CR_Y}{R_Y} \quad \dots [19.7]$$

Bj 189

Example 19.1

In a study of wing length and thorax length in *Drosophila melanogaster*, Reeve and Robertson (1953) estimated the genetic correlation between these two measures of body size from the responses to selection. There were two pairs of selection lines; one pair was selected for increased and for decreased thorax length, and the other pair for increased and for decreased wing length. In each line the correlated response of the character not directly selected was measured, as well as the response of the character directly selected. Two estimates of the genetic correlation were obtained by equation [19.7], one from the responses to upward selection and the other from the responses to downward selection. In addition, estimates of the genetic correlation in the unselected population were obtained from the offspring-parent covariance and also from the full-sib covariance. The four estimates were as follows:

<i>Method</i>	<i>Genetic correlation</i>
Offspring-parent	0.74
Full sib	0.75
Selection, upward	0.71
Selection, downward	0.73

The agreement between the estimates from selection and the estimates from the unselected population shows that the correlated responses were very close to what would have been predicted from the genetic analysis of the unselected population.

Close agreement between observed and predicted correlated responses, such as was shown in the above example, cannot always be expected and, indeed, is not often found, particularly if the genetic correlation is low. Furthermore, double selection experiments are often inconsistent in the estimates of the genetic correlation that they give. There are two reasons for the low predictability and the inconsistency of correlated responses. The first is the low precision of estimates of the genetic correlation in the base population, resulting from the large sampling errors already mentioned. The second reason is the sensitivity of genetic correlations to gene frequency changes (Bohren, Hill, and Robertson, 1966); the genetic correlation, and therefore the correlated response, can change rapidly during the course of the selection as a result of the selection itself and of random drift. For these reasons there must be some lack of confidence in applying the theory of correlated responses in practice. We shall, however, pursue the practical implications of the theory a little further in the next section, but with the caution that the theory cannot always be relied on to work well in practice.

Correlated selection differential When selection is applied to one character X, any phenotypically correlated character Y will have a *correlated*, or *apparent*, *selection differential* on it. In other words, the individuals selected for X will have a mean value of Y that is different from the population mean. At first sight it might seem that some use could be made of this correlated selection differential for predicting the correlated response, or for estimating the heritability of the correlated character, in a manner analogous to equation [11.7] ($h^2 = R/S$). Unfortunately, however, the correlated selection differential is of no use for either of these

purposes. The reason is briefly as follows. Let S'_Y be the correlated selection differential on Y. Then $S'_Y = b_{(P)YX}S_X$. Writing the correlated response in the form of equation [19.5a] gives

$$\frac{CR_Y}{S'_Y} = \frac{b_{(A)}R_X}{b_{(P)}S_X} \quad \dots [19.8a]$$

Substituting $b = r\sigma_Y/\sigma_X$ and $R_X/S_X = h_X^2$ leads to

$$\frac{CR_Y}{S'_Y} = \frac{r_A}{r_P} h_X h_Y \quad \dots [19.8b]$$

Thus, without knowing the genetic correlation r_A , it is not possible to use the correlated selection differential S'_Y , either to estimate the heritability of character Y or to predict the correlated response. Equation [19.8] can also be written in the form

$$\frac{CR_Y}{S'_Y} = \frac{\text{cov}_{(A)}}{\text{cov}_{(P)}} \quad \dots [19.8c]$$

which is analogous to the direct response, $R/S = V_A/V_P$.

Indirect selection

Consideration of correlated responses suggests that it might sometimes be possible to achieve more rapid progress under selection for a correlated response than from selection for the desired character itself. In other words, if we want to improve character X, we might select for another character Y, and achieve progress through the correlated response of character X. We shall refer to this as indirect selection; that is to say, selection applied to some character other than the one it is desired to improve. And we shall refer to the character to which selection is applied as the secondary character. The conditions under which indirect selection would be advantageous are readily deduced. Let R_X be the direct response of the desired character, if selection were applied directly to it; and let CR_X be the correlated response of character X resulting from selection applied to the secondary character Y. The merit of indirect selection relative to that of direct selection may then be expressed as the ratio of the expected responses, CR_X/R_X . Taking the expected correlated response from equation [19.5b] and the expected direct response from equation [11.4], we find

$$\begin{aligned} \frac{CR_X}{R_X} &= \frac{i_Y h_Y r_A \sigma_{AX}}{i_X h_X \sigma_{AX}} \\ &= \frac{i_Y r_A h_Y}{i_X h_X} \quad \dots [19.9] \end{aligned}$$

It can be seen from this expression that indirect selection will be better than direct selection if $r_A h_Y$ is greater than h_X . These two quantities are the accuracies of the two selection procedures; $r_A h_Y$ is the correlation between breeding values of the desired character X and phenotypic values of the selected character Y, while h is the accuracy of individual selection (i.e., direct selection) as explained in Chapter 13. Thus indirect selection cannot be expected to be better than direct selection

unless the secondary character has a substantially higher heritability and the genetic correlation is high. There are, however, practical considerations that may make indirect selection preferable. Three such practical matters may be mentioned.

1. If the desired character is difficult to measure with precision, the errors of measurement may so reduce the heritability that indirect selection becomes advantageous.

2. If the desired character is measurable in one sex only, but the secondary character is measurable in both, then a higher intensity of selection will be possible by indirect selection. Other things being equal, the intensity of selection would be twice as great by indirect as by direct selection; but a better plan would be to select one sex directly for the desired character and the other indirectly for the secondary character.

3. The desired character may be costly to measure, as for example the efficiency of food-conversion. Then it may be economically better to select for an easily measured correlated character, such as growth rate.

For a detailed evaluation of indirect selection, see Searle (1965). The following is an example of indirect selection giving a better response than direct selection for a character measurable in only one sex.

Example 19.2

(Data from Nagai *et al.*, 1978.) Mice were selected for two characters, nursing ability of females measured as the 12-day weight of the litter, and 6-week weight of individuals. Nursing ability will be designated as N and 6-week weight as W. The selection was done in two populations, P and Q, with different origins, and was continued for 12 generations. In each population one line was selected upwards for N, giving the direct response of N and the correlated response of W; a second line was selected for W giving the direct response of W and the correlated response of N. The responses are given in the table, correlated responses being shown in italics; all are in units of grams per generation.

Population	P		Q	
Character selected	N	W	N	W
Response of N	0.080	<i>0.134</i>	0.054	<i>0.125</i>
Response of W	<i>0.197</i>	0.680	<i>0.198</i>	0.868
Observed CR_N/R_N		1.675		2.315
Realized h^2	0.16		0.40	0.11
Realized r_A		0.70		0.73
$h_W r_A / h_N$		1.11		1.44
Expected [†] CR_N/R_N		2.2		2.9

[†] Assuming $i_W/i_N = 2$.

The genetic correlation in the P population is calculated by equation [19.7] as follows:

$$r_A^2 = \frac{CR_N}{R_N} \frac{CR_W}{R_W} = \frac{0.134}{0.080} \times \frac{0.197}{0.680} = 0.485; \quad r_A = 0.70$$

Example 19.2 continued

Similarly in the Q population, $r_A = 0.73$. There was thus very good agreement between the two populations in the estimation of r_A .

As can be seen from the ratio CR/R in the table, indirect selection was substantially better than direct selection for improving nursing ability. The reasons for this are that W has a higher heritability than N and can be selected in both sexes. The heritabilities, estimated as realized heritabilities from the direct responses, are given in the table. Again the two populations show good agreement for both characters. The intensities of selection actually applied are not given, but the expected intensities can be deduced from the proportions selected. The same proportions were selected for both characters, but females only were selected for nursing ability while both sexes were selected for weight. The net intensity of selection was therefore expected to be twice as great for weight as for nursing ability.

The expected ratio of correlated to direct responses of nursing ability can now be calculated by equation [19.9] from the observed heritabilities and genetic correlation and the presumed intensities of selection. For population P it is

$$\frac{CR_N}{R_N} = r_A \frac{i_W h_W}{i_N h_N} = 0.70 \times 2 \times \sqrt{\frac{0.40}{0.16}} = 2.2$$

The ratio for population Q is 2.9. In both cases the ratio realized was somewhat less than the expectation, presumably because the intensities of selection realized were not as much as twice as great for weight as for nursing ability.

Though indirect selection has been presented above as an alternative to direct selection, the most effective method in theory is neither one nor the other but a combination of the two. The most effective use that can be made of a correlated character is in combination with the desired character, as an additional source of information about the breeding values of individuals. This, however, is a special case of a more general problem which will be dealt with in the final section of this chapter. First we shall show how the idea of indirect selection can be extended to cover selection in different environments.

Genotype-environment interaction

The concept of genetic correlation can be applied to the solution of some problems connected with the interaction of genotype with environment. The meaning of interaction between genotype and environment was explained in Chapter 8, where it was discussed as a source of variation of phenotypic values, which in most analyses is inseparable from the environmental variance. The chief problem which it raises, and which we are now in a position to discuss, concerns adaptation to local conditions. The existence of genotype-environment interaction may mean that the best genotype in one environment is not the best in another environment. It is obvious, for example, that the breed of cattle with the highest milk-yield in temperate climates is unlikely also to have the highest yield in tropical climates. But it is not so obvious whether smaller differences of environmental conditions also require locally adapted breeds; nor is it intuitively obvious how much of the

improvement made in one environment will be carried over if the breed is then transferred to another environment. These matters have an important bearing on breeding policy. If selection is made under good conditions of feeding and management on the best farms and experimental stations, will the improvement achieved be carried over when the later generations are transferred to poorer conditions? Or would the selection be better done in the poorer conditions under which the majority of animals are required to live? The idea of genetic correlation provides the basis for a solution of these problems in the following way.

A character measured in two different environments is to be regarded not as one character but as two. The physiological mechanisms are to some extent different, and consequently the genes required for high performance are to some extent also different. For example, growth rate on a low plane of nutrition may be principally a matter of efficiency of food-utilization, whereas on a high plane of nutrition it may be principally a matter of appetite. By regarding performance in different environments as different characters with genetic correlation between them, we can in principle solve the problems outlined above from a knowledge of heritabilities of the different characters and the genetic correlations between them. If the genetic correlation is high, then performance in two different environments represents very nearly the same character, determined by very nearly the same set of genes. If it is low, then the characters are to a great extent different, and high performance requires a different set of genes. Here we shall consider only two environments, but the idea can be extended to an indefinite number of different environments (Robertson, 1959b; Dickerson, 1962; Yamada, 1962).

Let us consider the problem of the 'carry-over' of the improvement from one environment to another. Suppose that we select for character X – say growth rate on a high plane of nutrition – and we look for improvement in character Y – say growth rate on a low plane of nutrition. The improvement of character Y is simply a correlated response, and the expected rate of improvement was given in equation [19.6] as

$$CR_Y = ih_X h_Y r_A \sigma_{PY}$$

The improvement of performance in an environment different from the one in which selection was carried out can therefore be predicted from a knowledge of the heritability of performance in each environment and the genetic correlation between the two performances. We can also compare the improvement expected by this means with that expected if we had selected directly for character Y, i.e., for performance in the environment for which improvement is wanted. This is simply a comparison of indirect with direct selection, which was explained in the previous section. The comparison is made from the ratio of the two expected responses given in equation [19.9], i.e.,

$$\frac{CR_Y}{R_Y} = r_A \frac{i_X h_X}{i_Y h_Y}$$

This shows how much we may expect to gain or lose by carrying out the selection in some environment other than the one in which the improved population is required to live. If we assume that the intensity of selection is not affected by the environment in which the selection is carried out, then the indirect method will be

better if $r_A h_X$ is greater than h_Y , where h_X is the square root of the heritability in the environment in which selection is made, and h_Y is the square root of the heritability in the environment in which the population is required subsequently to live. If the genetic correlation is high, then the two characters can be regarded as being substantially the same; and if there are no special circumstances affecting the heritability or the intensity of selection, it will make little difference in which environment the selection is carried out. But if the genetic correlation is low, then it will be advantageous to carry out the selection in the environment in which the population is destined to live, unless the heritability or the intensity of selection in the other environment is very considerably higher.

This is the theoretical basis for dealing with selection in different environments. There have been several experiments testing the theory. In general they confirm the theory in finding correlated responses to be smaller than direct responses, i.e., selection is most effective if carried out in the environment for which the improvement is sought. These experiments, however, are not free of the inconsistencies mentioned earlier, particularly inconsistencies between the responses to upward and to downward selection. An experiment with mice is described briefly in the following example; for other examples, see two experiments with *Tribolium* in which the characters were larval growth (Yamada and Bell, 1969) and rate of egg-laying (Orozco, 1976).

Example 19.3

(Data from Falconer, 1960b.) Mice were selected for growth from 3 to 6 weeks on two diets: 'good' which was the normal diet, and 'bad' which was the normal diet diluted with 50 per cent indigestible fibre. The bad diet reduced growth by about 20 per cent at the beginning of the experiment. The direct and correlated responses were measured in each generation, the direct responses from first-litter progeny grown on the diet of selection, and the correlated responses from second-litter progeny grown on the other diet. Selection was carried out in both directions. There were inconsistencies between selection in opposite directions and between the earlier and later generations. For the purpose of illustrating the theory, these inconsistencies are avoided by taking the results over the first four generations only, and expressing the responses as the divergence between upward and downward selection. The table gives the information needed to calculate the genetic correlation from each pair of lines separately by equation [19.9] and from both pairs of lines together by equation [19.7]. The responses are grams per generation. As expected, both correlated responses were less than the direct responses, the ratios between the two indicating a genetic correlation of 0.66.

Divergence (g) per generation to generation 4.

	Character	
	Growth on good diet	Growth on bad diet
Intensity of selection, i	1.66	1.40
Realized heritability, h^2	0.41	0.36
Direct response, R	0.90	1.20
Correlated response, CR	0.48	0.98
Genetic correlation, by eqn [19.9], r_A	0.67	0.65
Genetic correlation, by eqn [19.7], r_A		0.66

Environmental sensitivity The way in which genotype–environment interaction arises from differences in sensitivity to the environment was explained in Chapter 8. The genetic correlation provides a means of quantifying the interaction for the purpose of predicting responses to selection. Understanding responses to selection in different environments may, however, be helped by thinking about environmental sensitivity. A high genetic correlation means that all genotypes react in nearly the same way to environmental differences; a plot like that of Fig. 8.2 would have regression lines that were all nearly parallel. A low genetic correlation means that genotypes react differently and have regression lines with different slopes, i.e., individuals have different environmental sensitivities. How does selection act on these differences of sensitivity? It is convenient to refer to environments as ‘good’ or ‘bad’ according to whether they increase or decrease the character; in practice an increase is generally sought, so an environment that increases the character is ‘good’. The effect of selection on sensitivity can be seen from Fig. 8.2. Upward selection in a good environment tends to pick individuals with high sensitivity, and downward selection in a bad environment does the same. In contrast, upward selection in a bad environment and downward selection in a good environment tend to pick individuals with low sensitivity. The two types of selection may be distinguished as *synergistic* when the selection and the environment act in the same direction (upwards in a good environment or downwards in a bad environment) and *antagonistic* when they act in opposite directions. Thus sensitivity will be increased by synergistic selection and reduced by antagonistic selection. These expectations have been born out by many experiments, reviewed by Falconer (1990).

What is wanted in practice is often not performance in a specific environment but performance in a range of environments, both good and bad, i.e., good average performance in different environments. Individuals cannot usually be measured in more than one environment. So, if individual selection is to be applied, the question arises of whether to select for high sensitivity by synergistic selection, or for low sensitivity by antagonistic selection. The review (Falconer, 1990) showed that more often than not (14 of 21 cases) the best overall performance was obtained by antagonistic selection. Examination of the theory, however, found no reason for expecting this to be so. If family selection can be applied, families can be divided between the environments and the mean performance of each family can be estimated. Details of how the two phenotypes of a family should be combined in an index to give the maximum improvement of average performance are given by James (1961).

Example 19.4

The mouse experiment of Example 19.3 provided data on environmental sensitivity and overall performance. In generation 7 an unselected control was measured and the responses in the two directions are given in the table as deviations from the control. The correlated responses are in italics. The environmental sensitivity of each line is the difference between its growth on the two diets, shown under ‘Effect of diet’. As expected, the most sensitive lines are those selected upwards on the good

Continued

Example 19.4 continued

diet and downwards on the bad diet, i.e., synergistic selection. Like the majority of experiments, the lines showing the best overall or average performance, shown under 'Mean of both diets', are the one selected upwards on the bad diet and the one selected downwards on the good diet, i.e., antagonistic selection.

Total response (g) to generation 7 as deviations from controls.

<i>Selection</i>		<i>Response</i>			<i>Sensitivity</i>
<i>Direction</i>	<i>Diet</i>	<i>Growth on good diet</i>	<i>Growth on bad diet</i>	<i>Mean of both diets</i>	<i>Effect of diet</i>
Up	good	2.3	0.6	1.45	5.4
Up	bad	1.6	3.1	2.35	3.5
Down	good	-2.8	-2.9	-2.85	3.6
Down	bad	-1.2	-3.2	-2.20	6.8

Environments that differ by some known factor, such as diet for example, are called macro-environments. A single macro-environment, however, has micro-environmental differences within it, and the conclusions about how selection affects sensitivity apply also to the micro-environmental variance within a single macro-environment. Individuals selected by phenotype have a good genotype and have also experienced a good environment. The selection is therefore synergistic and, if there is genotype-environment interaction, selection in either direction will increase environmental sensitivity. The increased sensitivity appears as an increase of the environmental variance, V_E , and a reduction of the heritability. The increased phenotypic variance seen in many selection experiments may be partly due to this cause, as was noted in Chapter 12.

Index selection

When selection is applied to the improvement of the economic value of animals or plants, it is generally applied to several characters simultaneously and not just to one, because economic value depends on more than one character. This is usually referred to as multiple trait selection. For example, the profit made from a herd of pigs depends on their fertility, mothering ability, growth rate, efficiency of food-utilization, and carcass qualities. How, then, should selection be applied to the component characters in order to achieve the maximum improvement of economic value? There are several possible procedures. One might select in turn for each character singly in successive generations (tandem selection); or one might select for all the characters at the same time but independently; rejecting all individuals that fail to come up to a certain standard for each character regardless of their values for any other of the characters (independent culling levels). The method that is expected to give the most rapid improvement of economic value, however, is to apply the selection simultaneously to all the component characters together, appropriate weight being given to each character according to its relative economic importance, its heritability, and the genetic and phenotypic correlations between the different

characters. The practice of selection for economic value is thus a matter of some complexity. The component characters have to be combined together into a score, or *index*, in such a way that selection applied to the index, as if the index were a single character, will yield the most rapid possible improvement of economic value.

The principles of index selection were introduced in Chapter 13 and will not be repeated in full here. The main difference in the index required here is that the breeding value to be predicted is not that of a single character but that of a composite of several characters evaluated in economic terms. The index is consequently more complex than the one developed in Chapter 13. We shall, however, start by considering the simpler problem of improving a single character by the use of an index, and then extend this to improving economic value. In practice, BLUP is used to estimate fixed effects and account for other complications in real data sets while simultaneously evaluating breeding value for merit, as explained in Chapter 13.

Construction of the index

The objective of the selection, whatever it may be, will be referred to as *merit*, and the breeding value for merit will be symbolized by H . The index to be constructed for the improvement of merit is, as before,

$$I = b_1 P_1 + b_2 P_2 + \dots + b_m P_m \quad \dots [19.10]$$

where P_1 to P_m are phenotypic measurements of m characters on which selection is to be based, and b_1 to b_m are the corresponding weighting factors to be determined. The b 's are partial regression coefficients of H on T . Information from relatives can be included in the index, so the P 's can be measurements of relatives in the manner explained in Chapter 13.

Single trait First consider selection aimed at improving just one character. The purpose of applying index selection is then to use secondary characters as aids to improvement of the one desired character. The index equations, whose solution gives the values of the b 's in the index, are exactly the same as equations [13.10], with character 1 as the character to be improved.

$$\left. \begin{aligned} b_1 P_{11} + b_2 P_{12} + \dots + b_m P_{1m} &= A_{11} \\ b_1 P_{21} + b_2 P_{22} + \dots + b_m P_{2m} &= A_{21} \\ &\vdots \\ b_1 P_{m1} + b_2 P_{m2} + \dots + b_m P_{mm} &= A_{m1} \end{aligned} \right\} \quad \dots [19.11]$$

The notation here is abbreviated as in Chapter 13. For example, P_{11} is the phenotypic variance of character 1, and P_{12} is the phenotypic covariance of characters 1 and 2; A_{11} and A_{12} are similarly the additive genetic variance and covariance. The variances and covariances can be expressed in terms of the heritabilities and correlations as follows, where the subscripts i and j refer to any two different characters and σ^2 is the phenotypic variance:

$$\left. \begin{aligned} P_{ii} &= \sigma_i^2 & A_{ii} &= h_i^2 \sigma_i^2 \\ P_{ij} &= r_P \sigma_i \sigma_j & A_{ij} &= r_A h_i h_j \sigma_i \sigma_j \end{aligned} \right\} \quad \dots [19.12]$$

When the values of the variances and covariances have been entered, the solution of equations [19.11] provides the values of the weighting factors, b , to be used in the index in equation [19.10]. The construction of an index is illustrated later, in Example 19.5. The expected response to selection will be dealt with after the different forms of the index equations have been explained.

Economic value Next consider the improvement of economic value. The economic value is the profit made from the sale of the individual. In practical breeding operations it is often possible to assign economic values to individuals. This is then the phenotypic value of merit, which is the character to be improved, and the index is constructed for the improvement of this single character. But the index equations, whose solution gives the value of the b 's in the index, differ in one respect from what was described above. The economic values of individuals cannot be known at the time they are being considered for selection, and therefore cannot be included as a character in the index. The index equations are then as follows. In order to facilitate comparison, character 1 is still taken to be the character to be improved, in this case merit.

$$\left. \begin{array}{l} b_2 P_{22} + b_3 P_{23} + \dots + b_m P_{2m} = A_{21} \\ b_2 P_{32} + b_3 P_{33} + \dots + b_m P_{3m} = A_{31} \\ \cdot \\ \cdot \\ b_2 P_{m2} + b_3 P_{m3} + \dots + b_m P_{mm} = A_{m1} \end{array} \right\} \dots [19.13]$$

The variances and covariances have to be estimated from past records of the economic values and the values of the characters in the index.

Multiple traits Finally, consider simultaneous selection for several characters. The objective is to improve the *aggregate breeding value*, or *net merit*, which is a particular combination of all the characters to be improved. Merit is now defined as

$$H = a_1 A_1 + a_2 A_2 + \dots + a_n A_n \dots [19.14]$$

Here the A 's are breeding values for the n characters to be improved, and the a 's are weighting factors which express the relative importance attached by the breeder to each character. The weighting factors can be economic values; that is to say, each a is the value in money units of 1 unit of the character. This is how an index is constructed if the aim is to improve economic value when there are no records of individuals' economic values, so that the index described above cannot be used. Assigning money values to the characters is, however, not necessarily the best method of improvement. Other criteria for weighting are discussed by Fowler, Bichard, and Pease (1976) in connection with the improvement of pigs. If the weighting factors are not in money units, they must express in some other way the relative importance to the breeder of 1 unit increase of each character. Yamada, Yokouchi, and Nishida (1975) describe indices constructed in this way.

The number of characters in the definition of merit (equation [19.14]) and in the index (equation [19.10]) may differ: there may be characters that are not in H but which may help to improve H through their correlations if included in I ; and,

conversely, there may be characters in H which cannot be measured and so are not in I . It is important to note, however, that if the aim is to improve economic value, then all the characters that influence economic value must be included in the definition of H .

The index equations, whose solution gives the b 's to be used in the index, are obtained in the same way as was described in Chapter 13, by maximizing r_{HI} , the correlation between merit and the index. They are as follows:

$$\left. \begin{array}{l} b_1 P_{11} + b_2 P_{12} + \dots + b_m P_{1m} = a_1 A_{11} + a_2 A_{12} + \dots + a_n A_{1n} \\ b_1 P_{21} + b_2 P_{22} + \dots + b_m P_{2m} = a_1 A_{21} + a_2 A_{22} + \dots + a_n A_{2n} \\ \vdots \\ b_1 P_{m1} + b_2 P_{m2} + \dots + b_m P_{mm} = a_1 A_{m1} + a_2 A_{m2} + \dots + a_n A_{mn} \end{array} \right\} \dots [19.15]$$

The variances and covariances can again be expressed in terms of the heritabilities and correlations by equations [19.12]. Example 19.6 below illustrates the construction of an index from these equations, simplified by considering only two characters.

Practice The foregoing account of indices will serve to explain the principles by which an index is constructed. In practice, the laborious calculations can be made by computer. The program REML estimates the parameters of the population that are needed, and BLUP calculates the aggregate breeding values of the individuals among whom selection is to be made. The procedures were outlined in Chapter 13.

Response

The index equations ([19.11], [19.13], [19.15]) are scaled in such a way that the regression of merit on index values is unity, i.e., $b_{HI} = 1$. The values of the b 's in the index (equation [19.10]) are thus adjusted so that the metric values of the index I correspond numerically with the units in which merit H is expressed, whatever they are, when both are deviations from the mean. In this way the index becomes a prediction of breeding value for merit. With $b_{HI} = 1$, it follows that $r_{HI} = \sigma_I / \sigma_H$, as shown in Chapter 13. The expected response to selection is the same as in Chapter 13, the predicted change in merit being given by

$$\dot{R}_H = ir_{IH}\sigma_H \quad \dots [19.16]$$

or, if the index has not been rescaled,

$$R_H = i\sigma_I \quad \dots [19.17]$$

The variance of the index, from which σ_I can be evaluated, is as in equation [13.12] when there is only one character in merit, i.e., for single-trait selection. Extended to include multiple-trait selection it is as follows. To simplify the notation, let $\Sigma_1 aA$ be the sum of the terms on the right-hand side of the first equation of [19.15], $\Sigma_2 aA$ that of the second equation, etc. Then the variance is

$$\sigma_I^2 = b_1 \Sigma_1 aA + b_2 \Sigma_2 aA + \dots + b_m \Sigma_m aA \quad \dots [19.18]$$

The standard deviation of the index, σ_I , provides a simple way of comparing the relative efficiencies of different indices for improving merit because, as can be seen from equation [19.17], the response of merit is simply proportional to σ_I .

The response of any one of the component characters of the index, or of merit, can be predicted as follows. Suppose we want to predict the response of character 1. This is a correlated response of character 1 to selection for the index, and it is predicted by adaptation of equation [19.5a], putting character 1 in place of Y and the index I in place of X. The response of the index is the same as that of merit given in equation [19.17]. The correlated response of character 1 then becomes

$$CR_1 = b_{(A)II} i \sigma_I = \frac{\text{cov}_{(A)II}}{\sigma_I^2} i \sigma_I = \frac{i}{\sigma_I} \text{cov}_{(A)II} \quad \dots [19.19]$$

Here $\text{cov}_{(A)II}$ is the additive genetic covariance of character 1 with the index, and it is obtained as follows. Multiplying equation [19.10] by A_1 gives the sum of products of A_1 with I as $b_1 P_1 A_1 + b_2 P_2 A_1 + \dots$. If each P is now written as $(A + E)$, the products AE drop out because breeding values and environments are uncorrelated. The required covariance can now be seen to be as follows, where the variances and covariances are written in the notation of the index equations:

$$\text{cov}_{(A)II} = b_1 A_{11} + b_2 A_{12} + \dots + b_m A_{1m} \quad \dots [19.20]$$

These variances and covariances must be known for construction of the index, so substitution into equation [19.19] gives the predicted response.

The following two examples will make clearer what is involved in constructing an index and will bring in one or two points of interest that have not been explained above.

Example 19.5

The use of an index for the improvement of a single character will be illustrated from an experiment to be described in Example 19.6. Suppose the character to be improved is body weight in mice, and we consider using the correlated character tail length in an index. Let body weight be character 1 and tail length character 2. The parameters needed to construct the index are given in the table, with values taken from Rutledge, Eisen, and Legates (1973).

Character	h^2	h	σ_P^2	σ_P	r_A	r_P
1 = Weight (g)	0.36	0.60	6.37	2.52	0.29	0.45
2 = Tail length (cm)	0.44	0.67	0.28	0.53		
$P_{11} = 6.37$	$P_{22} = 0.28$		$P_{12} = P_{21} = 0.6010$			
$A_{11} = 2.2932$	$A_{22} = 0.1232$		$A_{12} = A_{21} = 0.1557$			

The index equations for solution, from equations [19.11], are

$$\begin{aligned} b_1 P_{11} + b_2 P_{12} &= A_{11} \\ b_1 P_{21} + b_2 P_{22} &= A_{21} \end{aligned}$$

Continued

Example 19.5 continued

The values of the variances and covariances, calculated by equations [19.12], are given in the table. Substituting these in the above equations gives

$$\begin{aligned} 6.37b_1 + 0.6010 b_2 &= 2.2932 \\ 0.6010b_1 + 0.28 b_2 &= 0.1557 \end{aligned}$$

and the solution is

$$b_1 = 0.386; b_2 = -0.272$$

The index for selection is therefore

$$I = 0.386W - 0.272T$$

where W and T are the weight (g) and tail length (cm) respectively. The index can be rescaled for convenience by dividing all through by b_1 , to give

$$I' = W - 0.705T$$

The index values are altered by the rescaling, but not the order of merit of the individuals.

Note that tail length is given a negative weighting in an index for increasing body weight. In other words, tail length is an indicator of environment, rather than breeding value, for weight. The reason for this is that the environmental correlation, which is 0.56, is much higher than the genetic correlation of 0.29. This illustrates a point not made previously, that a character may be useful in an index as an indicator of environmental deviations rather than of breeding values.

The usefulness of a secondary character can be judged from its weighting coefficient b_2 . It can be shown that $b_2 = 0$ if the genetic and phenotypic regressions of character 2 on character 1 are the same; or, in terms of correlations, if $r_A/r_P = h_1/h_2$. Under these conditions a secondary character will give no benefit; in fact, errors of estimation will make it worse than useless (Sales and Hill, 1976).

To predict the response to selection, we have to calculate the variance of the index. For this purpose the unscaled index must be used. The variance, by equation [19.18], is

$$\sigma_I^2 = (0.386 \times 2.2932) + (-0.272 \times 0.1557) = 0.8428$$

and $\sigma_I = 0.918$. The response could then be predicted by equation [19.17] if the intensity of selection were known. In order to see how useful the secondary character would be, we can compare the expected responses to index selection and to simple selection, assuming the intensity of selection is the same. The response to simple selection, by equation [11.3], is $i h^2 \sigma_P$. The ratio of the responses, index selection/simple selection, is therefore $0.918/0.907 = 1.012$. The index would be only 1 per cent better than selection for body weight alone.

Finally, what would be the expected change of tail length resulting from selection for the index? The correlated response of character 1 is given by equations [19.19] and [19.20], but in this case we want the response of character 2. First, by equation [19.20],

$$\text{cov}_{(A)2I} = b_2 A_{22} + b_1 A_{21} = -0.0335 + 0.0601 = +0.0266$$

Then, by equation [19.19], the expected response of tail length is

Example 19.5 *continued*

$$CR_2 = +i(0.0266/0.9185) = +0.03i \text{ cm per generation.}$$

A very small increase of tail length is expected. It might seem at first that the negative weighting of tail length in the index should result in a decrease. But the correlated response depends on the genetic correlation, which is positive.

Example 19.6

The experiment with mice, from which the data for Example 19.5 were taken, applied index selection with the object of changing both body weight and tail length, and compared the observed with the expected responses (Rutledge, Eisen, and Legates, 1973). The objective was to change the body conformation by increasing one character and decreasing the other. Four lines were selected for seven generations, two selected for increased body weight and decreased tail length, and two selected in the opposite direction. The construction of the index for increasing body weight and decreasing tail length will be explained. The parameters needed are given in the table of Example 19.5. In addition we need the 'economic' weighting of the two characters. Equal 'economic' values were assigned to one standard deviation of change of each character. The weights, a , assigned were therefore the reciprocals of the phenotypic standard deviations, and these were $a_1 = 0.40$ and $a_2 = -1.89$.

The index, from equation [19.15], are

$$\begin{aligned} b_1 P_{11} + b_2 P_{12} &= a_1 A_{11} + a_2 A_{12} \\ b_1 P_{21} + b_2 P_{22} &= a_1 A_{21} + a_2 A_{22} \end{aligned}$$

Substituting the variances and covariances, and the weights, leads to

$$\begin{aligned} 6.37b_1 + 0.601b_2 &= 0.9173 - 0.2943 = 0.6230 \\ 0.601b_1 + 0.28b_2 &= 0.0623 - 0.2328 = -0.1706 \end{aligned}$$

and the solution is

$$b_1 = 0.195; \quad b_2 = -1.027$$

The index for selection is thus

$$I = 0.195W - 1.027T$$

where W and T are an individual's body weight and tail length respectively. For selection in the opposite direction, to decrease W and increase T , the signs in the index are simply reversed.

The variance of the index, by equation [19.18], is

$$\begin{aligned} \sigma_I^2 &= (0.195 \times 0.6230) + (-1.027 \times -0.1706) \\ &= 0.2967 \\ \sigma_I &= 0.5447 \end{aligned}$$

The intensity of selection realized, averaged over the four lines, was $i = 1.01$. The expected response based on the selection actually applied was, by equation [19.17],

$$R_H = 1.01 \times 0.5447 = 0.55 \text{ index units per generation.}$$

Continued

Example 19.6 *continued*

The observed responses were 0.26 and 0.30 in the lines selected for increased W with decreased T , and 0.42 and 0.45 in the lines selected in the opposite direction. The reason for the observed responses being somewhat less than expected is probably that the parameters for construction of the index were not accurately estimated.

(Some of the quantities calculated in this example differ a little from those given in the original paper. The reason for this is that the parameters used in the paper were derived from the base population before selection, but the published parameters used here are those of unselected lines maintained concurrently with the selection.)

Effect of selection on genetic correlations

There is one important consequence of multiple-trait selection to be discussed before we leave the subject. Just as the heritabilities are expected to change after selection has been applied for some time, so also are the genetic correlations. If selection has been applied to two characters simultaneously, the genetic correlation between them is expected eventually to become negative, for the following reason. Those pleiotropic genes that affect both characters in the desired direction will be strongly acted on by selection and brought rapidly toward fixation. They will then contribute little to the variances or to the covariance of the two characters. The pleiotropic genes that affect one character favourably and the other adversely will, however, be much less strongly influenced by selection and will remain for longer at intermediate frequencies. Most of the remaining covariance of the two characters will therefore be due to these genes, and the resulting genetic correlation will be negative. The consequence of a negative genetic correlation, whether produced by selection in this way or present from the beginning, is that the two characters may each show a heritability that is far from zero, and yet when selection is applied to them simultaneously neither responds. We have already discussed, in Chapter 12, what is essentially the same situation resulting from the combined effects of artificial and natural selection: a selection limit is reached even though the character to which artificial selection is applied still shows a substantial amount of additive genetic variance.

The theoretical expectation that selection should change the genetic correlation has been tested in several experiments but, as so often with genetic correlations, the evidence is conflicting. For a review and discussion of this question see Sheridan and Barker (1974).

Problems

- 19.1** The data below are taken from a sib analysis in a flock of broiler chickens. They refer to the weight gain (G) from 5 to 9 weeks of individual males and the weight of food (F) consumed in the same period, both in units of grams. The figures given are the components of variance and of covariance between half-sib families, and the total phenotypic variances and covariance. From these data calculate the heritability of the two characters, and the phenotypic, genetic, and environmental correlations between them.

	<i>Variance</i>		<i>Covariance</i>
	<i>Weight gain</i>	<i>Food consumption</i>	<i>G with F</i>
Between sires	1,602	6,150	2,229
Total	12,321	61,504	22,848

Data based on Pym, R.A.E. & Nicholls, P.J. (1979) *Brit. Poult. Sci.*, **20**, 73–86.

[Solution 40]

- 19.2 The data refer to two characters of *Drosophila*: body size measured as thorax length, and fertility measured as the number of eggs laid in 4 days. The phenotypic variances and the covariance were measured in a genetically variable population and in a genetically uniform group consisting of F_1 's of crosses between inbred lines. From these data, estimate the three correlations – phenotypic, genetic, and environmental – in the variable population. How does the meaning of the genetic correlation here differ from that of the genetic correlation in Problem 19.1?

<i>Population</i>	<i>Variances</i>		<i>Covariance</i>
	<i>Body size</i>	<i>Fertility</i>	
Variable	0.366	43.4	0.87
Uniform	0.186	16.6	0.27

Data from Robertson, F.W. (1957) *J. Genet.*, **55**, 428–43.

[Solution 50]

- 19.3 Consider again the data on broiler chickens in Problem 19.1. Suppose that selection for increased weight gain is to be applied in one line and for increased food consumption in another line. The proportions selected in both lines are to be 10 per cent of males and 20 per cent of females. Calculate the predicted responses per generation of the two characters when directly selected and when responding as correlated characters. [Solution 60]

- 19.4 Five generations of selection were applied to the broiler flock described in Problem 19.1. One line was selected for increased weight gain (G) and another was selected for increased food consumption (F). The total selection differentials applied over the five generations and the total responses were as follows, the responses being deviations from a control line.

	<i>Line selected for</i>	
	<i>G</i>	<i>F</i>
Selection differential (g)	574	1,312
Response of G (g)	186	120
Response of F (g)	412	525

Calculate the realized heritabilities of the two characters and the realized genetic correlation between them.

Data from Pym, R.A.E. & Nicholls, P.J. (1979) *Brit. Poult. Sci.*, **20**, 73–86. [Solution 70]

- 19.5 The litter size of mice could be increased by selection of females for their litter size, or by selection of both sexes for body weight. Which would be the better of these two simple procedures, given the following parameters?

Heritability of litter size	= 0.22
Heritability of body weight	= 0.35
Genetic correlation	= 0.43
Proportion of selected: females	= 25%
males	= 10%

[Solution 80]

19.6 In addition to the two procedures for increasing litter size considered in Problem 19.5, a third procedure would be to select females for litter size and males for body weight. There are several ways in which this could be carried out. Assume the procedure to be as follows. Males are weighed at the appropriate age (e.g., six weeks) and 25 per cent are selected out of a large number. The selected males are each mated to a randomly chosen group of four young females whose litter sizes are not yet known. When the females have had their first litters the best one of the four mated to each male is selected. The litters of these selected males and females are reared as the next generation. How much better would this procedure be than selecting only on females for litter size? Take the heritabilities and genetic correlation to be as given in Problem 19.5.

[Solution 90]

19.7 The data refer to the broiler chickens described in Problem 19.1. Suppose that it is desired to improve 5–9 week growth (G), using the weight of food consumed (F) as an aid to the selection. Calculate the appropriate index for evaluating the parents to be selected. The estimates of the parameters needed are as follows. In order to have the decimal points conveniently placed for the calculations, the units of weight are changed here from grams to 100 g units.

	G	F
h^2	0.52	0.40
σ_p	1.11	2.48
r_A		0.71
r_P		0.83

[Solution 100]

19.8 If selection for growth were applied by the index calculated in Problem 19.7, what would be the predicted improvement per generation, assuming the intensity of selection was $i = 1.5775$ as in Problem 19.3? How much better would the index be for improving growth than selection for growth alone without the aid of a secondary character?

[Solution 110]

19.9 If selection for growth were applied by the index as in Problem 19.8, what would be the expected rate of change of the secondary character food consumption?

[Solution 120]

19.10 From the data and calculations in Problem 19.7 calculate an index for improving economic value, given that the value of growth is 8 cents per 100 g of weight gain, and that of food consumption is -2 cents per 100 g.

Data from Pym, R.A.E. & James, J.W. (1979) *Brit. Poult. Sci.*, **20**, 99–107. [Solution 130]

19.11 Calculate the rate of improvement of economic value expected from selection by the index in Problem 19.10, when 10 per cent of males and 20 per cent of females are selected as in Problem 19.3. How much better would the index be for improving economic value than selection for growth alone?

[Solution 140]

20 Metric Characters under Natural Selection

Throughout the discussion of the genetic properties of metric characters, which has occupied the major part of the book, very little attention has been given to the effects of natural selection, and something must now be done to remedy this omission. The absence of differential viability and fertility was specified as a condition in the theoretical development of the subject: that is to say, natural selection was assumed to be absent. Though for many purposes this assumption may lead to no serious error, a complete understanding of metric characters will not be reached until the effects of natural selection can be brought into the picture. The operation of natural selection on metric characters has, however, a much wider interest than just as a complication that may disturb the simple theoretical picture and the predictions based on it. It is to natural selection that we must look for an explanation of the genetic properties of metric characters, which hitherto we have accepted with little comment. The genetic properties of a population are the product of natural selection in the past, together with mutation and random drift. It is by these processes that we must account for the existence of genetic variability; and it is chiefly by natural selection that we must account for the fact that characters differ in their genetic properties, some having proportionately more additive variance than others, some showing inbreeding depression while others do not. These, however, are very wide problems which are still far from solution, and in this chapter we can do little more than indicate their nature. Before considering the ways in which natural selection affects metric characters, we shall give a brief account of natural selection itself and what it means.

Natural selection

Fitness and its components

The 'character' that natural selection selects for is fitness. The fitness of an individual is the contribution of genes that it makes to the next generation, or the number of its progeny represented in the next generation. *Relative fitness* is the fitness of an individual relative to the population mean, i.e., W/\bar{W} , if W is the individual's fitness. If a population is neither expanding nor contracting in numbers, the mean fitness of its individuals is 1 and then absolute fitness and relative fitness are the same. There are difficulties in defining fitness precisely. One such difficulty lies in separating the fitness of an individual from that of its parents. In a mammal, for example, the survival of the juvenile progeny depends partly on their viability, which is an aspect of their own fitness, and partly on the parental care that

they receive, which is an aspect of the parents' fitness. This overlap of fitness from one generation to the next means that there is no precise time in an individual's life at which we can say that its attributes reflect its own fitness rather than that of its parents. The point of separation between the generations must therefore be a more or less arbitrary choice.

The mean fitness of a population is a concept that has to be used with great care. It was said above that the individuals of a population have a mean fitness of 1 if the population is neither increasing nor decreasing in numbers. This seems simple enough. But whether a population increases or decreases or remains constant in numbers depends to a large extent on the environmental resources available to it. Natural selection between individuals within a population may change the genetic constitution of the population, but the mean fitness will not change if the population is already at the limit of the carrying capacity of its environment. When the mean fitness is referred to in what follows, it will be assumed that the population is not limited by environmental resources.

The fitness of an individual is the final outcome of all its developmental and physiological processes. The differences between individuals in these processes are seen in variation of the measurable attributes which can be studied as metric characters. Thus the variation of each metric character reflects to a greater or lesser degree the variation of fitness; and the variation of fitness can theoretically be broken down into variation of metric characters. Consider, for example, a mammal such as the mouse. Figure 20.1 illustrates the hierarchy of characters contributing to the fitness of females. Nearly all of the characters shown have been studied

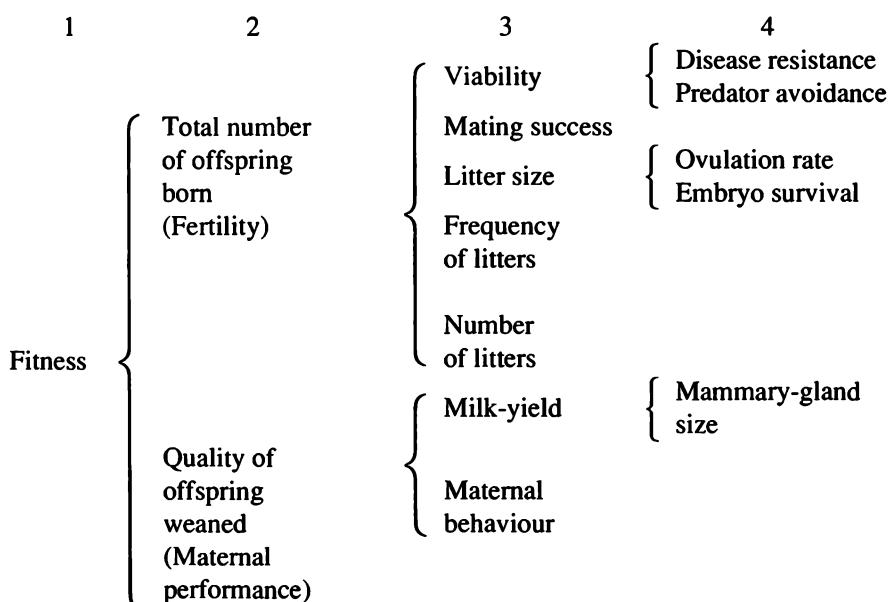


Fig. 20.1. Some of the components of fitness of a mammal such as the mouse, to show the hierarchy of causes of variation. Variation of each of these metric characters is associated, to a greater or lesser degree, with variation of fitness.

genetically as metric characters. Fitness itself can be broken down into two major components, the total number of offspring produced and the quality of these offspring, which might be measured as their weaning weights. The variation of the major components, if properly measured, would account for all the variation in fitness. The variation of the major components can in turn be attributed to other characters, some of which are shown in column 3 of the diagram. These again are influenced by others, a few of which are in column 4. The characters in column 4 are themselves influenced by many others. Among these, for example, are physiological functions such as the output of the various gonadotrophic hormones, which influence ovulation rate, embryo survival, and milk-yield. There are, in addition, characters whose influences on fitness are less direct and less obvious, but which are correlated with some of the components of fitness. Body size, for example, is correlated with several, perhaps all, of the characters in column 4. The problem we have to examine is how all these metric characters are affected by selection for fitness, and how the action of natural selection is related to the character's position in the hierarchy.

Measurement of fitness It is very difficult to measure fitness directly, particularly the fitness of individuals. It is less difficult to measure the major components of fitness separately. The overall fitness can then be estimated by combining the values of the components. This sort of information is available from demographic studies in which a cohort is followed from birth to death, and data obtained on age-specific survivorship, fertility, mating ability, and so on. In industrialized societies of man, by far the most important component of fitness is the number of children reared, since mortality between childhood and the end of reproduction is very low. The size of completed families therefore provides a fairly good measure of the fitness of the two parents jointly though, of course, it includes infant and childhood survival in the parents' fitness. An improved measure can be obtained by taking account of the rate of reproduction, i.e., the average age of the parents at the birth of their children (see Waller, 1971). A measure of fitness that combines all components into a single value, the 'competitive index', has been used in *Drosophila*. Individuals of the strain of interest are reared in competition with a genetically marked tester strain so that offspring produced by crossing can be identified. The competitive index is the relative number of progeny produced by the two pure strains. For details of this and other methods for estimating fitness in *Drosophila*, and references, see Sved (1989).

Relationships between metric characters and fitness

We are now in a position to discuss the ways in which natural selection affects characters of different sorts, as described above. We have to consider what sort of selection is being applied to the character, what this will do to the frequencies of the genes concerned, and how the genetic properties of the character are thereby influenced.

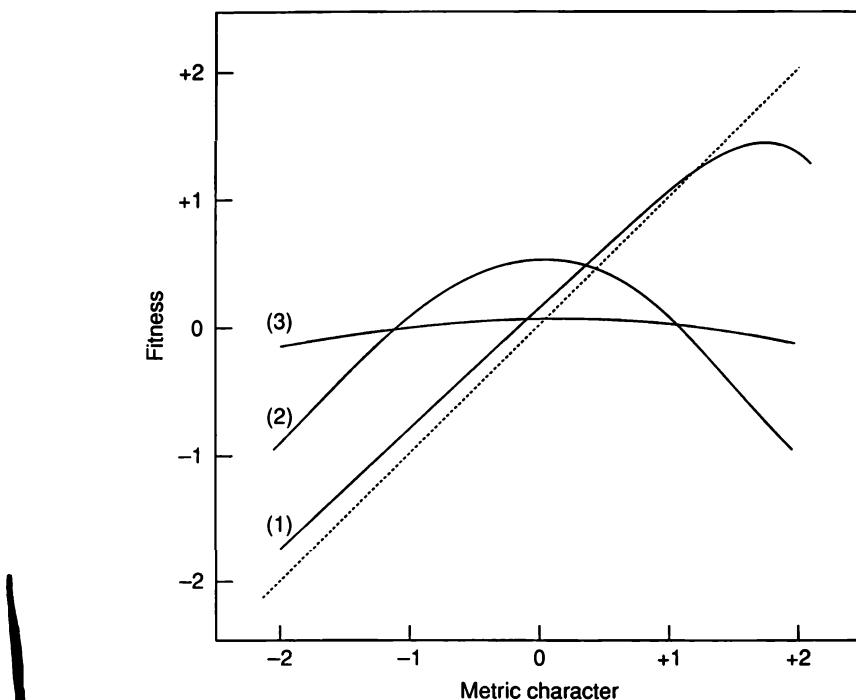


Fig. 20.2. 'Fitness profiles' as explained in the text. The scales on both axes are standard deviations from the means.

'Fitness profiles'

Natural selection acts on a metric trait if there are differences in fitness of individuals with different phenotypic values of the trait. The type of natural selection and its intensity can be determined from a plot of fitness against phenotypic value called a 'fitness profile'. This information could be obtained empirically from studies of quantitative trait phenotypes and fitness components in a cohort followed from birth to death, albeit with considerable difficulty (e.g., Clutton-Brock, Guinness, and Albon, 1982; Grant, 1986). More commonly, relative fitness is deduced from changes in the frequency distribution of trait phenotypes before and after an episode of selection. Schematic examples of fitness profiles are illustrated in Fig. 20.2. For actual examples of *Drosophila* fitness profiles, see Mackay (1985a). The dotted diagonal line is the profile that would be obtained if the metric character measured was fitness itself. Curve (1) is the profile of a trait under strong directional selection for high values, as expected for a major component of fitness. Profile (2) represents a character experiencing stabilizing natural selection. There is an intermediate optimum as the fittest individuals are those with values of the character at or near the mean. The fitness profile for a trait under disruptive selection is not shown: it is the inverse of that for stabilizing selection, with intermediates selected against. Finally, profile (3) represents a trait under very weak selection that is very nearly neutral with respect to fitness over the range of phenotypes observed. There are almost no differences of fitness among individuals with different values

of this character. In earlier chapters characters have been referred to as being 'closely connected' with fitness, but the precise meaning of the 'close connection' was not explained. It can now be seen that characters closely connected to fitness are the major components, with fitness profiles like curve (1). The closeness of the connection falls off as the profile approaches that of curve (2).

Responses to natural selection

Fitness

The response of fitness itself to selection has an elegant solution, known as *Fisher's fundamental theorem*, which states that the increase in fitness at any time is equal to the additive genetic variance of fitness at that time. This theorem has given rise to a great deal of discussion about its validity and its generality; see Frank and Slatkin (1992) and Edwards (1994). A proof of the theorem and an explanation of why it has caused so much difficulty is given by Price (1972). The conclusion can be very simply demonstrated for a single generation in a population with non-overlapping generations, by consideration of the weighted selection differential, as follows.

The response to selection for a metric character is predicted from the selection differential by equation [11.2] ($R = h^2S$). The selection differential S is the weighted mean superiority of the selected parents, the weights being the relative contribution of progeny from which the response is evaluated. Fitness must be expressed as *relative fitness*. If k is the number of offspring of any particular individual and \bar{k} is the mean number of offspring of all individuals in that generation, the relative fitness of the individual is $W = k/\bar{k}$. The mean relative fitness is $\bar{W} = 1$. The relative fitness is also the weight to be attached to the individual's contribution, $W - \bar{W}$, to the selection differential. Therefore, if N is the total number of individuals in the parental generation, the weighted selection differential on relative fitness is

$$\begin{aligned} S_W &= \frac{\sum W(W - \bar{W})}{N} \\ &= \frac{\sum W^2}{N} - \frac{\sum W}{N} \bar{W} \\ &= \bar{W}^2 - (\bar{W})^2 \\ &= V_{P(W)} \end{aligned} \quad \dots [20.1]$$

(The last step in the derivation was explained in connection with equation [3.4].) Thus the selection differential on fitness is equal to the phenotypic variance of fitness, and we may note incidentally that the intensity of selection is equal to the phenotypic standard deviation:

$$i_W = S_W/\sigma_W = \sigma_W \quad \dots [20.2]$$

Substituting equation [20.1] into equation [11.2] shows that the response of fitness to natural selection is equal to the additive genetic variance of fitness:

$$R_W = h_W^2 V_{P(W)} = V_{A(W)} \quad \dots [20.3]$$

Any increase in fitness predicted by the theorem will not necessarily lead to an increase in population numbers, because the numbers cannot exceed the carrying capacity of the habitat. Gene frequencies will change, however, if there is additive variance of fitness, and the changes of gene frequencies may cause changes of characters correlated with fitness. The changes in the components of fitness are therefore correlated responses, and these are generally of more interest than the change of fitness itself. We must therefore consider how the correlated responses can, in principle, be predicted.

Correlated responses

If a character is correlated with fitness, selection for fitness will produce an apparent, or correlated, selection differential on the character. The correlated selection differential, S'_Y , on a character Y is the weighted mean of Y , the weight being the individual's fitness. Thus

$$S'_Y = \frac{\sum W(Y - \bar{Y})}{N}$$

and by a derivation similar to that of equation [20.1] this leads to

$$S'_Y = \text{cov}_{P(YW)} \quad \dots [20.4]$$

i.e., the correlated selection differential is equal to the phenotypic covariance of the character with fitness. The correlated response can now be obtained from equation [19.8c], i.e., $CR_Y/S'_Y = \text{cov}_{(A)}/\text{cov}_{(P)}$. From this and equation [20.4], the correlated response is found to be

$$CR_Y = \text{cov}_{A(YW)} \quad \dots [20.5a]$$

i.e., the additive covariance of the character Y with fitness. Alternatively, the covariance can be written in terms of the genetic correlation and heritabilities. This gives

$$CR_Y = r_A h_Y h_W \sigma_Y \sigma_W \quad \dots [20.5b]$$

where σ denotes the phenotypic standard deviation. Thus, to predict a correlated response to natural selection it would be necessary to know the genetic correlation between the character and fitness, and the heritability of the character and of fitness. (Equation [20.5a] was derived by Robertson (1966) in connection with an analogous problem in dairy cattle, namely the correlated responses expected from the overall selection applied by farmers.) For a detailed treatment of correlated responses under natural selection see Crow and Nagylaki (1976).

It is important when making predictions of correlated responses to natural selection to ensure that the fitness and trait value estimates are derived from a single generation. For example, it used to be thought that natural selection was tending to reduce human intelligence because children from larger families have lower IQs than those from smaller families; in other words, there seemed to be a correlated selection differential for reduced IQ. In this case, however, the supposition about the selection differential is false for two reasons: first, because parents with zero

fitness have no children and so cannot appear in the data; and second, because it is based on the correlation between parents' fitness and children's IQ. When the parents' IQ is compared with their own subsequent number of children as a measurement of fitness, the correlated selection differential is found to be slightly positive (Waller, 1971).

Strength of selection

The way in which natural selection acts on a quantitative trait can be inferred from the empirically determined fitness profile. With the major components of fitness – like curve (1) in Fig. 20.2 – selection is unidirectional over most of its range. The strength, or intensity, of the selection acting on the trait (Y) can be expressed in terms of the correlated selection differential, S'_Y , and the phenotypic variance, $V_{P(Y)}$. From equation [20.4] it follows that the ratio of these two quantities is equal to the linear regression of fitness on the trait, i.e.,

$$b_{WY} = S'_Y / V_{P(Y)} \quad \dots [20.6]$$

This regression coefficient is known as the *selection gradient* (Lande and Arnold, 1983). If several traits are being considered together, the selection gradient of each is its partial regression coefficient. For comparisons across characters or species, S'_Y is scaled by dividing it by the phenotypic standard deviation of the trait before selection (Endler, 1986). The selection gradient is then a measure of the intensity of selection, i . The intensity of selection tells us how strongly the trait is being selected, but it does not allow us to deduce the change that natural selection will make in the trait; equation [20.5b] shows what other parameters would be needed to predict the response.

Characters that have an intermediate optimum – like curve (2) in Fig. 20.2 – are subject to stabilizing selection, which is bidirectional. There are two measures of the strength of stabilizing selection, used according to whether data are available on variances or on fitnesses. Individuals with the more extreme values, high or low, are selected against. The selection therefore causes the phenotypic variance of the trait to be less after the selection has occurred than it was before. The strength of the stabilizing selection can be assessed from the difference of variance in the same generation resulting from the selection, the difference being expressed as a proportion of the variance before selection. The measure of the strength of selection, denoted by j , is estimated by

$$j = (V_P^* - V_P) / V_P \quad \dots [20.7]$$

where V_P is the phenotypic variance before selection and V_P^* the variance in the same generation after selection (Lande and Arnold, 1983; Endler, 1986). Note that j is a negative quantity under stabilizing selection. The same measure can be applied to disruptive selection, which increases the variance; j is then positive.

The second measure is based on the fitness of individuals with different values of the trait. The assumption is made that fitness declines as the square of the deviation of the trait from its optimum value. Let y be the deviation, in standard deviation units, of the trait value from its optimum, and let $W(y)$ be the fitness of individuals with trait deviation y . Then the relative fitness, $w(y)$, of individuals with deviation y

is $w(y) = W(y)/W(y = 0)$. It can be shown that the regression, b_{wy^2} , of relative fitness on the square of the deviation is approximately linear. The slope of this regression is the stabilizing selection gradient (Lande and Arnold, 1983). The measure of the strength of selection, denoted by V_S , is a measure of the width of the fitness profile. When selection is weak the profile is wide and flat; when the selection is strong it is narrow and peaked. Thus a high value of V_S indicates weak selection and a low value indicates strong selection. V_S is obtained from the regression coefficient by

$$V_S = -1/(2b_{wy^2}). \quad \dots [20.8]$$

For purposes of comparison, it is expressed in terms of V_E , the environmental variance. With stabilizing selection b is necessarily negative, so V_S is positive; with disruptive selection it is negative.

Expressed in terms of V_S , the phenotypic variance after stabilizing selection has occurred is $V_P^* = V_P - [V_P^2 / (V_P + V_S)]$ (Bulmer, 1985, p. 151). Therefore the relationship between j and V_S is

$$j = -V_P / (V_P + V_S). \quad \dots [20.9]$$

Estimates of the strength of natural selection in natural populations have been summarized by Turelli (1984), Endler (1986), and Crow (1989). The strength is variable but is often in the same range used in artificial selection. Observed values of V_S for stabilizing selection range, very roughly, from $100V_E$ (weak selection) to $10V_E$ (strong selection), V_E being the environmental variance of the trait. Strong stabilizing selection is more common than strong disruptive selection. The true strength of selection could often be higher than it seems since selection at only one point in the life history is usually measured. The estimated magnitudes and directions of natural selection on single traits may also give a misleading impression of the targets and mode of natural selection, since selection acts on fitness and thus simultaneously on many phenotypically correlated traits, not all of which are identified or measured. Using multivariate regression to estimate directional and stabilizing selection gradients on multiple characters (Lande and Arnold, 1983) and partitioning these gradients for each stage of selection throughout the life cycle (Arnold and Wade, 1984a, b) partly addresses these problems. Nevertheless, it appears that many characters have fitness profiles falling between curves (1) and (2) of Fig. 20.2, with optima at some distance from the mean.

Equilibrium populations

Now we can see how the genetic properties of metric traits are shaped by the continued action of natural selection. If environmental conditions are stable over a very long period of time, the mode and intensity of natural selection are also constant, so populations will reach an equilibrium, at which gene frequencies do not change at any loci. Consequently the mean values of all metric characters remain constant. Probably few real populations are strictly in equilibrium, because the environment is unlikely to remain constant for sufficiently long, but most populations are probably near enough to equilibrium for the following considerations to apply. There is, however, one qualification: we are here neglecting mutation as a source of new variation.

Fitness

From Fisher's fundamental theorem, it is clear that response to selection for fitness will cease when additive genetic variance for fitness is depleted. Thus there will be no further response to selection for fitness in an equilibrium population, despite continued selection each generation. That is, the population has reached a selection limit for fitness. Genetic variance for fitness maintained at the limit must be largely non-additive, i.e., variance due to dominance and epistatic interactions. This could come from two sources: from genes at more or less intermediate frequencies that are overdominant with respect to fitness, or from deleterious recessives maintained at low frequencies by mutation balancing the selection. In both cases dominance is directional, so severe inbreeding depression for fitness is expected. This has been repeatedly confirmed: fitness of homozygous *Drosophila* chromosomes is only 10 per cent that of heterozygous chromosomes (Sved, 1971, 1975; Mackay, 1985a). Genes at intermediate frequencies cause more variation than genes at low frequencies, so it is possible that most of the variance of fitness comes from overdominant loci and most of the inbreeding depression from rare recessives (Crow, 1952).

Since the array of gene frequencies in an equilibrium population is the best, in the circumstances, for maximizing fitness, it follows that if selection is applied to any metric character that is not fitness itself, the gene frequencies at loci affecting the character must change if there is a response. Fitness must therefore be reduced as a correlated response, unless the character selected is controlled entirely by genes with no effects on fitness. This expectation is amply born out by experience: experimental selection for metric characters almost always results in a reduction of one or more of the major components of fitness. To give just one example: the mean fitness of *Drosophila* was estimated as a competitive index after five generations of selection for abdominal bristle number (Latter and Robertson, 1962). There were two lines selected upwards and two downwards. The mean fitness, relative to an unselected control, was 79 per cent in the upward selected lines and 65 per cent in the downward selected lines.

If artificial selection is carried out and is then suspended before much of the variation has been lost by fixation, natural selection must tend to bring the gene frequencies back toward their equilibrium values, and the mean of the character artificially selected is expected to revert toward its original value. This tendency for natural selection to resist changes of gene frequency is known as *genetic homeostasis* (Lerner, 1954). Its effect can often be seen in experimental selection when the weighted selection differential is less than the unweighted (see Example 11.5).

Major components

Continued natural selection on fitness components, often called life-history traits, has similar consequences as that on fitness itself: additive genetic variance is reduced, leading to low heritabilities, and the non-additive variance remaining is attributable to directional dominance, leading to inbreeding depression. Kearsey and Kojima (1967) compared 12 *Drosophila* characters. All the measures of major components of fitness showed epistatic interaction and strong directional dominance, while all the others – measures of body size and bristle number – showed little or no dominance

or interaction. In another experiment with *Drosophila* (Mackay, 1985a) fitness profiles of viability and fertility were obtained, and they closely resembled curve (1) of Fig. 20.2. These characters also showed a large amount of inbreeding depression. Roff and Mousseau (1987) and Mousseau and Roff (1987) have summarized extensive data that confirm generally low heritabilities of fitness components.

A somewhat different picture of fitness components emerges if the amount of additive variance itself, instead of the heritability, is considered. A survey of experiments (Houle, 1992) showed that if the variance is scaled to the mean, i.e., is expressed as a coefficient of variation, fitness components have more additive variance than other traits. The low heritabilities seem to be due to large amounts of non-additive and environmental variance rather than to small amounts of additive variance (see Houle, 1992, for a discussion).

The difference between fitness components and fitness itself is that the highest values of the separate components do not have the highest fitness. Fitness may be thought of as an index by which natural selection selects simultaneously for all the major components. We should then expect additive genetic correlations between characters that are major components of fitness to be negative, for the reasons given at the end of the previous chapter. As an example, consider number born in Fig. 20.1. At the low end of the range each additional young born results in nearly one additional offspring reaching adulthood, and thus an increase in total fitness. But as the number born increases, their 'quality' is progressively reduced by limitations in maternal performance until, above a certain number, the reduced quality outweighs the extra numbers and fewer offspring survive to adulthood. Such negative additive genetic correlations, sometimes called 'antagonistic pleiotropy', have been found for fitness components in randomly mating *Drosophila* populations (Rose and Charlesworth, 1981). Thus additive genetic variance for fitness components can be maintained by negative genetic correlations with other fitness components. In inbred strains, however, genetic correlations between fitness components are expected to be positive, because deleterious recessive genes made homozygous by inbreeding are likely to have deleterious effects on more than one component of fitness, and so contribute positively to the genetic correlation. High positive correlations were in fact found in the experiment cited above by Mackay (1985a).

If the environment to which an equilibrium population is adapted changes, the array of gene frequencies is no longer optimal. The changed environmental circumstances alter the relative weighting of the components of fitness, so that fitness itself now has some additive variance and can respond to natural selection. The application of artificial selection can be thought of as changed environmental circumstances in this way, altering the weighting of the components in the combined natural and artificial fitness. The components of fitness in human populations have changed drastically in the recent past as a result of medicine and contraception, psychological and behavioural factors having largely replaced physiological factors as determinants of fitness, particularly in rich countries.

Characters with intermediate optima

We have referred to intermediate optima fitness profiles as resulting from stabilizing selection in a purely descriptive sense, meaning only that intermediate

phenotypes have the highest fitness. Observation of an intermediate optimum, however, does not tell us how natural selection acts on the character or on the genes that affect the character. There are several different reasons why intermediates might be more fit (Robertson, 1967), which give rise to different predictions about the genetic constitution of these traits in an equilibrium population.

'Real' stabilizing selection The classic model of stabilizing selection is that the value of the character is a direct cause of fitness. We shall call this 'real' stabilizing selection to imply a causal relationship of trait value to fitness. A straightforward example of a character having a direct causal effect on fitness would be any measure of the thermal insulation of a mammalian coat. The conflicting needs for conserving heat during inactivity and dissipating heat during activity are balanced at an intermediate coat density. Intermediates are favoured because that value of the character is best. The selection is functional or true stabilizing selection. (This example, it must be said, is conjectural: if the experiment were done it might be found that over the range of variation in any real population the differences in fitness associated with the character were fairly small.) Robertson (1967) argued that real stabilizing selection is not likely to be common, since the model essentially subdivides organisms into as many compartments as there are imaginable traits, each of which causally affects fitness through its mean phenotypic value.

Real stabilizing selection has two main effects. First, it favours genotypes with the least variability (Curnow, 1964), irrespective of whether the genes affect the mean of the character or not. (The consideration of genotype \times environment interaction in Chapter 19 showed that stabilizing selection reduces environmental sensitivity.) In other words, it increases the 'canalization' of development (Waddington, 1957). Second, it tends to reduce the genetic variance of the character and this it does in two ways (Bulmer, 1971, 1976). The more immediate, and at first the largest, effect is through the creation of gametic phase disequilibrium. The selection causes allelic effects at different loci to be negatively correlated in individual genotypes. The covariance term in equation [8.10] is therefore negative and the genetic variance is reduced. In so far as the genes are linked, the selection tends to build up 'balanced' combinations in which linked genes are in predominantly repulsion linkage, so that the effect of the chromosome as a whole is minimized (see Mather, 1941; Lewontin, 1964). The selection, however, has to be very strong, or the linkage very close, to keep the genes in combinations that are appreciably different from a random arrangement (see Wright, 1969, p. 92). The second way by which the genetic variance is reduced is through changes of gene frequencies at loci that affect the mean of the character. Provided the genotypes do not differ much in variability, and provided the loci do not affect fitness in any other way than through the character, then stabilizing selection tends to change the gene frequencies toward fixation, and so to reduce the genetic variance (Robertson, 1956). However, the gene frequencies change only slowly, unless selection is intense or the genes have large effects. The consequences of real stabilizing selection are thus to reduce both environmental and genetic variance. Both these effects have been observed experimentally; for example, with sternopleural bristle number in *Drosophila* (Gibson and Bradley, 1974) and with pupa weight in *Tribolium* (Kaufman, Enfield, and Comstock, 1977).

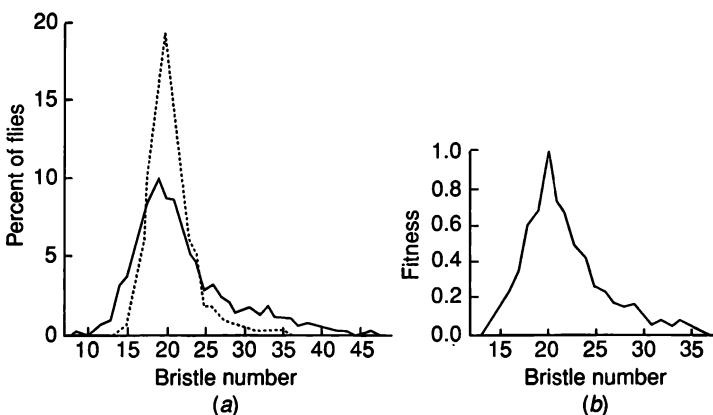


Fig. 20.3. (a) Distributions of sternopleural bristle number in *Drosophila*: continuous line, under weak natural selection; dotted line, under strong natural selection.
 (b) Fitness profile derived from the frequency distributions in (a). The fitness scale is relative to the fittest bristle class. The fitness measured is only the component, survival from egg to adult, and not the whole of fitness. (Adapted from Kearsey and Barnes, 1970.)

'Apparent' stabilizing selection An intermediate optimum for a quantitative trait could arise from pleiotropic effects of genes affecting the trait on fitness components. For example, an intermediate optimum for fertility might result from a negative correlation between fertility and viability of the offspring. Clutch size in birds is a well-known case of an intermediate optimum (Lack, 1966) that can be explained in this way. Clutch size (number of eggs laid) should be a major component of fitness, but the number of offspring that can be reared is limited by the available food supply. An intermediate clutch size results in the largest number reared, because of the balance between the two major components of fitness, number and quality of young. An intermediate optimum for mouse body size may similarly be caused by opposing correlations with different components of fitness. Body size is positively correlated with number born since large mice have larger litters (Falconer, 1965b), but might be negatively correlated with survival because large mice are placid and unreactive to disturbance, whereas small mice are alert and react vigorously to disturbance (MacArthur, 1949; Falconer, 1953). Under natural conditions one must suppose that larger mice would be less good at escaping predators than small ones. Likewise, intermediate optima for *Drosophila* body size result from opposing genetic correlations with fecundity, development time, and larval survival (Roff, 1981). In all of these cases stabilizing selection is spurious because the character with the intermediate optimum is not the direct target of selection.

A clear example of apparent stabilizing selection from pleiotropic effects unrelated to the character itself is provided by sternopleural bristle number in *Drosophila melanogaster* (Kearsey and Barnes, 1970). The sternopleural bristles are small bristles on the sides of the thorax of adult flies. The population studied was derived from a cross of two strains selected in opposite directions; it had a mean of 18.5 bristles in females, with a range of approximately 10–45. The

evidence for stabilizing selection is given in Figure 20.3(a), which shows the distributions of bristle number in flies grown in uncrowded conditions (solid line) and in crowded conditions (dotted line). In crowded conditions the natural selection for larval survival is much stronger and its effect in eliminating flies with the more extreme bristle numbers is clearly seen. A fitness profile can be constructed from the reduction in frequency of flies with different bristle numbers. This profile, however, is not of fitness itself but of one major component, larval survival. Figure 20.3(b) shows the profile, which has a sharp peak of fitness at the mean bristle number. The important point about this fitness profile is that the selection which gives rise to the intermediate optimum takes place in the larval stages, before the flies have developed any bristles. The superior fitness of flies with intermediate bristle number is therefore in no way caused by the character itself, but must result from the genes affecting larval survival having pleiotropic effects on bristles. The stabilizing selection is spurious, as in the previous examples, but in this case we do not know what the real criteria of selection are, nor why adults with intermediate bristle numbers are fittest in the larval stages.

The effect of apparent stabilizing selection on the genetic variance of the trait cannot be predicted without knowing what components of fitness are being selected and how the trait observed is correlated with these components. One possibility is the following (Robertson, 1956). The genes affecting the major components of fitness may have pleiotropic effects on the character in question, and these effects on the character may be more or less additive. Individuals with intermediate values of the character must then be heterozygous at more loci than extreme individuals. If the loci have overdominant effects on fitness, then natural selection favours heterozygotes and in consequence appears to favour intermediates for the character. The consequence of apparent stabilizing selection acting in this way would be the maintenance of the genetic variation for the character. In the case of the sternopleural bristles described above, however, apparent stabilizing selection could not be accounted for by heterozygote advantage because the same fitness profile was observed for homozygous lines (Linney *et al.*, 1971). Kimura (1983) proposes that if the number of loci controlling a character under stabilizing selection is very large, the selection acting at each locus must be very small. Allelic variants at these loci will then be very nearly selectively neutral, and their gene frequencies determined by a balance between non-recurrent mutation and drift, even though the trait phenotype is selected. This could explain the paradox between the prevalence of natural selection at the phenotypic level and of neutral or nearly neutral alleles at the molecular level.

Characters with minimum fitness of intermediates

Disruptive selection is the opposite of stabilizing selection: intermediates are selected against. Though not a frequent occurrence, it has been observed in natural populations (Endler, 1986). The most likely cause is the presence of alternative habitats which differ in some way that makes one phenotypic extreme favoured in one habitat and the other extreme in another habitat. An example of disruptive selection associated with differential habitat utilization is provided by ground finches on the Galapagos Islands. Birds with different bill shapes and sizes are

more efficient at procuring and processing different sized seeds. Birds with small narrow bills feed more efficiently on small, soft seeds, whereas birds with deep bills utilize large, hard seeds more efficiently; and this leads to reduced fitness of intermediate sized bills relative to the extremes (Schluter, Price, and Grant, 1985). Disruptive selection is expected to increase both genetic and environmental variance, and these effects have been observed experimentally. For example, when applied to larval development time in *Drosophila* (Prout, 1962), the environmental variance was increased; and when applied to pupa weight of *Tribolium* (Halliburton and Gall, 1981) the genetic and environmental variances were both increased.

Neutral characters

It is not clear whether many quantitative characters can be said to be truly neutral with respect to fitness, having a profile like curve (3) in Fig. 20.2. Finger ridge count in humans may be such an example. Note that saying a character is neutral with respect to fitness does not mean the trait has no function, but that the exact value of the character is not a determinant of fitness. Some traits do appear to have very broad optima, so that variation of the trait value over most of the observed range is not associated with differences in fitness. An indirect way to determine whether variation in a character is neutral is to perform a 'perturbation' experiment. A population is subjected to a few generations of directional selection for the character; then, when the mean has changed some way from its original value, selection is suspended and the population is allowed to breed at random, subject only to natural selection. If the mean does not revert to its original value, or does so only very slowly, it can be concluded that the character is neutral, or nearly so. Strictly speaking, reversed selection should also be applied, to prove that the mean can be brought back. Perturbation experiments for *Drosophila* abdominal and sternopleural bristle number suggest these characters may be very nearly neutral (Latter and Robertson, 1962). This conclusion is supported by empirically determined total fitness profiles of sternopleural bristle number for chromosome homozygotes (Spiers, 1974; Mackay, 1985a). On the other hand, the apparent stabilizing selection for sternopleural bristle number described above shows that the genes affecting bristles do also affect fitness, though not through the number of bristles. Also, the temporal and spatial constancy of bristle numbers in natural populations suggests that the genes concerned are not neutral with respect to fitness. Bristles are sense organs and the primary functions of these genes may affect fitness through the development of the peripheral nervous system. A complete understanding of how most metric traits are related to fitness (i.e., traits that are not major components of fitness) will be achieved only when we know what the primary functions of the genes are.

Origin of variation by mutation

Spontaneous mutation in natural populations generates new genetic variance, which has been ignored in the foregoing account of how natural selection affects metric traits. Selection, excepting only disruptive selection, reduces the variance, and mutation increases it. In the next section we shall have to consider whether the

balance between selection and mutation can account for the amounts of genetic variance found to exist in natural populations. First, we must describe what is known about the rate at which new variation is generated by mutation.

Mutational variance

The variance of any trait generated by mutation in one generation is called the *mutational variance*, symbolized by V_M . To allow comparisons to be made between traits and between species, V_M is expressed as a proportion of the environmental variance, V_E , of the trait. There are two ways in which V_M can be estimated. We saw in Chapters 12 and 15 that new mutations contribute to long-term selection responses and to the divergence between sublines of inbred strains. Therefore V_M can be estimated by making a population homozygous and dividing it into a number of replicate sublines that accumulate mutations over time. If the sublines are selected for the character of interest, the rate of response provides an estimate of the additive component of V_M . If the sublines are not selected, V_M is estimated from the divergence of the mean value of the trait between them. Both methods estimate only the new variance due to neutral mutations, since deleterious mutants are eliminated by natural selection. Several estimates of V_M for *Drosophila* abdominal and sternopleural bristle number have been obtained in large replicated experiments using both methods (for a review of these experiments as well as earlier studies, see Keightley, Mackay, and Caballero, 1993). Estimates of V_M for *Drosophila* bristle traits are consistently 10^{-3} times the environmental variance, V_E , i.e., $(V_M/V_E) = 10^{-3}$. Similar levels of mutational variance have been reported for *Drosophila* life-history traits (Houle *et al.*, 1994) and enzyme activities (Clark, Wang, and Hulleberg, 1995), and for mouse body size (Hill, Caballero, and Keightley, 1994). The average mutational variance for other characters in other species is also $10^{-3} V_E$, with a range from 10^{-4} to $10^{-2} V_E$ (Lynch, 1988).

If the heritability of the character is known, we can answer the question: how long would it take for mutation to generate the genetic variance found in natural populations? For example, bristle traits of *Drosophila* have heritabilities of about 0.5, and little non-additive variance. So $V_G = V_E$, and $V_M = 10^{-3} V_G$ per generation. Thus, if the base population had no genetic variance it would take 1,000 generations for mutation to generate the genetic variance of a natural population.

We have comparatively little information about the magnitudes of the individual parameters that make up V_M . If the mutant alleles at all loci have the same effect on the character and the same mutation rate, then $V_M = 2nua^2$, where n is the number of loci whose mutants affect the trait; u is the mutation rate per locus; and a^2 is the variance of mutant allelic effects (it is assumed that the mean effect of mutations at each locus is zero, so mutations increasing and decreasing the value of the trait are equally frequent). The n that is relevant here is the total number of loci at which mutations affecting the trait can arise, which must be larger than the number of loci contributing to selection response (Chapter 12) or the number contributing to segregating variation in a natural population (Chapter 21). The mutation rate at loci affecting quantitative traits is not likely to be less than that for loci with qualitative mutant phenotypes (10^{-5} to 10^{-8}), and could well be much higher. Mutations with quantitative effects are probably in gene regulatory regions that affect timing of

expression or protein activity, whereas mutations of qualitative effect are likely to be in exons and affect the amount and function of gene product; the mutational target size may be greater, therefore, for mutations of quantitative effect. The only direct evidence comes from experiments measuring per character mutation rates (nu). The rate of origin of spontaneous mutations affecting viability in *Drosophila*, i.e., survival from egg to adult, has been estimated by Mukai *et al.* (1972). New mutations were accumulated for 40 generations on replicate second chromosomes derived from a single progenitor, protected from natural selection and recombination by a balancer chromosome. The homozygous effects of these chromosomes on larval survival were tested at 10-generation intervals, from which the rate of origin of mutations on Chromosome 2 was deduced. There were two classes of mutated genes: those that were lethal or severely detrimental in homozygotes, and those that were mildly detrimental, with viabilities above about 0.6 of normal. After 40 generations, 24 per cent of chromosomes carried one or more lethals, and the rate of origin was 0.6 per cent per chromosome per generation. The detrimentals were about 10–20 times as frequent, with a rate of origin of about 10 per cent per chromosome per generation. Scaling up by $5/2$ to represent the whole genome, this means that after one generation of mutation, about 25 per cent of gametes carry a new mildly detrimental mutation; i.e., $nu = 0.25$. Similarly, per character mutation rates for mouse skeletal variants and maize morphological traits were in excess of 0.01 per gamete per generation (reviewed by Turelli, 1984). These high values of nu do suggest large numbers of mutable loci affecting quantitative traits, high mutation rates for alleles with quantitative effects, or both. Note that large n per character implies widespread pleiotropic effects of new mutations on multiple traits, due to the upper bound on n set by the number of loci per genome.

Information on homozygous (a), heterozygous (d) and pleiotropic effects of new mutations affecting quantitative traits comes mainly from studying spontaneous and induced mutations affecting viability and bristle number in *Drosophila*. As noted above, homozygous effects of mutations affecting viability range from lethal to quasi-normal. On average, the effect on heterozygous viability is similar for both classes of mutation, approximately 0.02, but there is an inverse relationship between degree of dominance and severity of effect, with lethals almost completely recessive and mildly detrimental mutations roughly additive (Crow and Simmons, 1983). Similar effects on bristle traits have been found in other experiments, reviewed by Caballero and Keightley (1994), and with *P* element insertional mutations by Mackay, Lyman, and Jackson (1992). (*P* elements are transposable elements of *Drosophila melanogaster* that cause mutations of the genes into which they insert after transposition.) The conclusions drawn from these experiments are as follows. (i) Most mutations have very small effects on bristle number, but a few mutations with large effects occur. The distribution of mutant effects is leptokurtic and the bulk of the increase in variance from new mutations is caused by those of large effect. (ii) There is variation in degree of dominance of new mutations affecting bristle number, with a tendency towards recessivity for mutations of large effect. (iii) Mutations with large homozygous effects on bristle number also have reduced homozygous viability. For *P* element insertional mutations, the correlations of absolute values of effects on bristle number and viability were approximately 0.4 for both abdominal and sternopleural bristle number.

Maintenance of genetic variation

Natural selection tends to reduce genetic variation for quantitative traits, as does genetic drift in finite populations, yet we observe genetic variation for practically all traits in natural populations. Can spontaneous mutations counteract these tendencies sufficiently to maintain the observed levels of genetic variation, or must we look to other balancing forces for an explanation, such as genotype \times environment interaction for fitness? This question has been addressed quite extensively in theory (for reviews see Bulmer, 1989, and Barton and Turelli, 1989). The exact answer depends on (i) the shape of the fitness profile and the intensity of selection, (ii) the effective population size, and (iii) the mutational variance, which depends on the number of loci, the distribution of mutant effects, and the per-locus mutation rate. We have seen that values of many of these parameters are not known, or are known only very roughly. Theoretical models for the maintenance of quantitative variation must be consistent with the observed values of these variables as far as they are known. This requirement is difficult to satisfy with simple models, but the problems raised indicate the direction of future empirical and theoretical work.

Balance between neutral mutation and random drift

We saw in Chapter 15 that when the new mutational variance is balanced by loss from random drift the genetic variance present in a population of effective size N_e is $V_G = 2N_e V_M$. The phenotypic variance is $2N_e V_M + V_E$ and the heritability is therefore

$$h^2 = \frac{2N_e V_M}{2N_e V_M + V_E}$$

This is the broad-sense heritability because V_M includes all the genetic variance, not just the additive. If we substitute $V_M = 10^{-3} V_E$ the heritability becomes

$$h^2 = \frac{0.002 N_e}{1 + 0.002 N_e}$$

and this gives the following values for different population sizes:

$N_e =$	100	1,000	10,000
$h^2 =$	0.17	0.67	0.95

(see Lynch and Hill, 1986). Thus mutation in the absence of selection is able to maintain a large amount of genetic variation except in very small populations. The very high heritabilities of a few characters such as human finger ridge counts (see Chapter 10) suggest these characters are subject to neutral mutation with no selection on the genes that influence them. On the other hand, heritabilities of most characters are much lower than those predicted by the neutral model, and we must conclude that for most characters selection also plays a part in reducing the genetic variance.

Mutation-selection balance

In Chapters 2 and 4 the mechanisms that maintain polymorphism were discussed. Now we have to extend the discussion to quantitative characters, the variation of

which is caused by polymorphic loci. For this, we have to bring into consideration the observed values of the mutational variance and the strength of selection, and find out whether the balance of the two forces can account for the observed levels of genetic variance.

Fitness traits For characters that are major components of fitness, observed levels of genetic variation in natural populations are consistent with the variation expected from a balance between mutation and natural selection. Most mutant alleles affecting these characters are deleterious and selection is unidirectional – against the mutants. It can be shown that the genetic variance expected at equilibrium between the input of new deleterious mutations and directional selection against them is approximately $V_G = V_M/s$, where s is the coefficient of selection against heterozygous mutants (Barton, 1990). Experiments on the egg-to-adult viability of *Drosophila* have estimated $V_G = 1 \times 10^{-2}$, $V_M = 1.3 \times 10^{-4}$, and $s = 0.02$ (Mukai *et al.*, 1972; and reviewed by Mukai, 1979). Therefore the expected equilibrium genetic variance is approximately 0.65×10^{-2} , which is in good agreement with the observed value.

'Real' stabilizing selection With characters under real stabilizing selection, when mutations are not unconditionally deleterious, the situation is more complicated. There are two main models, of which only an outline can be given. The first (Lande, 1975) assumes that there are an infinite number of possible alleles at each of n loci, and that for each locus the effects of alleles segregating in the equilibrium population and of mutant alleles are normally distributed. The equilibrium variance predicted by this model is

$$V_G = \sqrt{2nV_M V_S} \quad \dots [20.10]$$

where V_M is the mutational variance and V_S is the strength of stabilizing selection explained above. The assumption of normally distributed allelic effects at equilibrium will be a reasonable approximation only if the variance of the effects of mutant alleles is very small relative to the existing allelic variation at each locus. This requirement means that the model is only valid when the effects of mutant alleles are all small and consequently stabilizing selection is weak, and when mutation rates per locus are very high (Turelli, 1984). To find out whether this model can account for the levels of genetic variance observed, we consider the heritability, which may be as high as 0.5 for characters subject to stabilizing selection, and ask whether the model predictions are consistent with $h^2 = 0.5$. We take the observed value of $V_M = 10^{-3} V_E$, and $V_S = 100V_E$ for weak selection, and see if the number of loci implied by the model is reasonable. Then $V_G = (2n \times 10^{-3} \times 100)^{\frac{1}{2}} V_E$. When $h^2 = 0.5$, $V_G = V_E$, which gives $n = 5$. This means only five mutationally equivalent loci are necessary to produce the observed amount of genetic variation, which seems reasonable. However, if there are only a few loci, the per-locus mutation rate would have to be very high to produce the observed mutational variance, or the allelic effects would have to be large, which would be inconsistent with the model because the distribution of allelic effects would no longer be normal. The model therefore does not seem able to account for the amount of genetic variance observed.

The second model (Turelli, 1984) also assumes that the effects of new mutations are normally distributed, but that mutational effects are large compared with the existing allelic variation at each locus affecting the trait; that the per-locus mutation rate is much less than 10^{-5} ; and that the strength of selection, V_S , is in the observed range of $100V_E$ to $10V_E$. The equilibrium genetic variance is then

$$V_G = 4nuV_S \quad \dots [20.11]$$

Under these conditions the distribution of allelic effects at equilibrium is highly leptokurtic, with most of the variance contributed by rare alleles with large effects. To evaluate the model we assume strong selection with $V_S = 10V_E$ and we find what value is predicted for the product nu when $h^2 = 0.5$. Thus $V_G = 40nuV_E$ and $nu = 2.5 \times 10^{-2}$. To maintain appreciable heritabilities either n or u must be large. If we take $n = 100$ as a reasonable number of loci, then the per-locus mutation rate would have to be 2.5×10^{-4} , which is at least an order of magnitude higher than is thought to be reasonable. If we take $u = 10^{-5}$, ten times the accepted rate for major mutants, then n would have to be 2,500, which seems an unreasonably large number of loci. If n is very large, there must be widespread pleiotropy. If a mutant allele has a large effect on one trait and minor pleiotropic effects on many other traits, the variance maintained at the locus will be dominated by selection on the trait on which the allele has a large effect, so the contribution of the locus to genetic variation for the other traits on which allelic effects are small will be much less than predicted (Turelli, 1985).

As noted above, the concept of real stabilizing selection requires that selection ‘sees’ organisms as subdivided into as many compartments as there are imaginable traits, each of which causally affects fitness. Simple genetic load arguments suggest real stabilizing selection of the magnitude observed for individual traits cannot operate independently on many characters (Robertson, 1967; Barton, 1990). Real stabilizing selection also implies that a significant fraction of new mutations will be beneficial, and that the effect on fitness of a new mutation depends on the genetic background in which it occurs. This is at variance with the commonly accepted view that most mutations are unconditionally deleterious or at best nearly neutral (Kondrashov and Turelli, 1992). Maintenance of observed levels of genetic variation for quantitative traits by this direct mechanism seem unlikely.

‘Apparent’ stabilizing selection The appearance of stabilizing selection can occur if mutations have deleterious pleiotropic effects on fitness, since individuals with extreme phenotypes are less fit if they have more deleterious mutations (Barton, 1990) or if mutations with large effects on the trait also have large effects on fitness (Keightley and Hill, 1990). The idea that quantitative genetic variation can be maintained by a balance between mutation and directional selection against pleiotropic deleterious effects on fitness of new mutations is attractive because it takes into consideration observed properties of mutations. However, it is still difficult to account simultaneously for observed levels of segregating variation and strengths of natural selection with simple pleiotropic models. For example, given equally deleterious mutations with heterozygous fitness $1 - s$, and selection strong relative to mutation, the equilibrium genetic variance is $V_G = V_M/s$ and the strength of

apparent stabilizing selection is approximately $s = V_M/V_G$ (Barton, 1990). Thus heritabilities of 0.5 and strong stabilizing selection ($s = 0.02$) are possible if $V_M/V_E = s \approx 10^{-2}$. Estimates of V_M/V_E are an order of magnitude lower than estimates of average selection against heterozygous effects of new mutations. Thus one could explain high levels of segregating variation with this model by postulating mutations affecting quantitative traits are nearly neutral ($s = 10^{-3}$), but this would fail to explain observed strengths of stabilizing selection.

Estimates of mutational variance obtained are biased downward if mutations affecting the trait are deleterious; whether this bias is as much as by an order of magnitude depends on the joint distribution of effects of mutations on the trait and on fitness. Further evaluation of the validity of models of mutation-selection balance for maintaining genetic variance of traits with intermediate optima will depend on more accurate empirical determination of this distribution, as well as of mutation rates at loci causing quantitative variation. If experimental values of frequencies and effects of new mutations are not of the magnitude required, alternative explanations must be explored. For example, it is possible that effects of mutations affecting quantitative traits may be different in different environments. If so, temporal and spatial environmental variation could maintain genetic variation since heterozygotes would be on average more fit than homozygotes (Barton and Turelli, 1989).

Problems

20.1 Problem 11.2 was concerned with evolutionary change in a species of Darwin's Finch following selective survival with respect to bill depth. Prediction of the response to this natural selection was made from $R = h^2 S$ [11.2] on the assumption that 'the cause of the selective survival was the bill depth itself and not some other character correlated with it'. Show that the prediction would be valid if

$$\frac{r_A}{r_P} = \frac{h_Y}{h_W}$$

where Y is bill depth and W is fitness, and the correlations are between bill depth and fitness.
[Solution 2]

20.2 A rough idea of the effect of natural selection on IQ score can be got from the following data on a sample of Whites in Minnesota. The data refer to the IQ scores of individuals and the size of those individuals' completed families, i.e., the number of their children. It has to be assumed that family size is an adequate measure of fitness. The means, standard deviations, and heritabilities were

	Mean	s.d.	h^2
IQ score	103	15.4	0.6
Family size	3.4	2.3	0.1–0.2

The heritability of family size was not reliably estimated but was probably in the range indicated. The correlation between the two characters was +0.11. It has to be assumed that the genetic correlation was not different from the phenotypic correlation. On the basis of

these data and assumptions, what is the predicted change of IQ score per generation? What would be the apparent, i.e., correlated, selection differential on IQ scores in this population?

Data from Waller, J.H. (1971) *Social Biol.*, **18**, 122–36.

[Solution 65]

20.3 Make a ‘fitness profile’ like Fig. 20.2 for human birth weight from the following data. Records of all babies born in Italy in 1974 were analysed. The data here refer to males born after a normal pregnancy of 9 months, of which there were 413,572. Birth weights were grouped in classes whose mid-points are given. The mean birth weight was 3.46 kg and the standard deviation was 0.51 kg. For each birth weight class the mortality rate per thousand in the first four weeks, including stillbirths, is given. For the purpose of making the fitness profile it has to be assumed that survival to the age of four weeks is equivalent to fitness.

<i>Birth weight (kg)</i>	<i>Frequency (%)</i>	<i>Mortality per 1,000</i>
1.3	0.13	612
1.8	0.35	333
2.3	2.13	94
2.8	15.95	27
3.3	40.32	15
3.8	30.73	11
4.3	8.54	12
4.8	1.56	25
5.55	0.30	69

Data from Terrenato, L. *et al.* (1981) *Ann. Hum. Genet.*, **45**, 55–63, and Ulizzi, L. *et al.* (1981) *Ann. Hum. Genet.*, **45**, 207–12.

[Solution 139]

21 Quantitative Trait Loci

The genetic basis of quantitative variation described in the preceding chapters has, of necessity, considered only the aggregate effects of all the genes causing the variation. A complete description needs to take account of the properties of the genes individually – their gene frequencies and the magnitude of their effects on the trait of interest. The genes cannot be studied individually using the methods of classical Mendelian genetics because their effects are lost in the statistical ‘fog’ of all other background variation. In the absence of knowledge about the genes’ individual properties theoretical work has had to make some unrealistic assumptions, such as the gene frequencies at all loci are more or less the same, that the genes’ effects and dominance relations are all about the same, and in some contexts there are an indefinitely large number of genes affecting the trait. Recently, however, methods have become available for studying the individual genes; these genes are known as *Quantitative Trait Loci*, or QTLs. This chapter will explain the methods for identifying QTLs and of estimating their effects on quantitative traits. We shall see, however, that what is identified as a QTL is a segment of chromosome affecting the trait, not necessarily a single locus.

Identification of the individual genes could lead to several useful applications. First, it could improve the efficacy of selective breeding, especially for traits with low heritability or that can only be measured in one sex (see Soller and Beckmann, 1988; Lande and Thompson, 1990). Second, transgenic technology might be applied to quantitative traits. Third, in medicine, the identification of alleles causing predisposition to common multifactorial diseases, such as heart disease or diabetes, could lead to improved methods of prevention. And fourth, quantitative genetic theory will be made more realistic when the numbers and properties of the genes are known, and the more realistic theories will improve our understanding of evolution.

Major genes

Many loci affecting quantitative traits have been identified fortuitously, by chance discovery of alleles with effects on the trait that were large enough to be recognized by their individual segregation. These include the major morphological mutations of classical genetics that arose by spontaneous or induced mutation, in, for example, *Drosophila*, mice, and maize. Some genes of large effect have been found to be segregating in selected lines. Examples of these are alleles of the *scabrous*, *bobbed*, and *scute* bristle loci discovered in lines of *Drosophila* selected for bristle number (reviewed by Mackay, 1989), alleles of the *pygmy* locus (Example 7.1), the

obese and dwarf alleles (reviewed by Roberts and Smith, 1982) found in lines of mice selected for body size, and a gene (*hg*) causing rapid post-weaning weight gain in a line of mice selected for weight gain (Bradford and Famula, 1984). Other examples of alleles with major effects on commercial traits in domestic animals are given in Table 21.1. In many cases the alleles of large effect probably arose *de novo* by mutation in the selected lines (Chapter 12). Such major-effect alleles are at very low frequencies in unselected populations and contribute little to segregating quantitative variation. This is almost certainly due to their adverse pleiotropic side effects on fitness. *Drosophila* females homozygous for the *bobbed* mutation are less viable and have longer developmental times than wild type (Lindsley and Zimm, 1992); the dwarf, obese, and high growth genes in mice are either sterile or have reduced fertility when homozygous (Roberts and Smith, 1982; Bradford and Famula, 1984); and the halothane gene in pigs and the double muscling gene in cattle reduce viability and fertility (Hanset, 1982; Webb *et al.*, 1982).

Table 21.1 Major genes affecting quantitative traits.

Species	Trait	Gene	Reference
Poultry	Body size	Dwarf	Merat and Ricard (1974)
Pig	Leanness, porcine stress syndrome	Halothane sensitivity	Smith and Bampton (1977) Webb <i>et al.</i> (1982)
Cattle	Leanness, muscular hypertrophy	Double muscling	Rollins <i>et al.</i> (1972) Hanset and Michaux (1985a, b)
Sheep	Prolificacy	Booroola F	Piper and Bindon (1982) Piper <i>et al.</i> (1985)

Given that alleles with very large effects on quantitative traits exist, there has been considerable interest in ascertaining whether other alleles with large effects but without deleterious fitness effects segregate in natural populations or have contributed to selection response. Note that 'large' in this sense does not necessarily mean an effect over three standard deviations from the population mean, as would be required to qualify as a classical Mendelian mutation; effects of $0.5\text{--}1.0 \sigma_p$ are 'large' in this context. For example, the additive genetic variance attributable to a strictly additive allele with a standardized effect of one phenotypic standard deviation ($2a = 1.0 \sigma_p$) at a frequency of $p = q = 0.5$ is 12.5 per cent of the total phenotypic variance (equation [8.5]). An allele of this effect would not, however, be apparent in a segregating population because of the confounding effects of variation at other loci.

Methods of detection

There are several ways of finding major genes affecting quantitative traits; they are, in outline only, as follows.

(1) *Multimodal distribution* If a gene has an effect large enough relative to the background genetic and environmental variation (in excess of about $3\sigma_p$) it will produce a multinomial distribution in a segregating population. The best way to look for multimodality is in the generations derived from a cross between two

divergent strains. The distribution will be trimodal in the F_2 if the alleles are partially dominant, and bimodal in the cross to the more recessive strain; the F_1 will have shown which strain this is.

(2) *Backcrossing with selection* This method is a way of making the bimodal distribution in the backcross clearer, by reducing the background genetic variation. It is one of the earliest methods used and was proposed by Wright (1952). Two divergent strains produced by selection (or inbreeding) are crossed and repeated backcrosses are made to the more recessive strain. In every generation selection is made for individuals with the more dominant phenotype; i.e., if the backcrosses are made to the low strain, selection is made for high phenotypes. The selection keeps segregating any allele with a large effect in the selected direction. Its effect is detected by the bimodal distribution of heterozygotes *versus* homozygotes of the allele from the low strain. At the same time, the frequencies of other genes of small effect from the high strain are halved in each generation of backcrossing (Table 5.1), and the background genetic variation is thereby reduced, making the bimodal distribution clearer. This procedure was the one used, although unintentionally, in the development of the Booroola Merino sheep, in which the F allele with a large fecundity effect (Table 21.1) segregates (Piper and Bindon, 1988).

(3) *Non-normal distribution* A gene whose effect is not large enough to cause a multimodal distribution may nevertheless cause a detectable departure from normality. If the gene's frequency is intermediate the distribution will be platykurtic (more flat than normal); if it is extreme (near 0 or 1) the distribution will be skewed and leptokurtic (more peaked than normal).

(4) *Heterogeneity of variance* If a major gene is segregating there will be heterogeneity of the variance within families, because the major gene will be segregating in some families but not in others. This test and the preceding one, however, have little power and require very large sample sizes to detect departure from normality or heterogeneity of sibship variance, and also suffer from the problem that factors other than segregating major genes can cause departure from normality or heterogeneous within-family variance (reviewed by Hill and Knott, 1990; Mayo, 1989). Hammond and James (1970) used some of these methods to detect major genes affecting *Drosophila* abdominal bristle number in a segregating population and concluded they are ineffective, particularly if the heritability of the trait is low.

(5) *Offspring-parent resemblance* A different group of tests have been proposed by Karlin, Carmelli, and Williams (1979) and Karlin, Williams, and Carmelli (1981), collectively termed 'structured exploratory data analysis'. These are based on the intuitively obvious principle that, with polygenic inheritance and no major gene the mean of offspring will resemble more closely the mid-parent value than single parents, while if a major gene is segregating the reverse will be true. One of these tests, the 'major gene index', was applied to families of mice in a population known to be segregating for the *hg* gene and the test succeeded in detecting the major gene (Famula, 1986). These tests, however, are sensitive to non-normality of

the distributions and can lead to erroneous conclusions (Mayo, Eckert, and Nugroho, 1983; Kammerer, MacCluer, and Bridges, 1984).

(6) *Complex segregation analysis* The most powerful approach for detecting major genes affecting quantitative variation is complex segregation analysis (Morton and MacLean, 1974; reviewed by Hill and Knott, 1990), developed specifically for human pedigrees of parents and full sibs. Complex segregation analysis tests whether the inheritance of a trait is best explained by the segregation of a single major gene, by strictly polygenic inheritance, or by a major gene plus multiple loci with smaller effects. A full mixed model is specified that includes the allele frequency and additive and dominance effects at a single major locus, additive genetic effects from multiple polygenic factors, common environmental and random environmental effects. Maximum likelihood estimates of parameters are made for a series of increasingly complicated hypotheses: a pure environmental model, single gene model, polygene model, and the full model. The significance of each hypothesis is tested by comparing the likelihood of the data, given maximum likelihood estimates of model parameters, with that calculated assuming the appropriate null hypothesis for which the tested parameters are set to zero, using a likelihood ratio test. The likelihood functions are very complicated and their evaluation is computationally demanding, but the method is generally extensible to more complex genetic hypotheses including pleiotropy and linkage to a known marker. Complex segregation analysis has been applied to the inheritance of many known human diseases and risk factors for disease; in all cases there was a significant polygenic component and in some cases the additional presence of a major gene effect was indicated (reviewed by Sing *et al.*, 1988).

Inferring the presence of major genes affecting a quantitative trait by any of the above methods still does not tell us what these genes are, and the loci contributing to the polygenic fraction of the variation remain invisible. For this reason current approaches to resolving QTLs are directed towards identifying all relevant loci that may have a range of effects (from major gene down to the limit of experimental resolution), placing these loci on linkage maps, and, ultimately, molecular cloning of the relevant DNA sequences.

Methods for mapping QTLs

Experimental designs for estimating effects and map positions of QTLs are extensions of standard methods for mapping single genes, and are based on linkage disequilibrium between alleles at a marker locus and alleles at the linked QTL. The requirements for mapping QTLs are thus (i) a linkage map of polymorphic marker loci that adequately covers the whole genome, and (ii) variation for the quantitative trait within or between populations or strains.

Marker loci

Ideally, marker loci should be (i) highly polymorphic, so that pairs of individuals or lines are likely to carry different alleles at each locus; (ii) abundant, so comprehensive marker coverage of the genome is achieved; (iii) neutral, both with respect to

the quantitative trait of interest and to reproductive fitness; and (iv) co-dominant, so all possible genotypes at a marker locus can be identified. This final requirement is less stringent, as dominant/recessive markers can be used successfully in some designs, as described below.

Until recently, mapping the loci underlying quantitative variation was seriously hampered by the paucity of suitable markers. Cryptic protein variation, such as blood group antigens and electrophoretically distinguishable enzyme alleles, often satisfies the criteria of neutrality and co-dominance, but is neither sufficiently polymorphic nor sufficiently abundant to mark entire genomes. The situation has changed with the molecular biology revolution and the discovery of DNA-based markers that satisfy all essential criteria outlined above. The restriction fragment length polymorphisms (RFLPs), variable number of tandem repeat (VNTR), or minisatellite, loci, and microsatellite (or simple sequence repeat, SSR) loci described in Chapter 1 are all suitable genetic markers. RAPD (randomly amplified polymorphic DNA) markers primarily detect DNA sequence variation in an arbitrary 10-base sequence used as a primer in a polymerase chain reaction (PCR). The marker DNA is amplified whenever the 10-base sequence flanks a genomic sequence of appropriate size. RAPD markers are dominant, as the PCR product is typically present or absent. RAPD and SSR markers are highly abundant and polymorphic, and their detection using PCR means linkage maps can be constructed more rapidly and efficiently than is possible using RFLP markers. In some organisms, such as *Drosophila* and mice, the genomic locations (sites of insertion) of transposable element or ecotropic retrovirus sequences are highly variable and their presence at an insertion site can be used as a dominant polymorphic marker. Dense molecular marker linkage maps are currently available for the genomes of human, mouse, rat, *Drosophila*, and many livestock and plant species.

QTL genotypes

There are two general sorts of methods for identifying and mapping QTLs: those based on crosses between lines that differ for the trait of interest, and methods based on segregating populations. The most efficient experimental designs for locating QTLs use crosses between lines that are fixed for alternate alleles at both the QTL and the marker loci, because of the maximum linkage disequilibrium between the loci in the F_1 . Preferably, all alleles should be in *association*; that is to say, alleles that increase the value of the trait should be homozygous in one parental line, and the alleles that decrease the value of the trait fixed in the other parental line. Homozygosity and the arrangement of QTLs in association are most likely to be met if parental populations have resulted from divergent artificial selection for the trait of interest, and have been inbred subsequently. If each line has some increasing and some decreasing alleles fixed, the alleles are in *dispersion*; in these circumstances it is still possible to locate QTLs, but fewer will be found than when the alleles are in association, for the reason to be explained later.

Most commonly, the parental inbred populations are crossed to produce the F_1 generation, which is then either backcrossed to one or both parental lines (the BC design), or crossed *inter se* to produce the F_2 generation (the F_2 design). In species

that tolerate inbreeding, the F_2 can be inbred to produce recombinant inbred lines (Oliverio, 1979), and these are also useful for mapping. For species that either do not tolerate inbreeding and/or that have very long generation intervals, the principles of line cross analysis can still be applied, provided lines are available that segregate for marker loci, but are nevertheless divergent for the quantitative trait of interest, and thus are likely to be fixed for alternate QTL alleles. In this case parents must be screened for marker configurations that produce informative segregations (i.e., backcross or F_2 ratios) in the progeny. This is the procedure used in human genetic mapping. Detecting QTLs by linkage to marker loci is least efficient in randomly breeding populations, because all but very tightly linked loci are likely to be in linkage equilibrium.

The principle underlying identification of QTLs by linkage to marker loci is conceptually simple: individuals are scored for their genotype at the marker locus, and their phenotype for the quantitative trait. If there is a difference in mean phenotype among marker genotype classes, then we can infer the presence of a QTL linked to the marker. Marker loci can be considered singly or simultaneously. The number of QTLs detected by linkage with markers is always an underestimate of the number of loci because two QTLs closely linked to each other may appear as only one if in association, or may not be detected at all if in dispersion. In most experiments, a map distance of, very roughly, 20 centimorgans (cM) is the limit of resolution, so what is detected as a QTL is a segment of chromosome of this length, which may contain several loci affecting the trait, not necessarily in the same direction. Thus more QTLs are likely to be detected when the alleles are in association than when they are in dispersion. With more refined methods, however, the limit of resolution can be reduced to about 3 cM.

Single marker analysis

To illustrate the method for detecting QTLs by association with single markers, consider a marker locus (M) and a QTL (A) with c the recombination frequency between them. Let the genotypes of one parental line be M_1A_1/M_1A_1 and of the other parental line be M_2A_2/M_2A_2 . Following Fig. 7.1, the genotypic values of the A_1 and A_2 homozygous parents are a and $-a$, respectively. The genotypic value of the F_1 individuals (M_1A_1/M_2A_2) is d . Parental F_1 gametes (M_1A_1 and M_2A_2) are each produced with frequency $(1 - c)/2$, and recombinant F_1 gametes (M_1A_2 and M_2A_1) are each produced with frequency $c/2$. Random mating of the F_1 gives 10 possible F_2 genotypic classes. The contribution of each marker genotype class to the F_2 mean is obtained by multiplying the frequency of each genotype by its genotypic value, then summing within marker genotype classes. The procedure is illustrated in Table 21.2. We are not interested here in the contributions of the marker classes to the mean of the F_2 , but in the differences between the marker classes. We therefore need the actual means, which are obtained by dividing the contribution to the F_2 mean by the frequency of that marker class, which is the Mendelian segregation ratio of $\frac{1}{4}$ for the homozygotes and $\frac{1}{2}$ for the heterozygotes. The actual means are given in the last column of the table. The means of marker classes in backcrosses are calculated in the same way, but are simpler because there are only four genotypes and two marker classes.

Table 21.2 Genotypes in an F_2 with one marker locus, M, and a linked QTL, A.

F_2 genotype	Frequency	Value	Marker class	Frequency	Contribution to F_2 mean	Actual mean
M_1A_1/M_1A_1	$(1 - c)^2/4$	a	M_1/M_1	$\frac{1}{4}$	$a(1 - 2c)/4 + dc(1 - c)/2$	$a(1 - 2c) + 2dc(1 - c)$
M_1A_1/M_1A_2	$c(1 - c)/2$	d				
M_1A_2/M_1A_2	$c^2/4$	$-a$				
M_1A_1/M_2A_1	$c(1 - c)/2$	a	M_1/M_2	$\frac{1}{4}$	$d[(1 - c)^2 + c^2]/2$	$d[(1 - c)^2 + c^2]$
M_1A_1/M_2A_2	$(1 - c)^2/2$	d				
M_1A_2/M_2A_1	$c^2/2$	d				
M_1A_2/M_2A_2	$c(1 - c)/2$	$-a$	M_2/M_2	$\frac{1}{4}$	$-a(1 - 2c)/4 + dc(1 - c)/2$	$-a(1 - 2c) + 2dc(1 - c)$
M_2A_1/M_2A_1	$c^2/4$	a				
M_2A_1/M_2A_2	$c(1 - c)/2$	d				
M_2A_2/M_2A_2	$(1 - c)^2/4$	$-a$				

From Table 21.2 we can see that if the marker locus is unlinked to the QTL (i.e., $c = 0.5$), then all the marker classes have the same expected mean, $0.5d$. However, if the QTL is linked to the marker locus, the following contrasts of marker class means are functions of a , the genotypic value or additive effect, and d , the dominance deviation:

$$(M_1/M_1 - M_2/M_2)/2 = a(1 - 2c) \quad \dots [21.1a]$$

and, after some simplification,

$$M_1/M_2 - [(M_1/M_1 + M_2/M_2)/2] = d(1 - 2c)^2 \quad \dots [21.1b]$$

Thus a significant difference in the mean value of a quantitative trait between homozygous marker genotype classes can be taken as evidence of linkage of a QTL and the marker locus. However, estimates of a and d/a from single marker analysis are confounded with recombination frequency, and will generally underestimate the true values by $(1 - 2c)$. For example, a mean difference in phenotype of 0.2 standard deviation between the homozygous marker classes could be due to a QTL of this effect completely linked to the marker, or to a QTL of effect $a = 0.5$ standard deviation 46 cM away (using Haldane's mapping function $c = [1 - \exp(-2x)]/2$ to relate distance (x) in morgans to recombination fraction).



Example 21.1

The first example of an association between a marker locus and a quantitative trait was reported by Sax (1923), between a pigment locus and seed size in the bean, *Phaseolus vulgaris*. One of the parental lines, Improved Yellow Eye 1317, was homozygous for the dominant pigmentation factor, P , and had seeds that weighed on average 48 centigrams (cg). The other parental line, White 1228, was homozygous for the recessive pigmentation factor, p , and had an average seed weight of 21.0 cg. The genotypes at the pigmentation locus and average seed weights in the F_2 of the cross were:

Genotype	PP	Pp	pp
Seed weight (cg)	30.7	28.3	26.4

(The genotypes of the pigmented F_2 were deduced from the presence or absence of unpigmented pp progeny in the F_3 .) Equation [21.1a] gives the estimate of $a(1 - 2c)$ as $(30.7 - 26.4)/2 = 2.15$ cg. The effect is perfectly additive because the marker heterozygote is almost exactly midway between the two homozygotes. Equation [21.1b] gives $d(1 - 2c)^2 = -0.25$ cg. The difference in seed weight between the PP and pp genotypes in the F_2 (4.3 cg) accounts for 16 per cent of the total difference in seed weight between the two parental strains (27 cg). This is a large effect associated with the marker, but the conclusions we can draw about a QTL are limited. First, part, or even all, of the effect may have been due to the P locus itself having a pleiotropic effect on seed weight. Second, if there is a QTL linked to the P locus, its effect ($2a$) is correctly estimated as 4.3 cg only if there is no recombination with the marker ($c = 0$). The effect could equally have been due to a less closely linked QTL with a larger effect. And, third, the QTL identified may have been not one but two or more linked loci.

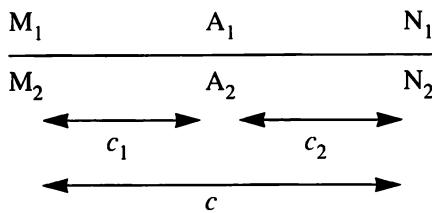


Fig. 21.1. Recombination frequencies between two marker loci, M and N, and a QTL, A.

Interval mapping analysis

The problem of confounding estimates of additive and dominance effects of a QTL linked to a single marker locus with recombination frequency can be solved by considering pairs of linked marker loci (M and N), separated by recombination fraction c , both of which are fixed for alternate alleles in the parental strains. In this case the map positions of the marker loci, and hence c , are known. Assume there is a QTL, A, between the two marker loci, with the recombination frequency c_1 between M and A, and c_2 between N and A; assuming no interference, $c_1 + c_2 = c$. The relationship between the marker loci in the F₁ is depicted in Fig. 21.1.

The genotypes of the two parental lines are thus M₁A₁N₁/M₁A₁N₁ (with genotypic value a) and M₂A₂N₂/M₂A₂N₂ (with genotypic value $-a$), and of the F₁ is M₁A₁N₁/M₂A₂N₂ (with genotypic value d). The analysis can be made in a backcross or an F₂ generation. The expected marker class means in a backcross to the M₁A₁N₁ homozygous parent are set out in Table 21.3, calculated in the same manner as in Table 21.2. Here the expected marker genotype frequencies depend on the recombination frequency between the two markers, so the means of the marker classes with parental F₁ gametes are divided by (1 - c)/2 and the means of the marker classes with recombinant F₁ gametes are divided by c /2. It is assumed that the two markers are closely enough linked that double recombination can be ignored. The contrasts between backcross marker class means, that give estimates of the effects of the QTL and its map position relative to the flanking markers, are given in equations [21.2]:

$$\frac{M_1N_1}{M_1N_1} - \frac{M_1N_1}{M_2N_2} = a - d \quad \dots [21.2a]$$

$$\frac{M_1N_1}{M_1N_2} - \frac{M_1N_1}{M_2N_1} = (a - d)(c_2 - c_1)/c \quad \dots [21.2b]$$

A disadvantage of the backcross design is that the estimate of the additive effect of the QTL is unbiased only if $d = 0$, and recessive or partly recessive QTLs may not be detected. This problem can be overcome by backcrossing to both parental lines, or by using an F₂ design. The expected genotypic values of the nine marker classes produced in an F₂ are given by Haley and Knott (1992).

Example 21.2

Before molecular markers became available most QTL mapping was done with *Drosophila* bristle numbers because (1) selected lines with divergent values were available, (2) there are major mutant genes spread over all three major chromosomes

Continued

Table 21.3 Genotypes in a backcross with two linked markers, M and N, and a linked QTL, A. The F_1 is backcrossed to $M_1A_1N_1$.

F_1 Gamete type	Frequency	Value	Marker class	Frequency	Contribution to BC mean	Actual mean
$M_1A_1N_1$	$(1 - c)/2$	a	M_1N_1/M_1N_1	$(1 - c)/2$	$a(1 - c)/2$	a
$M_1A_1N_2$	$c_2/2$	a	M_1N_1/M_1N_2	$c/2$	$(ac_2 + dc_1)/2$	$(ac_2 + dc_1)/c$
$M_1A_2N_2$	$c_1/2$	d				
$M_2A_1N_1$	$c_1/2$	a	M_1N_1/M_2N_1	$c/2$	$(ac_1 + dc_2)/2$	$(ac_1 + dc_2)/c$
$M_2A_2N_1$	$c_2/2$	d				
$M_2A_2N_2$	$(1 - c)/2$	d	M_1N_1/M_2N_2	$(1 - c)/2$	$d(1 - c)/2$	d

Example 21.2 *continued*

to use as markers, and (3) chromosomes can be studied one at a time. The early work is reviewed by Thoday (1979). The data below are taken from Wolstenholme and Thoday (1963).

The parental chromosomes used were a third chromosome from a line selected for high numbers of sternopleural bristles, and a tester third chromosome, unselected for bristle number, with several morphological markers. Two of the markers, the recessive gene *clipped* (*cp*) and the dominant gene *Stubble* (*Sb*), are separated by a distance of 12.9 cM. To determine whether there was a QTL between *cp* and *Sb* affecting sternopleural bristle number, flies with the selected chromosome (HH) were crossed to flies from the marker tester chromosome strain. The doubly heterozygous F₁ flies (*cpSb*/HH) were then backcrossed to a *cp* + tester stock. The mean bristle numbers of the four marker genotype classes in the backcross were as follows:

<i>Genotype</i>	<i>Bristle number</i>
(1) HH/ <i>cp</i> +	20.62
(2) HSb/ <i>cp</i> +	19.19
(3) <i>cpH</i> / <i>cp</i> +	18.95
(4) <i>cpSb</i> / <i>cp</i> +	18.00

Inspection shows clearly that there is a QTL affecting bristle number linked to the markers; the H alleles from the selected line are associated with higher numbers. From the differences in bristle numbers between the marker classes we can get the following estimates:

by equation [21.2a], $(a - d) = (1) - (4) = 2.62$ bristles, and

by equation [21.2b], $(a - d)(c_2 - c_1)/c = (2) - (3) = 0.24$ bristle,

where c_1 is the recombination frequency between the QTL and *cp*, and c_2 the recombination frequency between the QTL and *Sb*. The known distance between the markers gives $c = 0.129$. Substitution of $(a - d) = 2.62$ and $c = 0.129$ into the second equation above gives $c_2 - c_1 = 0.0118$. So, from $c_1 + c_2 = c$ we can estimate $c_1 = 0.059$ and $c_2 = 0.070$. Thus, the QTL is located between the markers, nearer to *cp* than *Sb*. When there is only one backcross we cannot separate *a* and *d* to estimate the effect and gene action of the QTL.

Genetical and statistical considerations

Although the principles of mapping QTLs are straightforward, many problems arise in practice regarding optimum methods of statistical analysis and the genetic interpretation. We now need to consider issues involved in deciding sample size, number and density of markers, optimal experimental design, and appropriate statistical analysis as well as limitations regarding genetic interpretation of experimental data.

Experimental design

Our description of mapping methods has been overly simplified in the sense that we have not specified how marker class means (or a contrast of two marker class

means such as equation [21.1a] or [21.2a]) are judged to be significantly different. Assume for the moment that the *t*-test is used for this purpose, and that we wish to design a single marker experiment to detect a difference of some arbitrary value δ between the two homozygous marker genotypes caused by a QTL completely linked to the marker ($c = 0$) in an F_2 cross. Given that the number of individuals (n) scored for the quantitative trait in each marker genotype class will be sufficiently large that we can assume the phenotypic values to be normally distributed, the n required is given by standard statistical theory (Sokal and Rohlf, 1981, p. 263) as:

$$n \geq 2(z_\alpha + z_{2\beta})^2 / (\delta/\sigma_w)^2 \quad \dots [21.3]$$

In this expression δ is the smallest difference between marker classes that the experimenter wants to detect as significant, and σ_w is the phenotypic standard deviation within marker classes; α and β are the significance levels set, α being the acceptable error rate of false positives (Type I errors) and β the acceptable error rate of false negatives (Type II errors); z is the ordinate of the normal distribution corresponding to its subscript. Suppose, for example, that the error rates are set at $\alpha = 0.05$ and $\beta = 0.1$, giving $z_\alpha = 1.96$ and $z_{2\beta} = 1.28$. Then if standardized effects (δ/σ_w) of 1 or over are to be detected, equation [21.3] shows that the number of individuals needed in each marker class is $n = 21$; if, however, δ/σ_w is set at 0.25 then $n = 336$. Thus very large sample sizes are required to detect QTLs with moderate or small effects; with small sample sizes only large-effect QTLs will be found. Similar power calculations give rise to the following general guidelines for the relative efficiencies of different experimental designs for QTL mapping.

1. Interval mapping is preferable to single marker analysis because, with a single marker, the QTL effects are confounded with the map distance of the QTL from the marker, as we have already seen. Interval mapping is also more efficient than single marker analysis. The sample size needed to detect a given standardized effect is increased by a fraction of $1/(1 - 2c)^2$ for single marker analysis (Soller, Brody, and Genizi, 1976).

2. The F_2 design is more powerful than the backcross design. Backcrosses to a single parent only detect heterozygous effects, which for the case of additive QTLs are half the homozygous effects detected in the F_2 , so four times as many individuals need to be scored to achieve the same power. With dominance, one backcross will be more efficient than the F_2 and the other less efficient (Soller, Brody, and Genizi, 1976). Backcrosses to both parents are necessary to estimate homozygous effects, which is also less efficient than the F_2 design.

3. If two parental populations are fixed for alternate alleles at the QTL but are segregating for marker alleles, the sample size to achieve the same power as the case for fixed marker alleles is increased. For example, the increase is by a factor of $1/(q_1 - q_2)^2$ for single marker analysis, where q_1 and q_2 are the gene frequencies of the marker in the two strains (Soller, Brody, and Genizi, 1976). Even for a favourable case with $q_1 = 0.8$ and $q_2 = 0.3$ (i.e., marker allele frequencies are relatively extreme), a four-fold increase in sample size would be necessary, assuming all F_2 individuals are scored. A considerable saving of effort, however, can be achieved if only those F_1 matings that give informative progeny are used. Informative matings

are those between two individuals that are heterozygous for the marker, and between a heterozygote and a homozygote. For details of how many individuals are needed see Beckmann and Soller (1988).

4. The power to detect a difference in mean between two marker genotypes does not depend on the absolute value of the difference (δ), but rather on the difference scaled by the within-marker-class standard deviation (δ/σ_w). Therefore, strategies to reduce σ_w can yield increased power. Reducing σ_w requires more accurate estimates of phenotypic values. This can be achieved by progeny testing individuals of the segregating generation, F_2 or backcross, or by inbreeding to produce recombinant inbred lines (Thoday, 1961; Lander and Botstein, 1989; Soller and Beckmann, 1990). Making recombinant inbred lines has the disadvantage that the linkage between the QTL and the markers is reduced by further recombination in the subsequent generations. In *Drosophila*, however, recombinant isogenic lines can be synthesized in a few generations with no further recombination, so for this species this method is best (Long *et al.*, 1995).

Multiple tests

The above discussion has referred to a QTL linked to a single marker or pair of markers. In reality, many markers are distributed throughout the genome and each one (or pair) is in turn tested for linkage to a QTL. Furthermore, the parental lines used typically are divergent for multiple traits, all of which are scored in the segregating generation, so the tests for linkage to the markers are repeated for each trait. This means that some ‘significantly’ positive associations will occur by chance, and a more stringent level of significance must be set. The number of false positives increases rapidly with the number of tests. Suppose that the desired significance level for a set of n independent tests is $\alpha = 0.05$, then the level for each separate test must be set at α/n . For example, if single marker associations were tested for 50 independent markers, the significance level for each test should be $\alpha = 0.001$. Re-evaluation of equation [21.3] with $z_{0.001} = 3.291$ shows that the sample size must be doubled to achieve the same power. The tests, however, are not independent because there will be linkage between some of the markers and some of the tests will therefore be partially redundant. So, treating the tests as independent sets too stringent a significance level. When the data are analysed by maximum likelihood, as explained below, proper allowance is made for the non-independence of markers.

Maximum likelihood estimation

The relative efficiencies of different designs were discussed above in the context of *t*-tests for purposes of illustration. However, the use of this test is technically not appropriate since it is based on an assumed normal distribution of phenotypes within marker class genotypes. Inspection of Table 21.1 shows this is not true: F_2 homozygous marker genotypes each contain the three QTL genotypes, so the distributions are mixtures of three normal distributions (assuming further that the environmental variance is normally distributed). The use of the *t*-test (or analysis of variance) to detect QTLs linked to markers is robust to all but extreme departures from normality, such as would be caused by very few QTLs of very large effect

distinguishing the two parental strains. More sophisticated methods based on maximum likelihood are, however, more appropriate for parameter estimation and significance tests since they take into account the correct distributional properties of the marker genotypes with respect to the segregating QTL. For details see Lander and Botstein (1989) and Knott and Haley (1992).

The procedure, in outline, is as follows. A likelihood function is specified in terms of the observed data (the numbers of individuals and their phenotypes in each marker class) and the parameters to be estimated (c , and the means and variances of the QTL genotypes). Trial values are assigned to the unknown parameters and an iterative computer program finds the likelihood function, L , for each trial value. The trial values that maximize L are the maximum likelihood estimates of the unknown parameters. Maximum likelihood estimation is thus advantageous for the single marker case since the recombination fraction between the marker and QTL can be put in the model and estimated. The test of significance is the logarithm (base 10) of the ratio L/L_0 (which is distributed as χ^2), where L is the observed maximum likelihood, and L_0 is the likelihood computed for the null hypothesis that there is no QTL segregating.

In the context of interval mapping the log likelihood ratio is called the LOD score (for 'log odds'), following the convention of human linkage mapping. See Lander and Botstein (1989) for details. The LOD score is computed for varying positions of the QTL within the interval; the maximum likelihood estimates of c and a are the values for which the LOD score is maximized. The estimates are usually presented graphically, as a plot of LOD score against chromosome position, in cM. Figure 21.2 shows an example. The value of the LOD score above which the presence of a QTL in the interval is judged significant for an overall error rate of 5 per cent must be computed from the number of independent intervals tested, which in turn depends on marker density, number of chromosomes and genome size. Typical LOD threshold values over a wide range of assumed values for these parameters are between 2 and 3, roughly corresponding to $\alpha = 0.001$ for each interval tested (Lander and Botstein, 1989). In the study of grain yield in maize shown in Fig. 21.2 there were eight linked markers, whose positions are shown on the x -axis, with the intervals between them in cM. The position marked by the triangle is the position of the QTL that maximizes the LOD score, and this is the most probable position for a QTL. The horizontal line at a LOD score of 2 marks the threshold of significance ($\alpha = 0.05$) for the experiment as a whole. The existence of a QTL affecting yield is clearly established.

Multiple QTLs

The parental lines chosen for mapping are clearly likely to differ at many loci affecting the traits of interest. Up to this point we have ignored the presence of QTLs that are unlinked to the markers under consideration, but that nevertheless segregate in the F_2 or backcross generation. Thus the variance within marker genotype classes, σ_w^2 , will contain a genetic component due to segregation of unlinked QTLs. Furthermore, QTLs identified by linkage to marker loci are not loci in the usual genetic sense (i.e., segments of DNA involved in producing a polypeptide chain) but are rather effective factors (Chapter 12) and may contain several loci

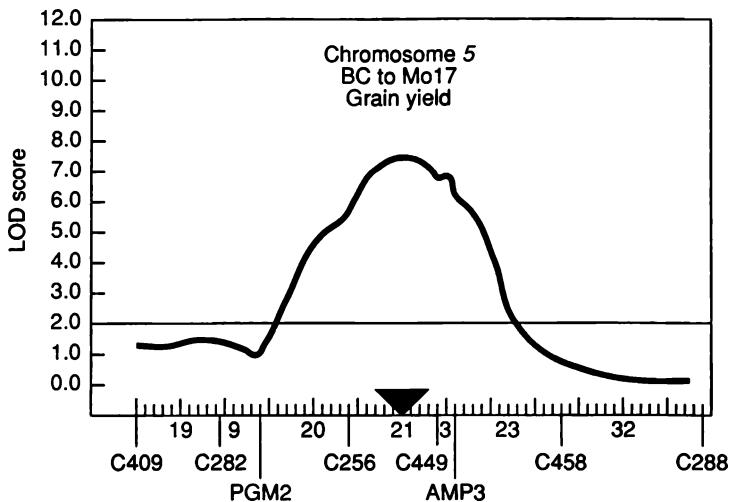


Fig. 21.2. Plot of LOD score against chromosomal position for QTLs affecting grain yield on maize Chromosome 5, for a backcross of the F_1 between two elite maize inbred lines, B73 and Mo17, to the Mo17 parent. The positions of isozyme (PGM2 and AMP3) and RFLP (labelled C---) markers are given on the x-axis, with the distances between markers given in cM. The most likely position of a QTL for yield is indicated by the shaded triangle, corresponding to the peak in LOD score. (*The unpublished figure and data have kindly been provided by C.W. Stuber.*)

affecting the trait. Therefore when a test reveals a QTL linked to a marker, the effect observed may be due to two or more loci, not just one locus. The effect observed is then the aggregate of the effects of the two or more loci. The alleles at the linked loci may be in association (all increase the trait) or in dispersion. Consequently, the effects of the separate loci may be smaller, if in association, or larger, if in dispersion, than the observed aggregate effect.

There are methods for dealing with multiple QTLs simultaneously which improve the estimates of map positions and of effects. For descriptions of these methods, see Jansen and Stam (1994) and Zeng (1994). Methods that account for multiple QTLs are optimal for analysis of experimental data.

Experimental results

The general result, firmly established by experimental work on many traits in many organisms, is that there are multiple QTLs scattered throughout the genome. Thus the polygenic model of quantitative variation is clearly confirmed. Furthermore, the ‘infinitesimal’ model, in which there is a nearly infinite number of loci each with a vanishingly small effect, is clearly disproved. The experimental results are summarized below.

Number of loci

All estimates of the number of QTLs are minimum estimates of the true number of loci affecting the trait, for three reasons: (i) experiments are limited in their power

to separate closely linked loci, (ii) there must always be other loci with effects too small to be detected by an experiment of a particular size, and (iii) the loci found are those differentiating the two strains compared; other loci would probably be found in other strains.

Some examples of the number of QTLs affecting bristle number of *Drosophila melanogaster* are given in Table 21.4. There are three major chromosomes and one very small one; most of the experiments looked for QTLs on only one or two of the chromosomes. Pairs of parental chromosomes tested were either from a line selected for high bristle number and an unselected tester stock (Wolstenholme and Thoday, 1963; Spickett and Thoday, 1966), or from lines selected for high and low bristle number (Shrimpton and Robertson, 1988a, b; Long *et al.*, 1995). All or most of the difference in bristle number between the tested parental chromosomes is accounted for by the QTLs found. This means that all the important QTLs on the chromosomes tested were detected.

Table 21.4 Numbers of QTLs affecting sternopleural (ST) and abdominal (AB) bristle numbers in *Drosophila melanogaster*. Transposable element insertion sites were used as markers by Long *et al.* (1995); in the other studies morphological mutant markers were used.

Trait	Chromosomes tested	Number of markers	Number of QTLs	% parental difference	Reference
ST	3	4	2	114	Wolstenholme and Thoday (1963)
ST	1, 2, 3	10	5	87.5	Spickett and Thoday (1966)
ST	3	7	18	103	Shrimpton and Robertson (1988b)
AB	1, 3	45	7	89.9	Long <i>et al.</i> (1995)

More recently, molecular marker maps of tomato, maize, mice, and other species have been used to map QTLs affecting a wide variety of characters. Some examples are given in Table 21.5; for a more comprehensive review, see Tanksley, 1993. The QTLs detected account for large fractions of the phenotypic variance in the F₂ or BC generations. Without knowing the heritabilities of the traits in the populations used for mapping we cannot say how much of the genetic variance was accounted for, but most of the important QTLs must have been detected.

Gene effects

Additive effects In most studies, QTLs with large additive effects have been found. However, not all QTLs have equal effects, and the general pattern emerging for traits as different as *Drosophila* bristles and maize vegetative and reproductive characters is one in which a few QTLs with large effects account for most of the divergence between the parental strains, with a larger number of QTLs with smaller effects accounting for the remainder of the difference. Figure 21.3 shows the distribution of the effects of QTLs affecting sternopleural bristle number in *Drosophila* (Shrimpton and Robertson, 1988b). Eighteen QTLs on the third chromosome were found, and their effects (a) ranged from 0.4 to 1.9 σ_p . Only three had effects greater than 1.0 σ_p . The small number with effects below 0.6 σ_p does not mean that the real distribution falls off at the lower levels of effect. Those with smaller effects have a lower probability of being detected and therefore only some of them appear in the data. The real distribution is probably more highly skewed, with more QTLs of small effect.

Table 21.5 Examples of mapping QTLs by linkage to molecular markers. The phenotypic variance is for the F₂ or BC population.

<i>Species</i>	<i>Number of markers</i>	<i>Trait</i>	<i>Number of QTLs</i>	<i>% phenotypic variance</i>	<i>Reference</i>
Tomato (<i>Lycopersicon</i> sp.)	70	Fruit mass	6	58	Paterson <i>et al.</i> (1988)
		Soluble solids	4	44	
		Fruit pH	5	48	
	71	Fruit mass	7, 9	72	Paterson <i>et al.</i> (1991) (1)
		Soluble solids	4, 3, 5	44	
		Fruit pH	5, 8, 2	34	
Maize (<i>Zea mays</i>)	76	Grain yield	6, 8	61, 59	Stuber <i>et al.</i> (1992) (2)
		Plant height	3, 5		
		Ear number	2, 2		
Human	289	Type I diabetes	18		Davies <i>et al.</i> (1994)

(1) Estimates from plants grown in two, or three, environments. % Phenotypic variance is for the first value listed.

(2) Estimates from backcrosses to each of the parental lines, each averaged over six environments.

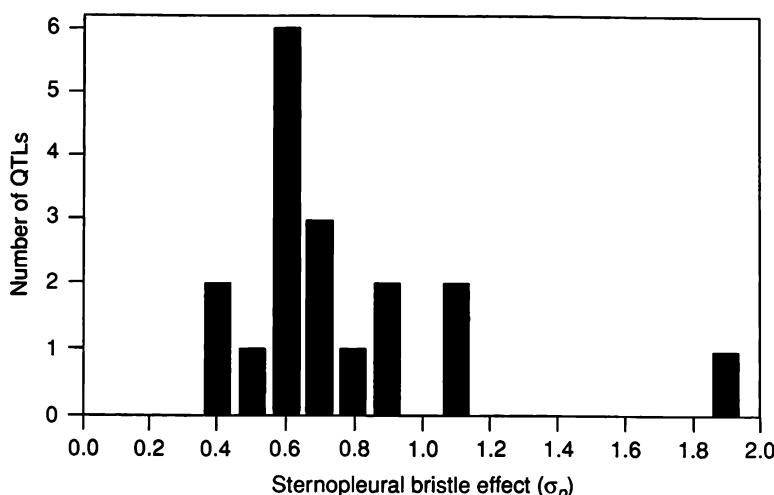


Fig. 21.3. Distribution of effects (a) of QTLs affecting sternopleural bristle number on Chromosome 3 of *Drosophila melanogaster*, in phenotypic standard deviation units. (Adapted from Shrimpton and Robertson, 1988b.)

Degree of dominance The degree of dominance of QTLs spans the entire range from additivity to complete dominance, and even to overdominance. This is illustrated in Fig. 21.4, which shows the distribution of the degree of dominance (d/a) among 74 QTLs identified in the F_2 from an interspecific cross of tomatoes. Dominance of the increasing and of the decreasing allele were equally frequent. The ratio d/a is difficult to estimate precisely, because it is subject to the sampling errors of both a and d . Estimates taking extreme values are especially open to suspicion because they result from very low values of a , and the ratio is then very sensitive to the sampling error of a . Cases of overdominance in particular need to be further confirmed.

The range of degree of dominance observed for QTLs contrasts with the complete dominance or recessivity normally shown by mutations with major phenotypic effects. Presumably, then, the alleles of QTLs responsible for quantitative variation actually produce quantitative differences in, rather than total absence of, the protein produced by the locus. This could be, say, altered activity if the gene product is an enzyme, or altered efficiency of binding if the gene product is a transcription factor. Few enzymes, however, act in isolation. Rather, they are steps in a metabolic pathway leading to an end product, and it is the amount, or the rate of production, of this end product that affects the phenotypes that we see. Considerations of enzyme kinetics in metabolic pathways lead to the conclusion that when there is a large difference in enzyme activity between two alleles, the allele with the higher activity will tend to be dominant, but when there is a small difference the alleles will tend to act additively (Kacser and Burns, 1981; see also Hartl, Dykhuizen, and Dean, 1985; Dean, Dykhuizen, and Hartl, 1988).

Epistasis Interaction between QTLs is difficult to detect because experiments with large numbers are needed. Strong epistatic interactions have been observed

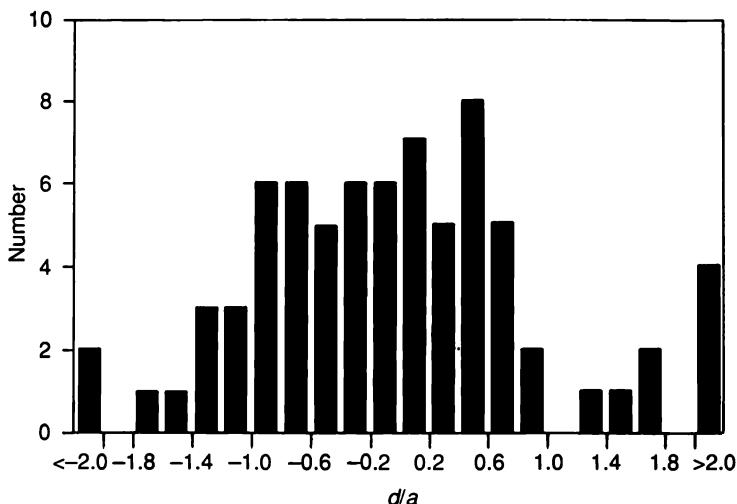


Fig. 21.4. Distribution of degrees of dominance (d/a) among 74 QTLs affecting vegetative traits of tomatoes, detected in the F_2 of a cross between the cultivated tomato and a wild species. (Adapted from deVicente and Tanksley, 1993.)

between QTLs affecting *Drosophila* bristle number (Spickett and Thoday, 1966; Shrimpton and Robertson, 1988a; Long *et al.*, 1995). The epistatic interaction effects detected by Long *et al.* (1995) were about the same magnitude as the main effects. Though epistasis may be common, this does not necessarily mean that it contributes a large proportion of the genetic variance in a random breeding population.

Correlated effects In view of the widespread occurrence of genetic correlation between traits, it is not surprising that many QTLs have been found to affect more than one trait. For example, several experiments with *Drosophila* (e.g., Shrimpton and Robertson, 1988b; Long *et al.*, 1995) have found that QTLs with the largest effects on the bristle trait for which the parental strains in the test had been selected also affected other bristle traits. And, in maize, a single chromosome region was found to affect as many as 78 of the 82 traits examined (Edwards, Stuber, and Wendel, 1987).

Some experiments have tested the same cross in different environments (Paterson *et al.*, 1991; Stuber *et al.*, 1992). Some of the QTLs were detected in more than one environment, as would be expected if performance in the different environments were genetically correlated.

Consistency

Some 'significant' QTLs may be false positives, and QTLs responsible for significant variation within and between populations can be missed if the tested strains are fixed by chance for alleles with similar effects. Therefore, QTLs should be confirmed by repeated experiments using the same and different strains. QTLs affecting *Drosophila* bristle number have been mapped using strains derived from

different base populations (Breese and Mather, 1957; Thompson and Thoday, 1974; Shrimpton and Robertson, 1988b; Long *et al.*, 1995); as have QTLs affecting tomato fruit traits (Weller, Soller, and Brody, 1988; Paterson *et al.*, 1988, 1991) and maize inflorescence traits (Doebley and Stec, 1991, 1993). While accord between different strains is far from perfect, there is a clear trend for estimated QTL map positions and effects to cluster in the same genomic regions. Of more interest, perhaps, are comparisons between species. Independent crosses mapping QTLs affecting seed weight in the cowpea (*Vigna unguiculata*) and mungbean (*Vigna radiata*) using a comparative RFLP linkage map revealed the QTL with the largest effect on seed weight in both species mapped to the same location (Fatokun *et al.*, 1992). It is possible that allelic variation at a restricted number of common loci is responsible for variation within and between populations, and even between species. Thus the use of experimentally tractable model systems, such as mouse models of human disease or of production traits in domestic animals, is well justified by the likely homology between QTLs in the model organism and the species of more practical interest.

From QTL to gene

Experiments to map QTLs typically succeed in localizing them to approximately 20 cM regions that potentially contain many loci affecting the trait. Linked QTLs within an interval can be separated by further recombination and their map positions pinpointed within roughly 3 cM by progeny testing, if no markers are available within the interval (Thoday, 1961; Lander and Botstein, 1989; but see McMillan and Robertson, 1974), or by fine-scale mapping, if the interval contains markers (Paterson *et al.*, 1990). This level of resolution may be sufficient to use the QTLs in selective breeding programmes, but is still several orders of magnitude away from identifying allelic differences at a single locus responsible for the difference in quantitative trait phenotypes. Identifying the actual loci affecting quantitative traits is necessary for risk assessment of polygenic human diseases, for application of transgenic technology to traits of agricultural importance, and for describing the genetic basis of quantitative variation in terms of allele frequencies and effects. There are two approaches for identifying a gene detected as a QTL in a particular genomic region; they are positional cloning, and association of variation in the quantitative trait phenotype with polymorphic markers at 'candidate' loci in the same region.

Positional cloning requires that the map position of the locus of interest is known to within a 0.3 cM interval, which is approximately the size of genomic inserts that can be contained in currently available cloning vectors. This can be achieved either by very high resolution meiotic mapping in experimental organisms, or by screening randomly mating populations for polymorphic markers in the region to which the QTL has been mapped that are in strong linkage disequilibrium with the quantitative trait phenotype. From this point it is conceptually straightforward but technically extremely arduous to identify the gene of interest and determine what are the polymorphisms associated with alleles of different effect. This method is feasible for loci defined by mutant alleles of large effect (reviewed by Takahashi,

Pinto, and Vituterna, 1994), and has been used to identify single loci affecting human diseases (for example, cystic fibrosis and Huntington's disease; reviewed by McKusick, 1994). The difficulty will be compounded significantly for loci with smaller effects, and the method has not yet been used to resolve QTLs to the level of single loci.

The most common strategy for going from mapped region to gene is the candidate gene approach. Often many loci of known function have been identified and cloned from the region to which the unknown locus maps. Known loci that could potentially give rise to the phenotype associated with the unknown locus are *candidate* loci, and the procedure is to search for associations of the phenotype with molecular polymorphisms at each candidate locus in the region. An approximate location of a QTL is not a prerequisite for proposing candidate loci known to be functionally related to a trait. Examples of the successful application of this approach to human diseases are the association of Apolipoprotein E (ApoE) alleles with total serum cholesterol and heart disease (reviewed by Sing *et al.*, 1988); the association of ApoE-4 alleles with late-onset Alzheimer's disease (Corder *et al.*, 1993), and the association of Type 1 diabetes with variation in the major histocompatibility HLA region and the insulin gene region (reviewed by Davies *et al.*, 1994).

If we are to apply the candidate locus approach to quantitative traits in general, we need to be able to propose relevant candidate loci functionally related to the traits. For the human diseases described above, detailed knowledge of the biological differences between affected and unaffected individuals guided the choice of candidate loci. For other quantitative traits, potential candidate loci may be those involved in the biochemical and developmental pathways leading to the phenotype of interest. For example, candidate loci that might account for variation in milk components in dairy cattle are casein and lactoglobulin loci (Pirchner, 1988); and candidate loci for quantitative variation in *Drosophila* bristle number may be loci that are necessary for bristle development (Mackay and Langley, 1990). Many candidate loci for quantitative traits thus have been identified by virtue of alleles with major mutant effects. Applying the candidate locus approach to QTLs is based on the assumption that segregating 'isoalleles' with small (i.e., not sufficiently large to qualify as Mendelian mutant) effects at these loci give rise to quantitative variation (Thompson, 1975; Mackay, 1985b; Robertson, 1985).

Examples that illustrate the power of this approach are the demonstration that the bovine β -Lg locus is associated with approximately half of the genetic variance of whey protein concentration in milk (Pirchner, 1988) and that the *Drosophila achaete-scute* and *scabrous* gene regions each account for over 20 per cent of the X and second chromosome genetic variation, respectively, of both abdominal and sternopleural bristle number (Mackay and Langley, 1990; Lai *et al.*, 1994). Furthermore, map positions of genomic regions identified by QTL mapping often roughly coincide with the location of a known major gene affecting the measured trait. QTLs affecting *Drosophila* bristle number map approximately to the locations of the major bristle loci *achaete-scute*, *Notch*, *bobbed*, *daughterless*, *scabrous*, *extramacrochaetae*, *hairy*, *malformed abdomen*, *Delta*, and *Enhancer of split* (Shrimpton and Robertson, 1988b; Long *et al.*, 1995). A dwarf locus, *compact*, is

located in the region associated with large effects on multiple maize yield traits (Edwards, Stuber, and Wendel, 1987), and the maize locus *teosinte-branched* maps to the region with large effects on inflorescence traits in two maize–teosinte crosses (Doebley and Stec, 1991, 1993).

The future for understanding quantitative traits in terms of complex genetics rather than statistical descriptions is bright. The various genome projects are yielding very dense linkage maps for humans, model organisms and species of agricultural importance that often show remarkable conservation of linkage groups across taxa. With the development of improved statistical methods for analysis of experimental crosses and pedigrees to detect segregating QTLs associated with molecular markers, and with the potential to resolve QTLs to the level of single genes, the description of the Mendelian genetic basis of quantitative variation is within reach.

Problem

21.1 The data below come from an experiment (Long *et al.*, 1995) in which QTLs affecting bristle numbers in *Drosophila melanogaster* were mapped on two of the three major chromosomes. The data here refer only to Chromosome 3. Two-way selection for abdominal bristles was applied to a population derived from a large sample of flies from a natural population. After 25 generations of selection the high and low lines were each made homozygous for all its chromosomes, except the very small 4th, which was ignored. (This was done by special techniques for manipulating *Drosophila* chromosomes.) Then, in order to reduce unwanted variation and to have a common background on which to compare the effects of Chromosome 3, Chromosomes 1 and 2 of the high line were replaced by their low-line homologues. These homozygous lines then differed only in their 3rd chromosome; they were the ‘parental lines’ for analysis. The parental lines were crossed. By means of the special techniques, 3rd chromosomes from F₁ females in which recombination had occurred were made homozygous, while the low-line homologues of Chromosomes 1 and 2 were retained as homozygotes. The recombinant 3rd chromosomes were then propagated in isogenic lines, in each of which one homozygous recombinant chromosome was replicated in many individuals. Forty individuals in each isogenic line were scored for abdominal bristle number and also for sternopleural bristle number.

	<i>Abdominal bristles</i>		<i>Sternopleural bristles</i>	
<i>Parental lines</i>	High	Low	High	Low
Mean	21.4	7.7	20.9	16.3
<i>Interval 1</i>	HH	LL	HH	LL
<i>n</i>	13	31	13	31
Mean	14.3	11.9	19.5	16.7
SS (Corrected)	277.2	374.6	17.4	11.2
Variance	23.1	12.5	1.4	0.4

The markers used to locate QTLs were the insertion sites of a transposable element known as *roo*. There were 29 sites on Chromosome 3 at which the parental lines differed, with an average distance of 3.8 cM between adjacent markers. The data here refer to one of the intervals, interval 1, at one end of the chromosome. Only the lines that had not recombined in this

interval are considered. There are thus two marker classes, HH and LL homozygotes, of which there were 13 and 31 lines respectively. In addition to these there were 5 lines that had recombined in the interval.

What conclusions can be drawn about a QTL in this interval? What is the source of the variance within marker classes? What might be the reason for sternopleural bristles having a much lower variance than abdominal bristles?

[Solution 141]

Appendix Tables

Appendix Table A Truncated normal distribution – large sample. p = proportion of population with values exceeding the truncation point T . x = deviation of T from the mean, in standard-deviation units. i = mean deviation of individuals with values exceeding T , in standard-deviation units from the population mean. For values of p greater than 50 per cent: take x and i tabulated for $(1 - p)$; give x a negative sign; multiply i by $(1 - p)/p$, retaining the positive sign. Errors from linear interpolation of p are positive, the largest in both x and i being approximately +0.001 when $p > 0.10$ per cent. (Abridged from Falconer, 1965a).

$p\%$	x	i	$p\%$	x	i	$p\%$	x	i
0.01	3.719	3.960	0.75	2.432	2.761	10	1.282	1.755
0.02	3.540	3.790	0.80	2.409	2.740	11	1.227	1.709
0.03	3.432	3.687	0.85	2.387	2.720	12	1.175	1.667
0.04	3.353	3.613	0.90	2.366	2.701	13	1.126	1.627
0.05	3.291	3.554	0.95	2.346	2.683	14	1.080	1.590
0.06	3.239	3.507	1.00	2.326	2.665	15	1.036	1.554
0.07	3.195	3.464				16	0.994	1.521
0.08	3.156	3.429	1.0	2.326	2.665	17	0.954	1.489
0.09	3.121	3.397	1.2	2.257	2.603	18	0.915	1.458
0.10	3.090	3.367	1.4	2.197	2.549	19	0.878	1.428
			1.6	2.144	2.502	20	0.842	1.400
			1.8	2.097	2.459	21	0.806	1.372
0.10	3.090	3.367	2.0	2.054	2.421	22	0.772	1.346
0.12	3.036	3.317	2.2	2.014	2.386	23	0.739	1.320
0.14	2.989	3.273	2.4	1.977	2.353	24	0.706	1.295
0.16	2.948	3.234	2.6	1.943	2.323	25	0.674	1.271
0.18	2.911	3.201	2.8	1.911	2.295	26	0.643	1.248
0.20	2.878	3.170	3.0	1.881	2.268	27	0.613	1.225
0.22	2.848	3.142	3.2	1.852	2.243	28	0.583	1.202
0.24	2.820	3.117	3.4	1.825	2.219	29	0.553	1.180
0.26	2.794	3.093	3.6	1.799	2.197	30	0.524	1.159
0.28	2.770	3.070	3.8	1.774	2.175	31	0.496	1.138
0.30	2.748	3.050	4.0	1.751	2.154	32	0.468	1.118
0.32	2.727	3.030	4.2	1.728	2.135	33	0.440	1.097
0.34	2.706	3.012	4.4	1.706	2.116	34	0.412	1.078
0.36	2.687	2.994	4.6	1.685	2.097	35	0.385	1.058
0.38	2.669	2.978	4.8	1.665	2.080	36	0.358	1.039
0.40	2.652	2.962	5.0	1.645	2.063	37	0.332	1.020
0.42	2.636	2.947				38	0.305	1.002
0.44	2.620	2.932				39	0.279	0.984
0.46	2.605	2.918	5.0	1.645	2.063	40	0.253	0.966
0.48	2.590	2.905	5.5	1.598	2.023	41	0.228	0.948
0.50	2.576	2.892	6.0	1.555	1.985	42	0.202	0.931
			6.5	1.514	1.951	43	0.176	0.913
			7.0	1.476	1.918	44	0.151	0.896
0.50	2.576	2.892	7.5	1.440	1.887	45	0.126	0.880
0.55	2.543	2.862	8.0	1.405	1.858	46	0.100	0.863
0.60	2.512	2.834	8.5	1.372	1.831	47	0.075	0.846
0.65	2.484	2.808	9.0	1.341	1.804	48	0.050	0.830
0.70	2.457	2.784	9.5	1.311	1.779	49	0.025	0.814
0.75	2.432	2.761	10.0	1.282	1.755	50	0.000	0.798

Appendix Table B Truncated normal distribution – small sample. The tabulated values are the intensity of selection, i , when n individuals are selected from a total of N . Errors from linear interpolation of N are negative, the largest being approximately -0.0075 ; interpolation of n gives positive errors, maximum about $+0.006$. (Abridged from Becker, 1984, where much more extensive tables may be found.)

N										
n	2	3	4	5	6	7	8	10	12	n
1	0.564	0.846	1.029	1.163	1.267	1.352	1.424	1.539	1.629	1
2	—	0.423	0.663	0.829	0.954	1.055	1.138	1.270	1.372	2
3	—	—	0.343	0.553	0.704	0.821	0.916	1.065	1.179	3
4	—	—	—	0.291	0.477	0.616	0.725	0.893	1.019	4
5	—	—	—	—	0.253	0.422	0.550	0.739	0.877	5
6	—	—	—	—	—	0.225	0.379	0.595	0.748	6
7	—	—	—	—	—	—	0.203	0.457	0.627	7
8	—	—	—	—	—	—	—	0.318	0.509	8
9	—	—	—	—	—	—	—	0.171	0.393	9
10	—	—	—	—	—	—	—	—	0.274	10
N										
n	14	16	18	20	25	30	40	50	60	n
1	1.703	1.766	1.820	1.867	1.965	2.043	2.161	2.249	2.319	1
2	1.456	1.525	1.585	1.638	1.745	1.829	1.957	2.052	2.127	2
3	1.271	1.347	1.412	1.469	1.584	1.674	1.810	1.911	1.990	3
4	1.119	1.201	1.271	1.332	1.455	1.550	1.694	1.799	1.882	4
5	0.986	1.075	1.150	1.214	1.345	1.446	1.596	1.705	1.792	5
6	0.866	0.962	1.042	1.110	1.248	1.354	1.510	1.624	1.713	6
7	0.755	0.858	0.943	1.016	1.161	1.271	1.434	1.552	1.644	7
8	0.650	0.760	0.851	0.928	1.081	1.196	1.365	1.487	1.582	8
10	0.447	0.577	0.681	0.767	0.936	1.061	1.242	1.372	1.472	10
15	—	0.118	0.282	0.405	0.624	0.777	0.991	1.139	1.252	15
20	—	—	—	—	0.336	0.530	0.782	0.951	1.076	20
N										
n	70	80	100	150	200	250	300	350	400	n
1	2.377	2.427	2.508	2.649	2.746	2.819	2.878	2.927	2.968	1
2	2.189	2.242	2.328	2.478	2.580	2.657	2.718	2.769	2.813	2
3	2.055	2.111	2.201	2.357	2.463	2.543	2.607	2.660	2.705	3
4	1.950	2.008	2.101	2.263	2.372	2.455	2.520	2.574	2.621	4
5	1.862	1.922	2.018	2.185	2.297	2.382	2.449	2.504	2.552	5
6	1.786	1.848	1.947	2.118	2.233	2.320	2.388	2.445	2.493	6
8	1.659	1.724	1.828	2.007	2.127	2.217	2.288	2.346	2.396	8
10	1.553	1.621	1.730	1.916	2.040	2.132	2.206	2.266	2.317	10
15	1.342	1.417	1.536	1.738	1.871	1.970	2.048	2.112	2.166	15
20	1.175	1.257	1.386	1.601	1.742	1.846	1.928	1.995	2.051	20
25	1.032	1.121	1.259	1.488	1.636	1.745	1.830	1.900	1.958	25

Glossary of Symbols

Numbers in square brackets refer to chapters where the meaning applies.
Some meanings with restricted use are not listed.

A_1, A_2	Alleles at a locus under consideration.
A	Breeding value.
a	Genotypic value of homozygote A_1A_1 , as deviation from the mid-homozygote value.
B or b	As subscript, indicates between families or groups.
b	Regression coefficient; e.g. b_{OP} = regression of offspring on parent.
c	[1,21] Frequency of recombination.
CR	Correlated response to selection.
D	Dominance deviation.
d	Genotypic value of heterozygote as deviation from the mid-homozygote value.
E	Environmental deviation.
e^2	$= 1 - h^2$.
E_c	Common environment; i.e., environmental deviation of family mean from population mean.
E_g	Environment due to permanent, or general, effects.
E_s	Environment due to temporary, or special, effects.
E_w	Within-family environment; i.e., environmental deviation of individual from family mean.
F	Coefficient of inbreeding.
F_1	First generation of cross between lines or populations.
F_2	Second generation of cross, by random mating among F_1 .
FS	Full sibs.
f	Coancestry = coefficient of kinship.
f	Subscript referring to females.
f	[13] Subscript meaning between families.
G	Genotypic value.
GCA	General combining ability.
H	Frequency of heterozygous genotype, A_1A_2 .
H	[14] Amount of heterosis; i.e., deviation of cross mean from mid-parent value.
HS	Half sibs.
h^2	Heritability ('narrow sense').
I	Interaction deviation, due to epistasis.
I	[13, 19] Index for selection.
i	Intensity of selection; i.e., selection differential in units of phenotypic standard deviation.
j	[20] A measure of the strength of stabilizing selection .

<i>k</i>	Numbers in various contexts. In [4, 10, 20] family size, i.e., number in family.
<i>L</i>	[2] Load.
<i>L</i>	[4, 11] Generation length.
<i>M</i>	Population mean.
<i>m</i>	[18] Population mean.
<i>m</i>	Subscript referring to males.
<i>m</i>	[10] Correlation between breeding values of mates.
<i>N</i>	Population size; e.g., number of breeding individuals in a population or line.
<i>N</i>	[10, 13] Number of families.
<i>N_e</i>	Effective population size.
<i>n</i>	Numbers in various contexts. In [10, 13] specifically number of offspring per family.
<i>O</i>	Offspring.
<i>P</i>	Parent.
<i>P̄</i>	Mid-parent.
<i>P</i>	Frequency of homozygous genotype A ₁ A ₁ .
<i>P</i>	Panmictic index, = 1 - <i>F</i> .
<i>P</i>	Phenotypic value.
<i>p</i>	Gene frequency of A ₁ , the allele that increases the character.
<i>p</i>	[11, 18] Proportion selected, or exceeding point of truncation of a normal distribution.
pg	The pygmy gene of mice, used in several examples.
<i>Q</i>	Frequency of homozygous genotype A ₂ A ₂ .
<i>q</i>	Gene frequency of A ₂ , the allele that reduces the character.
<i>R</i>	Response to selection – specifically to individual selection.
<i>R_T</i>	[12] Total range; i.e., difference in mean between two populations at opposite selection limits.
<i>r</i>	[8] Repeatability, i.e., correlation between repeated measurements of the same individual.
<i>r</i>	Coefficient of relationship; i.e., correlation of breeding values between related individuals.
<i>r</i>	[10] Phenotypic correlation between mates.
<i>r</i>	[19] Correlations between two characters: <i>r_A</i> = correlation of breeding values, <i>r_E</i> = environmental correlation, <i>r_P</i> = phenotypic correlation.
<i>S</i>	Selection differential in actual units of measurements.
<i>SCA</i>	Specific combining ability.
<i>s</i>	Coefficient of selection against a specified genotype.
<i>s</i>	[13] Subscript referring to sib-selection.
<i>T</i>	Total in various contexts.
<i>t</i>	Time in number of generations. As subscript it means 'at generation <i>t</i> '.
<i>t</i>	Phenotypic correlation (intraclass) between members of families.
<i>u</i>	Mutation rate (from A ₁ to A ₂).
<i>u</i>	[9, 15] Coefficient of the dominance variance in the covariance of relatives.
<i>V</i>	Variance (causal component) of the value of deviation indicated by a subscript: <i>V_P</i> = phenotypic, <i>V_G</i> = genotypic, <i>V_A</i> = additive genetic, <i>V_D</i> = dominance, <i>V_I</i> = Interaction (epistatic), <i>V_{NA}</i> = non-additive genetic, <i>V_E</i> = environmental.
<i>V_M</i>	Variance generated by mutation in one generation.
<i>V_S</i>	[20] A measure of the strength of stabilizing selection.
<i>v</i>	Mutation rate (from A ₂ to A ₁).

<i>W</i> or <i>w</i>	As subscript, indicates within families or groups.
<i>W</i>	[20] Fitness under natural selection.
<i>X</i>	Subscript denoting any particular individual, e.g., [5] F_X = inbreeding coefficient of individual X.
<i>X</i>	One of two correlated characters.
<i>x</i>	[11, 18] The normal deviate; i.e., deviation, in standard-deviation units, of point of truncation from population mean.
<i>Y</i>	The other of two correlated characters.
<i>y</i>	Difference in gene frequency between two lines.
<i>z</i>	Height of the ordinate of a normal distribution, in standard-deviation units.
α	Average effect of a gene substitution.
α_1, α_2	Average effects of alleles A_1 and A_2 respectively.
Δ	Change of, as Δq = change of gene frequency, ΔF = rate of inbreeding.
Σ	Summation of the quantity following the sign.
σ	Standard deviation (σ^2 = variance) of the quantity indicated by subscript.

Equivalence of symbols used by Mather and Jinks as defined in Mather and Jinks (1977, p. 219)

Mather
and

Jinks This book

<i>d</i>	<i>a</i>
[<i>d</i>]	Σa
<i>D</i>	$\Sigma d^2 = 2V_A$ when all $p = q = \frac{1}{2}$ (Equation [8.7]).
<i>D_R</i>	$2V_A$ in random-breeding population.
<i>E_w</i>	V_{Ew}
<i>E_b</i>	V_{Ec}
<i>E₁</i>	V_{Ew}
<i>E₂</i>	$V_{Ec} + \frac{1}{n}V_{Ew}$
<i>h</i>	<i>d</i>
[<i>h</i>]	Σd
<i>H</i>	$\Sigma d^2 = 4V_D$ when all $p = q = \frac{1}{2}$ (equation [8.7]).
<i>H_R</i>	$4V_D$ in random-breeding population.
<i>u</i>	<i>p</i>
<i>v</i>	<i>q</i>

Solutions of Problems

[Numbers in square brackets refer to the numbered equations in the text.]

1 (1.1)

(1) The total number counted is 6,129. With this large number the frequencies need 5 decimal places to avoid rounding errors. The genotype frequencies are

$$\text{MM: } P = 1,787/6,129 = 0.29156$$

$$\text{MN: } H = 3,039/6,129 = 0.49584$$

$$\text{NN: } Q = 1,303/6,129 = 0.21260$$

Check that these frequencies add to 1.

(2) Putting the numbers for P , H , and Q into [1.1] gives the gene frequencies as

$$\text{M: } p = [1,787 + (\frac{1}{2} \times 3,039)]/6,129 = 0.53948$$

$$\text{N: } q = [1,303 + (\frac{1}{2} \times 3,039)]/6,129 = 0.46052$$

Check that $p + q = 1$.

(3) By [1.2] the expected genotype frequencies are

$$\text{MM: } (0.53948)^2 = 0.29104$$

$$\text{MN: } 2 \times 0.53948 \times 0.46052 = 0.49688$$

$$\text{NN: } (0.46052)^2 = 0.21208$$

Check that the expected frequencies add to 1.

(4) Very close agreement. To test, we must convert the expected frequencies to expected numbers for comparison with the observed numbers. Multiplying the frequencies in (3) by the total number gives the expected numbers as

M	MN	N
1,783.8	3,045.4	1,299.8

Check that the numbers add to 6,129. χ^2 is calculated as $\Sigma[(\text{Obs.} - \text{Exp.})^2/\text{Exp.}]$, from which $\chi^2 = 0.027$. This very low value confirms the close agreement. This χ^2 has one degree of freedom because the observed numbers were used to estimate the gene frequency, and the expected numbers must be made to fit this as well as the total; in other words, there are three numbers with two constraints, so one degree of freedom is left.

2 (20.1) The observed selection differential on bill depth (Y) was a correlated selection differential, S' , following selection for fitness (W). The prediction made was $R = h^2 S'$. The response, however, is a correlated response and should be predicted from S' by [19.8b]:

$$CR_Y = \frac{r_A}{r_P} h_W h_Y S'$$

Therefore CR_Y would be correctly predicted by R if

$$\frac{r_A}{r_P} h_W h_Y = h_Y^2$$

i.e., if

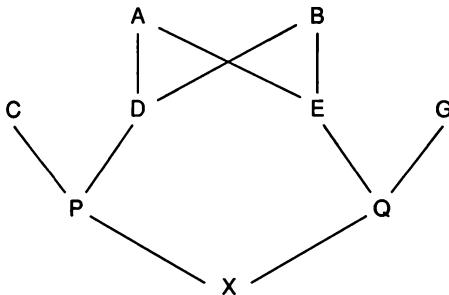
$$\frac{r_A}{r_P} = \frac{h_Y}{h_W}$$

3 (3.1) If drawn from a random-breeding population the genotypes would be in Hardy–Weinberg proportions. These, calculated as in Problem 1.1, are

aa	ab	bb	Total
101.0	821.0	1,669.0	2,591

The observed numbers show an excess of both homozygotes and a corresponding deficiency of heterozygotes. This discrepancy is highly significant. ($\chi^2_1 = 12.9, P < 0.001$.) The data suggest that the population was a mixture of sub-populations with different gene frequencies.

4 (5.1) The following pedigree of a single first-cousin marriage will serve to illustrate all three relationships.



The solutions can be got in two ways, by [5.1] or by [5.2]. Applying [5.1] to the pedigree:

- (1) The paths are PDAEQ and PDBEQ, giving $F_X = (\frac{1}{2})^5 + (\frac{1}{2})^5 = 1/16$.
- (2) C and G are now also full sibs, so there are two more paths with $n = 5$, giving $F_X = 4 \times (\frac{1}{2})^5 = 1/8$.
- (3) Let D be the uncle who marries his niece Q. The paths are DAEQ and DBEQ; $F_X = 2 \times (\frac{1}{2})^4 = 1/8$.

To apply [5.2] to (1) and (2) we need the four coancestries, CE, CG, DE, DG. With (1) all are 0 except DE which is $\frac{1}{4}$ because D and E are full sibs. $F_X = \frac{1}{4}(\frac{1}{4}) = 1/16$. With (2) CG is also $\frac{1}{4}$; $F_X = \frac{1}{4}(\frac{1}{2}) = 1/8$. With (3) the coancestries needed are AE, AG, BE, BG, of which AE and BE are $\frac{1}{4}$, being parent and offspring, and the others are 0; $F_X = 1/8$.

5 (6.1) The range of values is small enough that the observations do not need to be grouped into wider classes. To construct the table, make a column of the leaf numbers in order, as under X in the table. Then go through the data making a mark for each plant against its leaf number. For ease of counting, make each fifth mark diagonally through the previous four, making a ‘gate’. Finally count the marks, as under n in the table. The calculations of means and variances are shown at the foot of the table. The arithmetic is simplified if the leaf numbers are coded as deviations from 12, as shown under x . The main difference is that the F_2 is more variable.

X	x	x^2	F_1			F_2		
			n	nx	nx^2	n	nx	nx^2
12	0	0	—	—	—	1	0	0
13	1	1	1	1	1	3	3	3
14	2	4	2	4	8	5	10	20
15	3	9	7	21	63	4	12	36
16	4	16	11	44	176	3	12	48
17	5	25	1	5	25	3	15	75
18	6	36	3	18	108	2	12	72
19.	7	49	—	—	—	1	7	49
20	8	64	—	—	—	2	16	128
21	9	81	—	—	—	1	9	81
Σ	—	—	25	93	381	25	96	512
Mean			15.72 ± 0.24			15.84 ± 0.49		
Variance			1.46			5.97		
Mean =	$12 + \frac{\Sigma nx}{25}$					$\text{Variance} = \frac{1}{24} \left[\Sigma(nx^2) - \frac{(\Sigma nx)^2}{25} \right]$		
Standard error of mean =	$\sqrt{\frac{\text{variance}}{25}}$							

6 (7.1) Multiply frequency by activity, sum over genotypes, and (if per cent frequencies have been used) divide the total by 100.

freq. \times activity	
AA	1,171.2
AB	7,438.2
BB	6,448.4
AC	515.2
BC	<u>1,060.0</u>

$$\text{Mean} = 16,633.0/100 = 166.33$$

7 (8.1) The first assumption is that the varieties crossed were homozygous at all loci. Tobacco is normally self-pollinating so this is likely to be true. The F_1 variance is then wholly environmental in origin. The F_2 variance is both environmental and genetic in origin. The second assumption is that the environmental variance in the F_2 is the same as that in the F_1 . With this assumption the genetic variance is obtained by subtraction.

$$\begin{aligned} F_2 \text{ variance} &= V_G + V_E = 5.97 \\ F_1 \text{ variance} &= V_E = 1.46 \\ &\quad V_G = 4.51 \end{aligned}$$

$$\text{Degree of genetic determination} = \frac{V_G}{V_G + V_E} = \frac{4.51}{5.97} = 0.76, \text{ or } 76 \text{ per cent.}$$

8 (9.1) The children are related as half sibs (see Problem 5.2) so, from Table 9.3, $r = \frac{1}{4}$.

9 (11.1) Use Appendix Table A to get the intensity of selection, i , from the proportion selected, p . Then apply [11.3] taking σ_p as the square root of the variance. The working is as follows.

- (1) (a) $R = 1.271 \times 0.37 \times 3.271 = 1.54$ g.
 (b) $R = 0.798 \times 0.37 \times 3.271 = 0.97$ g.
 (c) When p is greater than 50 per cent, take i for $1 - p$ and multiply by $(1 - p)/p$. $i = 1.271 \times 0.25/0.75 = 0.424$; $R = 0.51$ g.
- (2) $R = 1.755 \times 0.18 \times 1.304 = 0.41$ day.
- (3) Intensity of selection on females = 1.159. Males are not selected, so $i = \frac{1}{2} \times 1.159 = 0.5795$; $R = 0.5795 \times 0.22 \times 2.074 = 0.26$ young per litter. When selection is for fertility the offspring are already born when the individuals whose fertility has been measured are ready to be selected. An alternative way of looking at the process is to regard the offspring of both sexes as being selected on the basis of their mother's fertility. The regression of offspring on mothers is $\frac{1}{2} h^2$, so the response in this instance is $R = 1.159 \times (\frac{1}{2} \times 0.22) \times 2.074 = 0.26$ young per litter.

10 (17.1) The variances can be transformed to logarithms by [17.2] as follows.

	<i>Small</i>	<i>Control</i>	<i>Large</i>
C	0.143	0.111	0.128
$1 + C^2$	1.0204	1.0123	1.0164
$\sigma^2 (\log s) \times 100$	0.3809	0.2306	0.3068
$\sigma (\log s)$	0.062	0.048	0.055
Mean of logs	1.074	1.362	1.597
Response in logs	0.288	0.235	

If the responses are equal when transformed to logarithms, the ratio of the arithmetic means will be equal:

$$L/C = 39.85/23.16 = 1.72$$

$$C/S = 23.16/11.97 = 1.93$$

The asymmetry is much reduced. Alternatively, the means of log-transformed data can be calculated from the formula for $(\log x)$ in [17.1]. The values are given above. The responses in log-units are nearly equal. This is to be expected from the fact that the response is proportional to the standard deviation ([11.3]), and the standard deviations of log-units are nearly equal.

11 (1.2) Non-tasters are homozygotes for the non-tasting gene. With Hardy-Weinberg frequencies, the frequency of homozygotes is the square of the gene frequency. So $q = \sqrt{0.3} = 0.55$.

12 (2.1) First get the coefficient of selection, s , against white-flowered plants. The fitness relative to blue is $143/229 = 0.62$, and $s = 1 - 0.62 = 0.38$. White-flowered plants are homozygotes and their frequency is q^2 , assuming random pollination. From [2.12] the mutation rate is

$$u = sq^2 = 0.38 \times 7.4 \times 10^{-4} = 2.8 \times 10^{-4}$$

Note that the fitness, 0.62, is that of plants as females. The calculation assumes that their fitness as males was equally reduced.

13 (3.2) Calculate the gene frequencies and Hardy-Weinberg expectations separately for each race and compare with the observed numbers. The χ^2 tests agreement between observed and expected numbers.

	p (of a)	aa	ab	bb	χ^2_1
Arctic	0.1214	18.0	260.0	941.0	1.8
Coastal	0.2649	96.3	534.3	741.4	2.2

The gene frequencies are different in the two races, so an excess of homozygotes is expected in the mixed sample. Each race has genotype frequencies in good agreement with the Hardy–Weinberg expectation for its own gene frequency. So the subdivision into these two races, each having mated at random within the race, is sufficient to account for the genotype frequencies in the total sample.

14 (5.2) The twins are genetically equivalent to a single individual. The two marriages are therefore equivalent to one individual with two spouses, so the children are related as half sibs and their coancestry is 1/8. (See [5.7].) If worked out from the pedigree by [5.1] the pair of twins must be shown by a single individual in the pedigree.

15 (6.2) The data have to be grouped into classes. Grouping by 1 g intervals makes 15 classes, which is satisfactory. The classes, X , are tabulated by the integral part of the weight, i.e., ignoring the decimal part. The class intervals are 4.0–4.9, 5.0–5.9 etc., and the class mid-points are 4.45, 5.45 etc. The mean is therefore $0.45 + \bar{X}$. Different groups will give slightly different estimates of the mean and variance.

X	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
n	1	2	5	1	0	0	1	6	4	8	10	7	2	2	1

	All	Pygmy	Normal
Mean	12.61	6.12	14.04
Variance	12.34	0.75	3.40

The distribution is bimodal, with no overlap. The 9 very small mice are clearly distinct from the others in some way. In fact, they were homozygous for a dwarfing gene called pygmy, which is used for examples in Chapters 7 and 8. The presence of the pygmy gene greatly increases the variance.

16 (7.2) This can be done by use of [7.2], but it is probably simpler to calculate the Hardy–Weinberg frequencies and get the mean by summing activity \times frequency.

	<i>Activity</i>	<i>Frequency</i>		
		(1)	(2)	(3)
AA	122	0.04	0.25	0.64
AB	154	0.32	0.50	0.32
BB	188	0.64	0.25	0.04
Mean		174.48	154.50	134.88

17 (8.2) This only requires the substitution of α , d and q in [8.3a] and [8.4]. The values of α and d were found in solving the Chapter 7 problems.

	α	d	q	$2pq$	$V_A = 2pq\alpha^2$	$V_D = (2pqd)^2$
(1)	(1)	33.6	-1	0.2	361.27	0.10
	(2)	33.0	-1	0.5	544.50	0.25
	(3)	32.4	-1	0.8	335.92	0.10
(2)		0	50	0.4	0.48	0
(3) Gene b:		2.5	2.5	0.5	0.50	3.125
Gene c ^e :		11.4	28.5	0.2	0.32	41.59
Both genes:						83.17
					44.71	84.74

18 (9.2) The solution to Problem 8.2 (3) gave $V_A = 44.71$ and $V_D = 84.74$, to which we have to add $V_E = \frac{1}{2}(V_A + V_D) = 43.15$. Adding the three components gives $V_P = 172.60$. From the covariances in Table 9.3 we then get

(1) Regression of offspring on mid-parent	$= V_A/V_P$	= 0.259
(2) Regression of offspring on one parent	$= \frac{1}{2}V_A/V_P$	= 0.130
(3) Full-sib correlation	$= (\frac{1}{2}V_A + \frac{1}{4}V_D)/V_P$	= 0.252
(4) Half-sib correlation	$= \frac{1}{4}V_A/V_P$	= 0.065
(5) Double first-cousin correlation	$= (\frac{1}{4}V_A + \frac{1}{16}V_D)/V_P$	= 0.095

19 (11.2) For reasons to be explained in Chapters 19 and 20, this question cannot be answered without making an important assumption, namely that the cause of the selective survival was the bill depth itself and not some other character correlated with it such as, for example, wing length. The assumption seems a reasonable one in the circumstances described. With this assumption, then, the selection differential is $S = 9.96 - 9.42 = 0.54$ mm. To predict the response we need to know the heritability, which will be taken to be 0.82 from Problem 10.8. The predicted response, by [11.2], is $R = 0.82 \times 0.54 = 0.44$ mm, an increase of 5 per cent. The predicted mean in the progeny of the survivors is $9.42 + 0.44 = 9.86$ mm. The assumption made is the subject of Problem 20.1.

20 (17.2) Calculate the heterosis as the difference between the cross and the mid-parental value. Do this first for the arithmetic values given. Then convert all the arithmetic values given to logarithms and calculate the heterosis from these. The heterosis on the two scales is shown below. We cannot use [17.1] to evaluate the mean of logarithmic values because the coefficients of variation are not given, so the scale transformation has to be done less accurately by taking the logarithms of the arithmetic means given. Logarithms to base 10 are used here. Natural logarithms, \log_e , could equally well have been used. The relationship between the two is $\log_{10}x = 0.4343 \log_e x$.

Arithmetic			Logarithmic		
L	C	S	L	C	S
L 1.94	1.135	0.025	L 0.028	0.025	0.023
C —	0.92	0.53	C —	0.019	0.019
S —	—	-0.07	S —	—	-0.002

On the arithmetic scale the heterosis varies greatly according to the size of the lines crossed; it is not easy to see if crosses between size groups differ from crosses within size groups. On the logarithmic scale the heterosis is nearly the same in all crosses, both between and within size groups, except the S × S cross, which is anomalous on both scales. The difference in the absolute magnitude of the heterosis on the two scales has no meaning.

21 (1.3) For an approximate answer the working is easier if frequencies are expressed as fractions. First get the gene frequency from $q^2 = 1/20,000$; $q = 1/141$. Carriers are heterozygotes, with frequency

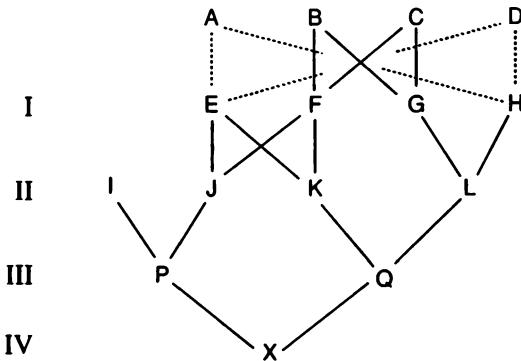
$$\begin{aligned} 2q(1-q) &= 2 \times \frac{1}{141} \times \frac{140}{141} \\ &= \frac{2}{141} \quad (\text{approx.}) \\ &= 1 \text{ in } 70 \text{ (approx.)} \end{aligned}$$

22 (2.2) Homozygotes for white will be extremely rare and can be neglected. The frequency of white-flowered plants is then the frequency of heterozygotes, H . By [2.15] the mutation rate from blue to white is $u = sH/2 = \frac{1}{2}(0.38 \times 7.4 \times 10^{-4}) = 1.4 \times 10^{-4}$.

23 (3.3) $N = 40$. By [3.7], $\Delta F = 1/80 = 0.0125$

$$\begin{aligned} \text{By [3.12], } F(t=5) &= 1 - (0.9875)^5 = 0.061 \\ F(t=10) &= 1 - (0.9875)^{10} = 0.118 \end{aligned}$$

24 (5.3) First redraw the pedigree showing the paths of transmission more clearly, and put in the parents of generation I, thus:



There are 6 paths, 2 through the common ancestors E and F, with $n = 5$, and 4 through A, B, C, and D, all with $n = 7$. None of the six common ancestors is inbred. By [5.1]

$$\begin{aligned} F_X &= 2(\frac{1}{2})^5 + 4(\frac{1}{2})^2 \\ &= (\frac{1}{2})^4 + (\frac{1}{2})^5 \\ &= \frac{1}{16} + \frac{1}{32} \\ &= \frac{3}{32} \\ &= 0.09375 \end{aligned}$$

The parent, Q , is the child of a double first-cousin marriage, with $F = \frac{1}{8}$, as seen in Problem 5.1. Note that the inbreeding of the parent does not affect the inbreeding of the children.

25 (6.3) There are 5 genotypic classes, with measurement values of $-4, -3, -2, -1, 0$, according to the number of loci that are homozygous for the recessive allele. The frequencies of these classes are given by the terms of the binomial expansion of $(a + b)^4$, where a is the probability of being homozygous at any particular locus. Here $a = (0.3)^2 = 0.09$, and $b = 0.91$. The terms of the binomial expansion are

$$a^4 \quad 4a^3b \quad 6a^2b^2 \quad 4ab^3 \quad b^4$$

The coefficients, 1, 4, 6, 4, 1, are most easily got from Pascal's triangle with $n = 4$, given below up to $n = 6$.

n						
1						
2						
3		1	3	3	1	
4		1	4	6	4	1
5	1	5	10	10	5	1
6	1	6	15	20	15	6
						1

The required frequencies, to 3 decimal places, are

Measurement class	-4	-3	-2	-1	0	Total
Frequency	0.000	0.003	0.040	0.271	0.686	1.000

The extreme asymmetry is the consequence of the low frequency of the recessive homozygotes.

26 (7.3) This can be done in three ways. (i) Calculate M from [7.2] for several different gene frequencies and graph M against q . This, of course, gives only an approximate answer.

(ii) Treat the metric value as if it were fitness and use [2.19] to find the equilibrium gene frequency. For this we need the fitness of each homozygote relative to the heterozygote. $(1 - s_1) = 110/150 = 0.733$, $(1 - s_2) = 90/150 = 0.600$; $s_1 = 0.267$, $s_2 = 0.400$. Then, if \hat{q} is the equilibrium frequency of A_2 , by [2.19] $\hat{q} = 0.267/0.667 = 0.4$.

(iii) Differentiate [7.2] with respect to q and equate to 0. (In using [7.2] care must be taken to ensure that p is the frequency of the allele that confers the higher value, in this case A_1 .) Substituting $p = 1 - q$ in [7.2] and rearranging gives

$$\begin{aligned} M &= a + 2(d - a)q - 2dq^2 \\ \frac{dM}{dq} &= 2(d - a) - 4dq \end{aligned}$$

$$\hat{q} = \frac{d - a}{2d}$$

The mid-homozygote value is 100, and $a = 10$, $d = 50$. Thus $\hat{q} = 40/100 = 0.4$.

Substituting these values of a , d and \hat{q} in [7.2] gives $M = 26$ as the deviation from the mid-homozygote value. The population mean is therefore $100 + 26 = 126$.

27 (8.3) The ratio V_D/V_G is [8.4] divided by [8.8]. Let c be the degree of dominance, so that $d = ca$. Then $2pqa^2$ cancels out and the ratio reduces to

$$\frac{V_D}{V_G} = \frac{2pqc^2}{2pqc^2 + [1 + c(q - p)]^2}$$

where q is the frequency of the recessive allele. Before working this out for different gene frequencies it is easier to substitute the value of c and then simplify further. Simplified expressions are given below, with the values of V_D/V_G for four gene frequencies. More values will have to be calculated for drawing the graphs.

	$d = \frac{1}{2}a$	$d = a$	$d = 2a$
q	$\frac{q - q^2}{q^2 + 3q + \frac{1}{2}}$	$\frac{1 - q}{1 + q}$	$\frac{q - q^2}{q^2 + \frac{1}{8}}$
0.2	0.140	0.667	0.970
0.4	0.129	0.429	0.842
0.6	0.090	0.250	0.495
0.8	0.045	0.111	0.209
Maximum at $q =$	0.143	$\rightarrow 1$	1.000
	0.250	$\rightarrow 0$	0.250

Note that most of the variance caused by a fully recessive allele at low frequency is dominance variance; but when dominance is less than complete the proportion of dominance variance is not great.

28 (9.3) The father-child and mother-child correlations are obviously consistent. To make comparisons with the midparent-child correlation we have to convert the correlations to regressions. In doing this we have to make two assumptions: that the variances in parents and in children are the same, and that the children are single children, not the means of several. With these assumptions, the regressions of children on single parents are equal to the correlations and are estimates of $\frac{1}{2}V_A/V_P$, and the estimates of V_A/V_P are 1.00 and 0.98. The midparent-child correlation estimates $(\sqrt{\frac{1}{2}})V_A/V_P$, giving $V_A/V_P = 0.69/\sqrt{\frac{1}{2}} = 0.98$. The three correlations are therefore all consistent.

29 (11.3) The intensity of selection is obtained from Appendix Table B; it is different in the two sexes. For males, $n = 4$, $N = 60$, giving $i_m = 1.882$. For females, $n = 8$, $N = 60$, $i_f = 1.582$. The mean (see [11.6b]) is $i = 1.732$. The predicted response per generation, from [11.3], is $R = 1.732 \times 0.81 \times 111 = 155.7$ g.

If the response continued at the same rate the mean after five generations would be $738 + (5 \times 155.7) = 1,517$ g. With such a high heritability, however, the reduction of variance from selection is not negligible. A very rough prediction can be made by taking the mean proportion selected, i.e., 10 per cent. Interpolation in Table 11.2 then gives $R_2 = 0.78 \times R_1 = 121$ g. Ignoring the small subsequent reduction of the response, the predicted mean after five generations is $738 + 155.7 + (4 \times 121) = 1,378$ g.

30 (17.3) Since the effect increases with the mean we might first try a log-transformation; or more simply, look at the ratio H/L to see if it is constant. The difference between the X chromosomes after transformation to logs is given on the left below. It is a considerable improvement over the arithmetic difference, but it still increases with the mean. We therefore need a stronger transformation. This could be achieved by subtracting some constant before transformation to logs. One might guess that the 4 larger bristles should be discounted on the grounds that they are nearly invariant. The transformation would then be to $\log(x - 4)$, where x is the bristle number as counted. This transformation works well, as shown below, and renders the X chromosome effect independent of the autosomal level.

<i>Difference of logs</i>	<i>Log (x - 4)</i>		
	<i>High</i>	<i>Low</i>	<i>Difference</i>
A 0.088	0.740	0.574	0.166
B 0.090	0.970	0.835	0.135
C 0.143	1.272	1.092	0.180
D 0.147	1.490	1.319	0.171
E 0.164	1.641	1.459	0.182

The required transformation can be arrived at more rationally as follows. Plot the High against the Low arithmetic values, on arithmetic paper. The points lie nearly on a straight line. We are looking for a scale on the axes which will make the line pass through the origin, i.e., zero on both axes. This will give a graph of the form $y = bx$, so that the ratio y/x is constant. If the line plotted is extended downwards it will be found to pass through, or close to, the point $H = 4$, $L = 4$. This means that $(H - 4)/(L - 4)$ is constant, and the required transformation is $\log(x - 4)$.

31 (1.4)
$$\frac{\text{Heterozygotes}}{\text{Normals}} = \frac{2pq}{1-q^2} = \frac{2q(1-q)}{(1+q)(1-q)} = \frac{2q}{1+q}$$

Putting

$$\frac{2q}{1+q} = \frac{1}{3}$$

gives the solution, $q = \frac{1}{5} = 0.2$.

(Note: Remember that when the gene frequencies of two alleles are written as p and q , $p + q = 1$, and so $p = 1 - q$. In doing the algebra of gene frequencies it is usually best to substitute $p = 1 - q$, or $q = 1 - p$, as a first step.)

32 (2.3) By [2.4] the gene frequency of a will be

$$10^{-4}/(10^{-4} + 10^{-5}) = 1/(1 + 10^{-1}) = 10/11 = 0.90909$$

The Hardy-Weinberg frequencies are then $AA = 0.0083$, $Aa = 0.1653$, $aa = 0.8264$.

33 (3.4) The expected mean is the gene frequency in the base population, i.e., 0.3. This would be found if the number of students was large.

The sample subjected to electrophoresis can be regarded as a sixth generation of parents, so that there have been six generations of random drift. First get $F(t = 6)$, as in Problem 3.3, but with $N = 20$. This gives $F = 0.141$. Then, by [3.14], the variance of the gene frequencies would be $\sigma_q^2 = 0.3 \times 0.7 \times 0.141 = 0.030$. The standard deviation of the students' estimates would be $\sqrt{0.030} = 0.17$.

34 (5.4) First get the inbreeding coefficient by [5.15] as

$$F = \frac{1 - 0.01}{1 + 0.01} = 0.9802$$

Then, by [3.15], the frequency of heterozygotes relative to the Hardy-Weinberg frequency is

$$H/H_0 = 1 - F = 0.0198$$

The Hardy-Weinberg frequency is

$$H_0 = 2 \times 0.2 \times 0.8 = 0.32$$

The required frequency of heterozygotes in the population is therefore

$$H_t = 0.0198 \times 0.32 = 0.63 \text{ per cent}$$

35 (6.4) The binomial frequencies have first to be worked out for the two kinds of loci separately. In each case there are 3 genotypic classes, with binomial frequencies a^2 $2ab$ b^2 , where a and b are as follows.

$$\text{Loci with } q = 0.3: \quad a = 0.09, \quad b = 0.91$$

$$\text{Loci with } q = 0.7: \quad a = 0.49, \quad b = 0.51$$

The binomial frequencies and genotypic classes of the two kinds of loci are shown in the margins (top and left) of the following table.

		<i>Loci with q = 0.3</i>		
Class		-2	-1	0
Freq.		0.008	0.164	0.828
Loci with $q = 0.7$	-2	0.240	{ -4 0.002 0.039 0.199}	-3 -2 -1
	-1	0.500	{ -3 0.004 0.082 0.414}	-2 -1 -1
	0	0.260	{ -2 0.002 0.043 0.215}	0 0 0

The two kinds of loci are put together in the body of the table. The genotypic class is got by adding the two marginal classes, and the frequency is got by multiplying the two marginal frequencies. There are five genotypic classes. Adding together the frequencies in the cells representing the same class gives the frequency distribution as follows.

Measurement class	-4	-3	-2	-1	0	Total
Frequency	0.002	0.043	0.283	0.457	0.215	1.000

36 (7.4) The genotypic values as defined in Fig. 7.1 are $a_b = \frac{1}{2}(95 - 90) = 2.5$; $a_c = \frac{1}{2}(95 - 38) = 28.5$. (Subscript c denotes the c^c gene.) In both cases $d = a$, and [7.2] then reduces to $M = a(1 - 2q^2)$, where q is the frequency of the recessive and reducing allele. This gives

$$M_b = 2.5[1 - 2(0.5)^2] = 1.25 \quad \text{and} \quad M_c = 28.5[1 - 2(0.2)^2] = 26.22$$

Putting both genes together as in [7.3], $M = 1.25 + 26.22 = 27.47$. This is the deviation from the mid-point of the two double homozygotes. The value of the double dominant homozygote is 95 as stated. Given that the gene effects are additive, the value of the double recessive homozygote is

$$95 - 2a_b - 2a_c = 95 - 5 - 57 = 33$$

The mid-homozygote value is therefore $\frac{1}{2}(95 + 33) = 64$. This makes the mean granule number $64 + 27.47 = 91.47$.

An alternative and quicker way to get the mean is from the values and frequencies of the four genotypes, as shown below. The values, i.e., granule numbers, entered are those given in Example 7.3.

<i>Genotype</i>	<i>Freq.</i>	B-	bb
C-	0.96	{ 95 0.72}	{ 90 0.24}
c ^e c ^e	0.04	{ 38 0.03}	{ 34 0.01}

$$\text{Mean} = (95 \times 0.72) + (90 \times 0.24) + (38 \times 0.03) + (34 \times 0.01) = 91.48$$

37 (8.4) We have to get V_A by [8.3a] and V_D by [8.4] for each gene separately and then add them together. The genotypic values, a and d , for doing this must be taken from the means in the margins of table (ii) in the solution to Problem 7.9.

$$\text{Gene b: } a = d = \frac{1}{2}(0.228 + 0.342) = 0.285; \quad q = \sqrt{0.4} = 0.6325$$

$$\text{Gene c}^e: \quad a = d = \frac{1}{2}(0.060 + 0.240) = 0.150; \quad q = \sqrt{0.2} = 0.4472$$

$$\text{Gene b: } \alpha = 0.285(1 + 0.6325 - 0.3675) = 0.3605$$

$$\text{Gene c}^e: \quad \alpha = 0.150(1 + 0.4472 - 0.5528) = 0.1342$$

	$V_A = 2pq\alpha^2$	$V_D = (2pqd)^2$
Gene b	0.0604	0.0176
Gene c ^e	0.0089	0.0055
Both genes	0.0693	0.0231

The interaction variance, V_I , is calculated directly from the interaction deviations in table (iv) of the solution to Problem 7.9. The values in the tables are deviations from the population mean, so their variance is simply the mean of their squares. To get V_I , therefore, multiply the square of each interaction deviation by the frequency of the genotype and add:

$$V_I = 0.48(0.04)^2 + 0.32(-0.06)^2 + 0.12(-0.16)^2 + 0.08(0.24)^2 = 0.0096$$

$$V_A = 0.0693 = 67.94\%$$

$$V_D = 0.0231 = 22.65\%$$

$$V_I = 0.0096 = 9.41\%$$

$$V_G = \underline{\underline{0.1020}} = \underline{\underline{100.00\%}}$$

To check, work out V_G directly from the values in table (ii) of Problem 7.9. The variance of the additive expectations in table (iii) gives $V_A + V_D$.

38 (9.4) With standardized litters the full-sib correlation is a little higher than the daughter-dam regression. This could be due to dominance or common environment or both. The size of the litter in which a female is reared affects her own subsequent litter size for the following reasons. Females reared in larger litters have to share their prenatal and pre-weaning

nutrition with a larger number of competitors and they are consequently smaller at weaning and as adults. Being smaller, they ovulate fewer eggs and have smaller litters. Sibs reared as litter mates share the environment of the litter in which they were reared. The variation of litter size when litters are not standardized thus causes environmental covariance which increases the full-sib correlation, as seen in the data. The size of litter in which a female is reared is the mother's litter size. So, when litters are not standardized, mothers with larger litters tend to have daughters with smaller litters. There is therefore a negative environmental covariance of daughters' with mothers' litter sizes. This counter-balances the positive genetic covariance and the resultant daughter-dam regression is nearly zero when litters are not standardized. Note how this maternal effect causes a positive environmental covariance of litter mates but a negative environmental covariance of offspring with parents.

39 (11.4) The selection differential in each generation has first to be calculated as $S = P - M$. This is the selection to which the response is seen in the next generation. Each selection differential is therefore entered in the table against the progeny generation. Generation 0 has had no selection applied to it. The figures in the table under R , for response, are simply the generation means. Next, the selection differentials are added successively to give the cumulated selection differential as shown under ΣS . For the divergence, the values of R and ΣS in each generation are got by subtracting those of the Low line from those of the High line. The realized heritability is estimated by the regression of R on ΣS , with the values for generation 0 included. Alternatively, it can be estimated, though less reliably, as the ratio of the total response to the total selection. For the High line this is $(2.44 - 2.16)/0.45 = 0.62$.

Gen.	High			Low			Divergence	
	R	S	ΣS	R	S	ΣS	R	ΣS
0	2.16	0	0	2.16	0	0	0	0
1	2.26	0.16	0.16	2.06	-0.14	-0.14	0.20	0.30
2	2.26	0.08	0.24	2.03	-0.06	-0.20	0.23	0.44
3	2.33	0.11	0.35	2.02	-0.06	-0.26	0.31	0.61
4	2.45	0.08	0.43	2.05	-0.06	-0.32	0.40	0.75
5	2.44	0.02	0.45	2.01	-0.04	-0.36	0.43	0.81
Reg. R on ΣS	0.631			0.362			0.512	
Total response	0.62			0.42			0.53	
Total selection								

40 (19.1) Heritability (see Table 10.4)

Weight gain:
$$h_G^2 = 4 \times \frac{1,602}{12,321} = 0.52$$

Food consumption:
$$h_F^2 = 4 \times \frac{6,150}{61,504} = 0.40$$

Phenotypic correlation:
$$r_P = \frac{22,848}{\sqrt{(12,321 \times 61,504)}} = 0.83$$

Genetic correlation:
$$r_A = \frac{2,229}{\sqrt{(1,602 \times 6,150)}} = 0.71$$

Environmental correlation:

$$r_E = \frac{22,848 - (4 \times 2,229)}{\sqrt{[12,321 - (4 \times 1,602)][61,504 - (4 \times 6,150)]}} = 0.94$$

Alternatively, the environmental correlation can be calculated from [19.1], for which the following are needed

$$\begin{array}{ll} h_G & = 0.7211 & e_G & = 0.6928 \\ h_F & = 0.6325 & e_F & = 0.7746 \\ h_G h_F & = 0.4561 & e_G e_F & = 0.5366 \end{array}$$

Substituting into [19.1] gives

$$\begin{aligned} 0.83 &= (0.71 \times 0.4561) + (r_E \times 0.5366) \\ r_E &= 0.94 \end{aligned}$$

41 (1.5) The genes can be counted and their frequencies determined by extension of [1.1].

$$\begin{array}{ll} A: & 0.096 + \frac{1}{2}(0.483 + 0.028) = 0.3515 \\ B: & 0.343 + \frac{1}{2}(0.483 + 0.050) = 0.6095 \\ C: & 0 + \frac{1}{2}(0.028 + 0.050) = 0.0390 \\ & \hline \text{Total} & 1.0000 \end{array}$$

The Hardy–Weinberg expectation of CC is $(0.0390)^2 = 0.0015$. The expected number in a sample of 178 is 0.27. None was found because the expectation was well below 1.

42 (2.4) None. The equilibrium by [2.4] is the same when both rates are increased by the same proportion.

43 (3.5) Problem 3.4 gave $\sigma_q^2 = 0.03$. The initial gene frequencies were 0.3 and 0.7. Then by [3.5] the genotype frequencies will be

$$\begin{array}{ll} A_1A_1: & 0.09 + 0.03 = 0.12 \\ A_1A_2: & 0.42 - 0.06 = 0.36 \\ A_2A_2: & 0.49 + 0.03 = 0.52 \end{array}$$

44 (5.5) The solution comes from [5.15] rearranged to give C in terms of F . F is got by [3.15], but for this we need the Hardy–Weinberg frequency of heterozygotes, H_0 . The gene frequencies, by [1.1], are 0.6 and 0.4. So $H_0 = 0.48$. Then, by [3.15],

$$\begin{aligned} 1 - F &= 0.12/0.48 = 0.25; \\ F &= 0.75. \end{aligned}$$

[5.15] rearranged becomes

$$C = \frac{1-F}{1+F} = \frac{0.25}{1.75} = 0.143$$

The indicated frequency of cross-pollination is 14 per cent.

45 (6.5) To get the frequencies from the binomial expansion in this case we have to work with genes, not genotypes. Because there is no dominance, the measurement is determined by the number of increasing alleles, each one adding 1 unit of measurement. With 3 loci, the

genotype can have from 0 to 6 increasing alleles, making 7 classes. The frequencies are given by the expansion of $(p + q)^6$, where p and q are the gene frequencies, 0.4 and 0.6.

Measurement class	0	1	2	3	4	5	6	Total
Frequency	p^6	$6p^5q$	$15p^4q^2$	$20p^3q^3$	$15p^2q^4$	$6pq^5$	q^6	
Frequency, %	0.4	3.7	13.8	27.6	31.1	18.7	4.7	100.0

46 (7.5) It is best to get the average effect of the gene substitution, α , first from [7.5]. For this we have to evaluate a and d as defined in Fig. 7.1. Taking the values of the enzyme activities of the genotypes AA, AB and BB as given in Problem 7.1, a and d are calculated as

$$\begin{aligned} a &= \frac{1}{2}(188 - 122) = 33 \\ d &= 154 - \frac{1}{2}(188 + 122) = -1 \end{aligned}$$

In reality there is probably no dominance, i.e., $d = 0$, but the solution will be worked out with $d = -1$ as if it were real. The gene frequencies, q , specified in Problem 7.2 are those of allele A which is the allele conferring the lower value, and this is what is required in [7.5].

(1) $q = 0.2$. Substitution into [7.5] gives

$$\alpha = 33 + [-1(0.2 - 0.8)] = 33 + 0.6 = 33.6.$$

The average effects of the alleles separately are given by [7.6]. Here α_i refers to the allele whose frequency is p , which is B. So, from [7.6]

$$\begin{aligned} \alpha_B &= 0.2 \times 33.6 = 6.72 \\ \alpha_A &= -0.8 \times 33.6 = -26.88 \end{aligned}$$

Check that $\alpha_B - \alpha_A = \alpha$

$$\begin{aligned} (2) \quad q = 0.5: \quad \alpha &= 33 + 0 = 33; & \alpha_B &= 16.5; & \alpha_A &= -16.5. \\ (3) \quad q = 0.8: \quad \alpha &= 33 - 0.6 = 32.4; & \alpha_B &= 25.92; & \alpha_A &= -6.48. \end{aligned}$$

(Note: with strictly no dominance ($d = 0$), α is equal to a and is the same for all gene frequencies, but α_A and α_B remain dependent on the gene frequency.)

47 (8.5) For (1) we need the correlation, r , between first and second litters, and for (2) we need the regression, b , of second on first, and the two means. Let X represent first litters and Y represent second litters.

$$\begin{array}{lll} \Sigma X = 104 & \Sigma Y = 103 \\ \Sigma X^2 = 1,106 & \Sigma Y^2 = 1,101 & \Sigma XY = 1,089 \\ \bar{X} = 10.4 & \bar{Y} = 10.3 \end{array}$$

The corrected sums of squares and products are

$$\Sigma x^2 = 24.4 \quad \Sigma y^2 = 40.1 \quad \Sigma xy = 17.8$$

The repeatability is estimated as the product moment correlation, which is

$$r = 17.8 / \sqrt{(24.4 \times 40.1)} = 0.57$$

The estimate from this small sample is higher than would normally be found in larger samples. The repeatability could be estimated as the intraclass correlation, which works out to be 0.59, but this is not strictly valid when the variances of X and Y differ, which they do: $\sigma_x^2 = 2.7$, $\sigma_y^2 = 4.5$.

- (2) The regression of second on first litter sizes is

$$b_{YX} = 17.8/24.4 = 0.73$$

Expected size of second litters:

- (a) $10.3 + 0.73(14 - 10.4) = 12.9$
 (b) $10.3 + 0.73(5 - 10.4) = 6.4$

These are the predicted mean sizes of the second litters of (a) all mice whose first litters were 14 and (b) all mice whose first litters were 5.

- 48 (10.1) According to [10.5] the correlation or regression has to be multiplied by $1/r$, the values of r being given in Table 9.3. In the cases of (4) and (7) the factors analogous to $1/r$ are explained in the text and are shown in parentheses below.

	$1/r$	h^2
(1)	2	0.42
(2)	2	0.54
(3)	2	0.68
(4)	(1)	0.32
(5)	4	0.08
(6)	4	0.12
(7)	(2)	0.18

- 49 (11.5) The unweighted selection differential is the difference between the mean of the parents and the mean of their generation; the calculation is shown in the table. Note that selection was for reduced size, so a selection differential with negative sign is what was desired. To get the weighted selection differential calculate the weighted mean of the parents, weighting by the number of offspring. If P is the parental value and n is the corresponding number of offspring, the weighted mean is $\Sigma nP/\Sigma n$. For females this is

$$[(7.6 \times 1) + (12.4 \times 9) + \dots]/69 = 917.6/69 = 13.30$$

The rest of the calculation is shown in the table.

	<i>Unweighted</i>		<i>Weighted</i>	
	<i>Females</i>	<i>Males</i>	<i>Females</i>	<i>Males</i>
Mean of parents (a)	12.59	13.01	13.30	13.75
Mean of parents' generation (b)	13.14	14.80	13.14	14.80
Selection differential (a - b)	-0.55	-1.79	+0.16	-1.05
Mean of sexes		-1.17		-0.445

Natural selection for fertility in females opposed the artificial selection for small size, to an extent that the effective selection differential was in the wrong direction. The similar but much smaller effect in males was probably accidental.

- 50 (19.2) The variances and covariance in the uniform population are environmental only. Subtraction of these from the values in the variable population estimates the genotypic variances and covariance (see Example 8.1).

<i>Population</i>	<i>Cause of variation</i>	<i>Correlation</i>
Variable	$G + E$	$0.87/\sqrt{(0.366 \times 43.4)} = 0.22 = r_P$
Uniform	E	$0.27/\sqrt{(0.186 \times 16.6)} = 0.15 = r_E$
$V - U$	G	$0.60/\sqrt{(0.180 \times 26.8)} = 0.27 = r_G$

The genetic correlation, r_G , estimated in this way is the correlation of genotypic values. The genetic correlation, r_A , in Problem 19.1 was estimated from the sire components and is the correlation of breeding values.

51 (1.6) The gene frequency in males is the frequency of affected males, given as 0.07. Under Hardy-Weinberg equilibrium the gene frequency is the same in females as in males.

(1) The frequency of heterozygous women is

$$2q(1 - q) = 2 \times 0.07 \times 0.93 = 0.13,$$

or 13 per cent. (2) The frequency of colour-blind (i.e. homozygous) women is $q^2 = 0.0049$, or about 1 in 200. (3) The frequency of the marriage is the product of the frequencies in men and in women, $0.07 \times 0.0049 = 0.000343$, or about 1 in 3,000.

52 (2.5) The selection coefficient, originally $s = 1$, is halved by the treatment. At equilibrium, present and future, the frequency of homozygotes, by [2.13], is $q^2 = u/s$. Halving s will double the frequency of homozygotes when the new equilibrium is reached. The increase of gene frequency comes from mutation so it will take a very long time to reach the new equilibrium.

53 (3.6) The observed frequency of heterozygotes is $H_t = 0.1343$. The gene frequencies in the population as a whole, by [1.1], are 0.1413 and 0.8587. The frequency of heterozygotes in a single random-breeding population with these gene frequencies is $H_0 = 0.2427$. The panmictic index, by [3.15], is

$$P = \frac{0.1343}{0.2427} = 0.553$$

and the coefficient of inbreeding is

$$F = 0.447$$

54 (5.6) In the first period $\Delta F = 1/32$ by [4.1]. After 10 generations $1 - F = P = (31/32)^{10} = 0.728$ by [3.11]. In the second period $\Delta F = 1/64$. At the end, referred to the beginning of the second period as base, $P = (63/64)^{10} = 0.854$. Referred to the start of the first period as base, by [5.17],

$$P = 0.854 \times 0.728 = 0.622$$

$$F = 0.378$$

equivalent to two generations of full-sib mating (Table 5.1).

55 (6.6) A symmetrical distribution results when $a = b = \frac{1}{2}$ in $(a + b)^n$. (1) With recessives, $a = q^2$, where q is the frequency of the recessive alleles; $q = \sqrt{\frac{1}{2}} = 0.707$. (2) With no dominance, $a = q$; $q = 0.5$.

56 (7.6) The breeding values are obtained from Table 7.3, where A_1A_1 corresponds with BB. The values of α needed were found in Problem 7.5.

	(1) $q = 0.2$ $\alpha = 33.6$	(2) $q = 0.5$ $\alpha = 33.0$	(3) $q = 0.8$ $\alpha = 32.4$
BB $2q\alpha$	13.44	33	51.84
AB $(q - p)\alpha$	-20.16	0	19.44
AA $-2p\alpha$	-53.76	-33	-12.96

These values are deviations from the population mean. Check that the mean breeding value is zero in each population: multiply the breeding value by the genotype frequency (Hardy–Weinberg) in that population and sum over genotypes.

57 (8.6) (1) The mean square for litter order is not relevant except to show that the variance between litters of different order (first, second, etc.) has been removed from the within-sow variance, i.e., from V_{Ew} . The repeatability is given by the intraclass correlation, $r = \sigma_b^2/(\sigma_b^2 + \sigma_w^2)$, where σ_b^2 is the component between sows and σ_w^2 is the component within sows. The mean square within sows is σ_w^2 . The mean square between sows is composed of $\sigma_w^2 + 10\sigma_b^2$. (The 10 is because each sow had 10 litters.) Thus

$$\begin{aligned}\sigma_b^2 &= (25.56 - 3.23)/10 = 2.233 \\ r &= 2.233/(2.233 + 3.23) = 0.409\end{aligned}$$

Estimation of the repeatability by the intraclass correlation assumes that the variances do not differ in successive litters.

(2) Basing the measure on the mean of more than one litter reduces V_P (see [8.14]), and the relative reduction is given by [8.15]. V_A is unchanged. The heritability when only one litter is used is V_A/V_P , and when n litters are used it is $V_A/V_{P(n)}$. The heritability with n litters relative to the heritability with one litter is therefore $V_P/V_{P(n)}$, which is simply the reciprocal of [8.15].

n	$V_{P(n)}/V_P$	h_n^2/h^2
2	0.704	1.42
3	0.606	1.65
4	0.557	1.80

Taking two litters would increase the heritability by 42 per cent, and taking four litters by 80 per cent.

— 58 (10.2) The inconsistency between sons and daughters is removed if correction is made for the difference in variance between males and females. The correction factors, by which the regressions and their standard errors are to be multiplied, are: for daughter–father, $\sigma_m/\sigma_f = 2.5/2.3 = 1.087$; for son–mother, $\sigma_f/\sigma_m = 0.920$. The estimates of the heritability, obtained by making this correction and then doubling the regression and its standard error, are as follows.

	<i>Father</i>	<i>Mother</i>
Sons	0.646 ± 0.116	0.835 ± 0.105
Daughters	0.633 ± 0.096	0.840 ± 0.096
Mean	0.64 ± 0.075	0.84 ± 0.071

The estimates from mothers are substantially higher than those from fathers, which can be attributed to a maternal effect. Consequently the regressions on mid-parent are not useful, and the regressions on fathers provide the most reliable estimates. There are no reasons to prefer the sons or the daughters, so we take the mean as $h^2 = 0.64 \pm 0.075$. The standard error is obtained as $\frac{1}{2} \sqrt{[(0.116)^2 + (0.096)^2]}$.

Now consider the regressions on mothers. By doubling the regression, as in the table, we have also doubled the covariance due to the maternal effect. Therefore $\frac{1}{2}(0.84 - 0.64) = 0.10$ estimates the environmental covariance of mothers and their children, expressed as a proportion of V_P .

59 (11.6) On average, 2 lambs from each ewe must be selected in order to replace the parents. After one breeding season there are not enough lambs to provide replacements, so the parents must be kept for at least 2 seasons. After 2 breeding seasons each ewe has on average 2.4 lambs; selecting 2 out of 2.4 ($p = 83$ per cent) makes $i = 0.305$ (from Appendix Table A because the numbers are large). The generation interval is the mean age of the parents at the birth of their selected offspring, which in this case is 2.5 years. The intensity of selection per year is then 0.122. The table shows this calculation for each year of age at which the parents might be discarded, up to 7. The intensity of selection per year is maximal when the parents have bred for 5 seasons and are 6 years old. The parents should therefore be discarded after their 5th breeding season. The proportion selected in each year will then be 1 out of 3 for the following reason. Each year 1 out of 5 pairs are replaced, having produced on average 1.2 lambs in that year. The proportion of the total lambs needed to replace them is therefore

$$\frac{1}{5} \times \frac{2}{1.2} = \frac{1}{3}$$

Or, when due for replacement each pair has produced on average a total of 6 lambs. So to replace each pair, $2/6 = 1/3$ must be selected.

Age of parents when discarded	Generation interval (L)	Total lambs per ewe (N)	$p = 2/N$ (%)	i	i/L
3	2.5	2.4	83	0.305	0.122
4	3.0	3.6	56	0.704	0.235
5	3.5	4.8	42	0.931	0.266
6	4.0	6.0	33	1.097	0.274
7	4.5	7.2	28	1.202	0.267

60 (19.3) Taking the intensity of selection from Appendix Table A gives

Males: $i = 1.755$

Females: $i = 1.400$

Mean: $i = 1.5775$

The direct responses are predicted by [11.3] and the correlated responses by [19.6]. The data needed from Problem 19.1 are

$$h_G^2 = 0.52 \quad h_F^2 = 0.40 \quad r_A = 0.71 \\ \sigma_G = 111 \text{ g} \quad \sigma_F = 248 \text{ g}$$

giving, for substitution into [19.6], $h_G h_F r_A = 0.324$.

Response of weight gain

Direct: $R = 1.5775 \times 0.52 \times 111 = 91.1$ gCorrelated: $CR = 1.5775 \times 0.324 \times 111 = 56.7$ g

Response of food consumption

Direct: $R = 1.5775 \times 0.40 \times 248 = 156.5$ gCorrelated: $CR = 1.5775 \times 0.324 \times 248 = 126.8$ g

61 (1.7) The gene frequency in the parents is known and should be used to calculate the expectations. The frequency of *so* was $8/40 = 0.2$. The Hardy–Weinberg genotype frequencies in the progeny are, by [1.2], 0.04, 0.32, 0.64. Multiplying these by the total number counted, 1,441, gives the expected numbers (to the nearest whole number) as

<i>so/so</i>	<i>so/cn</i>	<i>cn/cn</i>
58	461	922

There was an excess of homozygotes and a corresponding deficiency of heterozygotes. Possible reason: assortative mating due to some of the female parents having mated with their own stock males before being put in the vials. The discrepancy is highly significant, with $\chi^2 = 125$. This χ^2 has two degrees of freedom because the observed numbers of progeny were not used to estimate the gene frequency, the only constraint being that the expected numbers must add to the observed total.

62 (2.6) $q_0^2 = 1/2,500 = 0.0004$, $q_0 = 0.02$. By [2.12] the original mutation rate is $u_0 = sq_0^2$, and with $s = 1$, $u_0 = q_0^2$. The change of gene frequency from mutation is given by [2.3] and from selection, approximately, by [2.8]. Putting u_1 for the new mutation rate, the net change is

$$\begin{aligned}\Delta q &= u_1(1 - q_0) - sq_0^2(1 - q_0) \\ &= (u_1 - sq_0^2)(1 - q_0)\end{aligned}$$

Substituting $sq_0^2 = u_0$

$$\Delta q = (u_1 - u_0)(1 - q_0)$$

Putting $u_1 = 2u_0$, and substituting $u_0 = q_0^2$

$$\begin{aligned}\Delta q &= q_0^2(1 - q_0) \\ &= 0.0004 \times 0.98 \\ &= 0.000392\end{aligned}$$

$$q_1 = q_0 + \Delta q$$

$$= 0.020392$$

$$q_1^2 = 0.0004158 \text{ or } 1 \text{ in } 2,405$$

The incidence would be increased by 4 per cent of its original level. There would be 16 additional cases per million births.

63 (3.7) (1) The gene frequencies in the sample are 0.6 and 0.4, from which the Hardy–Weinberg frequency of heterozygotes is 0.48. The observed frequency is in excess of the expectation, suggesting some form of selection against one or both homozygotes. (2) With the sample coming from so few parents, chance differences of gene frequency between male and female parents become important. Here $N = 8$, and the expected frequency of heterozygotes, by [3.16], is

$$H = 0.48(1 + 1/16) = 0.51$$

This is close to the observed frequency and so the evidence for selection disappears.

64 (5.7) This can be worked out by pedigree analysis, using [5.1], or by coancestries, using the rule in [5.3]. But it is simpler to get the inbreeding coefficient directly from the frequency of homozygotes. This gives the inbreeding coefficient by definition, because the genes come from highly inbred lines and all homozygotes must therefore be homozygous for alleles that are identical by descent. Call the inbred lines A and B. The F_2 individuals, taken all together, produce A and B gametes in equal proportions, as do the F_1 . So the backcross to the F_1 produces $\frac{1}{2}$ AA + $\frac{1}{2}$ BB, and the backcross to A produces $\frac{1}{2}$ AA. Both therefore produce 50 per cent of homozygotes and the inbreeding coefficient of both progenies is 0.5.

65 (20.2) Let Y denote IQ score and W denote fitness as measured by family size. The change in IQ score is predicted by [20.5b]:

$$CR_Y = r_A h_Y h_W \sigma_Y \sigma_W$$

Taking h_W^2 to be 0.1 gives

$$\begin{aligned} CR_Y &= 0.11 \times \sqrt{(0.6 \times 0.1)} \times 15.4 \times 2.3 \\ &= 0.95 \end{aligned}$$

Taking h_W^2 to be 0.2 gives $CR_Y = 1.35$. The predicted change is an increase of about one IQ point per generation.

The correlated selection differential is given by [20.4] as the phenotypic covariance:

$$\begin{aligned} S'_Y &= \text{cov}_P = r_P \sigma_Y \sigma_W \\ &= 0.11 \times 15.4 \times 2.3 \\ &= 3.9 \text{ IQ points} \end{aligned}$$

66 (7.7) The breeding values and dominance deviations are given in Table 7.3. In solving Problem 7.3 we found $a = 10$, $d = 50$, $q = 0.4$. (q is the frequency of the reducing allele as required.) The average effect of the gene substitution must first be found from [7.5]. This is

$$\alpha = 10 + 50(0.4 - 0.6) = 0$$

All the breeding values are therefore zero. (The reason for this is that the population is at its maximum mean value, which would be its equilibrium if the character were fitness.) Substitution of p , q , and d gives the dominance deviations as

$$\begin{array}{ccc} A_1A_1 & A_1A_2 & A_2A_2 \\ -16 & +24 & -36 \end{array}$$

Check by seeing that the mean dominance deviation of individuals in the population is zero.

67 (12.1) The calculations are shown in the table. The following explanations may be needed.

$$\sigma_A = h\sigma_P = \sqrt{0.2} \times 2.10 = 0.94.$$

Total response at the limit (one-way), $R = 23.55 - 11.90 = 11.65$.

Half-life: This can be deduced as follows. Half the total response is 5.8. Given $S = 2.25$ and $h^2 = 0.2$, the response per generation by [11.2] is $2.25 \times 0.2 = 0.45$. Given that the response was linear, the number of generations required to give the response of 5.8 is $5.8/0.45 = 13$. This estimates the half-life.

Theoretical maximum response, by [12.2] noting that $i\sigma_P$ = selection differential = 2.25, $R_{(\max)} = 2 \times 33 \times 0.2 \times 2.25 = 29.70$.

Theoretical maximum half-life, assuming all genes to be additive, is $1.4 N_e = 46$.

The number of loci and their standardized effects (n and $2a/\sigma_p$) cannot be calculated without knowing the lower selection limit. One might guess that downward and upward selection would have produced equal responses, making the total range $R = 23.3$; the figures in parentheses are based on this assumption. The assumption, however, makes the growth at the lower limit improbably small, i.e., $11.90 - 11.65 = 0.25$ g. A more reasonable guess would be that downward and upward selection would have produced the same proportional change; upward selection doubled the growth, so downward selection would have halved the growth, making the lower limit 5.95 and the total range $R = 17.6$. The first entered figures are based on this assumption. Remember, however, that estimates of gene numbers depend on several other assumptions that are unlikely to be true.

One-way response,	H/C	= 23.55/11.90	= 2.0
	R/σ_A	= 11.65/0.94	= 12.4
	R/σ_P	= 11.65/2.10	= 5.5
$R_{(\max)}/\sigma_P$		= 29.70/2.10	= 14.1
N_e		(given)	= 33
Duration		(given)	= 34
Half-life		(deduced)	= 13
Half-life/ N_e		= 13/33	= 0.39
Observed Maximum:	Response	= 11.65/29.70	= 0.39
	Half-life	= 13/46	= 0.28
No. of 'loci' [12.1]:		$n = \frac{(17.6)^2}{8 \times (0.94)^2}$	= 44 (77)
$2a/\sigma_P$		$= 2h\sqrt{(2/n)}$	= 0.19 (0.14)

68 (10.3) Since we are working with correlations and not covariances the components will all be proportions of the total phenotypic variance V_P . The paternal half sibs give an estimate of

$$V_A/V_P = 4 \times 0.140 = 0.560.$$

In view of the standard errors this is not inconsistent with the estimate from the regression of children on fathers in Problem 10.2. The environmental variance common to children of the same mother is estimated from the difference between the maternal and paternal half-sib correlations:

$$V_{Ec}/V_P = 0.257 - 0.140 = 0.117.$$

Environmental resemblance between children of the same mother is to be expected in consequence of the environmental resemblance between children and mothers found in Problem 10.2. The two covariances are nearly the same, though this is not a necessary part of the expectation. The full-sib correlation estimates $(\frac{1}{2}V_A + \frac{1}{4}V_D + V_{Ec})/V_P$, so

$$\begin{aligned}\frac{1}{4}V_D/V_P &= 0.406 - 2(0.140) - 0.117 = 0.009 \\ V_D/V_P &= 0.036\end{aligned}$$

That this is not significantly different from zero can easily be seen without working out its standard error. The remaining component, environmental variance within sibships, is got by the difference from the total of 1. The full partitioning, in percentages, is

$$\begin{aligned}V_A &+ V_D &+ V_{Ec} &+ V_{Ew} = V_P \\ 56 &+ 4 &+ 12 &+ 28 = 100\end{aligned}$$

69 (14.1) The change of mean is given by [14.4] as $-2F\sum dpq$. After one generation of selfing $F = 0.5$ (Table 5.1), so the inbreeding depression due to the four loci is $\sum dpq$, where d is the difference between the heterozygote value and the mid-homozygote value (Fig. 7.1). The mid-homozygote value is given below as the difference from the 'AA' value, and is one half of the 'aa' value in the table of data.

Locus	Mid-hom. value	d	pq	dpq
(1)	-10	0	0.25	0
(2)	-15	+20	0.25	5
(3)	-15	-5	0.16	-0.8
(4)	-30	+30	0.09	2.7
			$\Sigma dpq =$	6.9

There would be a reduction in yield of 6.9 g due to these loci.

70 (19.4) The realized heritabilities, by [11.7], are as follows.

$$h_G^2 = 186/574 = 0.32$$

$$h_F^2 = 525/1312 = 0.40$$

The genetic correlation, by [19.7], is

$$r_A^2 = \frac{120}{186} \times \frac{412}{525} = 0.5063$$

$$r_A = \pm 0.71$$

Because the direct and correlated responses are in the same direction the sign of r_A must be positive, so $r_A = +0.71$.

71 (1.8) Hardy–Weinberg frequencies are not expected because the gene frequency was different in the male and female parents. The gene frequency of *so* in males was $16/20 = 0.8$, and in females $4/20 = 0.2$. Putting these as the gametic frequencies in Table 1.2 gives the genotype frequencies in the progeny as

<i>so/so</i>	<i>so/cn</i>	<i>cn/cn</i>
0.16	0.68	0.16

With a gene frequency of 0.5 the Hardy–Weinberg expectations are 0.25, 0.50, 0.25. Note the excess of heterozygotes resulting from the unequal gene frequencies in male and female parents.

72 (2.7) Let q be the frequency of the mutant allele, so that $q_0 = 1$. Let m be the proportion of immigrants ($m = 0.01$) with $q_m = 0$. Then [2.1] gives

$$\begin{aligned} q_1 &= mq_m + (1 - m)q_0 \\ &= (0.01 \times 0) + (0.99 \times 1) = 0.99 \\ q_2 &= (0.01 \times 0) + (0.99 \times 0.99) = (0.99)^2 \\ q_{10} &= (0.99)^{10} = 0.9044 \end{aligned}$$

Frequency of wild-type allele = $p = 1 - 0.9044 = 0.0956$.

After the last immigrants have bred the genotypes will be in Hardy–Weinberg proportions. Therefore

- (1) Frequency of wild-type flies = $p^2 = (0.0956)^2 = 0.0091$
- (2) Frequency of mutant phenotype = $1 - p^2 = 0.9909$
 Frequency of heterozygotes = $2pq = 0.1729$
 Frequency of heterozygotes among mutants = $0.1729/0.9909 = 0.1745$

73 (3.8) Start from the expected frequency of heterozygotes, given as

$$H = 2pq + \frac{1}{2}\bar{D}^2 = 2pq + \frac{1}{2}\sigma_D^2$$

where D is the difference of gene frequency between the male and female parents. Let there be M male and F female parents, with $2M$ and $2F$ genes sampled. The binomial sampling variances of the gene frequencies are $pq/2M$ in male parents, and $pq/2F$ in female parents, where p and q are the overall gene frequencies in the whole population. The sampling variance of the difference of gene frequency is

$$\sigma_D^2 = pq/2M + pq/2F$$

The modified equation is therefore

$$\begin{aligned} H &= 2pq + pq\left(\frac{1}{4M} + \frac{1}{4F}\right) \\ &= 2pq\left[1 + \left(\frac{1}{8M} + \frac{1}{8F}\right)\right] \end{aligned}$$

74 (5.8) Think of the part of the population made up only of cousin marriages. This is a subdivided population with $F = 1/16$. (See Problem 5.1.) The risk to the children is the frequency of homozygotes, given in Table 3.1 as $q^2 + pqF$. Call this risk Q . To evaluate Q we need the gene frequency, q . Since most marriages in the whole population are non-consanguineous we can take q to be approximately the square root of the incidence. (There is a small error in doing this because, with some cousin marriages, the genotypes are not quite in Hardy–Weinberg proportions; see Problem 5.9.) Finally, the risk to the children of cousin marriages relative to the population as a whole is $R = Q/I$, where I is the population incidence.

	(1) Cystic fibrosis	(2) PKU
Incidence, $I (= q^2)$	4×10^{-4}	90.91×10^{-6}
$q = \sqrt{I}$	2×10^{-2}	9.53×10^{-3}
Fpq	12.25×10^{-4}	590×10^{-6}
$Q = q^2 + Fpq$	16.25×10^{-4}	681×10^{-6}
$R = Q/I$	4.1	7.5

The risk is increased 4-fold for cystic fibrosis and 7½-fold for PKU, but in absolute terms the risks are still small.

75 (15.1) Base population parameters:

$$V_P = 4.0; \quad V_G = V_A = 0.52 \times 4.0 = 2.08; \quad V_E = 4.0 - 2.08 = 1.92$$

This is slow inbreeding so we use column (1) of Table 15.1. For $F = 0.5$ this gives

	<i>Genetic</i>	<i>Environmental</i>	<i>Phenotypic</i>
Between lines	$2FV_G = 2.08$	0	2.08
Within lines	$(1 - F)V_G = 1.04$	1.92	2.96
Total	$(1 + F)V_G = 3.12$	1.92	5.04
Heritabilities:	(1) within lines (2) overall	$1.04/2.96 = 0.35$ $3.12/5.04 = 0.62$	

76 (7.8) The relevant values found for the two genes were

$$\text{Gene b: } a = d = 2.5; \quad q = 0.5$$

$$\text{Gene c}^e: \quad a = d = 28.5; \quad q = 0.2$$

First get the average effect of each gene substitution from [7.5]:

$$\text{Gene b: } \alpha = 2.5 + 2.5(0.5 - 0.5) = 2.5$$

$$\text{Gene c}^e: \quad \alpha = 28.5 + 28.5(0.2 - 0.8) = 11.4$$

The genotype we are concerned with corresponds to A₂A₂ in Table 7.3. Substituting the above values for each locus separately gives the following.

	<i>Breeding value</i> = $-2p\alpha$	<i>Dominance deviation</i> = $-2p^2d$
Gene b:	$-2 \times 0.5 \times 2.5 = -2.50$	$-2 \times (0.5)^2 \times 2.5 = -1.25$
Gene c ^e :	$-2 \times 0.8 \times 11.4 = -18.24$	$-2 \times (0.8)^2 \times 28.5 = -36.48$
Both genes:	-20.74	-37.73

Adding the breeding values of the separate loci gives the breeding value of the joint genotype; similarly for the dominance deviation. The breeding value calculated is the deviation from the population mean, which was found to be 91.47 granules. In absolute units, therefore, the breeding value is $91.47 - 20.74 = 70.73$ granules.

77 (13.1) The heritabilities are calculated by [13.4] and [13.5], given also in Table 13.4. The relative responses are calculated from the expressions in the right-hand column of Table 13.4.

	h_f^2 [13.4]	h_w^2 [13.5]	R_f/R	R_w/R
(1)	0.265	0.077	0.93	0.72
(2)	0.390	0.077	1.06	0.74
(3)	0.100	0.100	0.79	0.61
(4)	0.147	0.500	0.68	0.97
(5)	0.136	0.500	0.62	1.05

Note that, as can readily be seen from [13.4] and [13.5], when $t = r$, $h_f^2 = h^2 = h_w^2$. In these circumstances individual selection gives the best weighting of the individual and the family mean. Note also the circumstances that make family selection or within-family selection better than individual selection.

78 (10.4) The expectations of the mean squares are

$$B = \sigma_w^2 + 2\sigma_B^2$$

$$W = \sigma_w^2$$

from which

$$\begin{aligned}\sigma_B^2 &= (B - W)/2 \\ \sigma_W^2 &= W\end{aligned}$$

The intraclass correlation is

$$\begin{aligned}r &= \sigma_B^2 / (\sigma_B^2 + \sigma_W^2) \\ &= \frac{\frac{1}{2}(B - W)}{\frac{1}{2}(B - W) + W} \\ &= \frac{B - W}{B + W}\end{aligned}$$

79 (14.2) The population mean, by [7.3], is $M = \Sigma a(p - q) + 2 \Sigma dpq$. This is a deviation from the multiple mid-homozygote value. The mean with the favourable alleles all homozygous will be Σa , also a deviation from the multiple mid-homozygote value. Therefore the increase will be

$$\begin{aligned}&\Sigma a - M \\ &= \Sigma a - \Sigma a(p - q) - 2 \Sigma dpq \\ &= \Sigma [a(2q)] - 2 \Sigma dpq \\ &= 2(\Sigma aq - \Sigma dpq)\end{aligned}$$

We need to know the value of a for each locus. This is half the difference between the homozygote values. The value of Σdpq was obtained in Problem 14.1 as 6.9.

Locus	a	aq
(1)	10	5
(2)	15	7.5
(3)	15	3
(4)	30	3
Σaq	=	18.5

$$\text{Increase} = 2(18.5 - 6.9) = 23.2 \text{ g.}$$

80 (19.5) The solution comes from [19.9] with selection for body weight giving the correlated response of litter size. The intensities of selection corresponding to the proportions selected, from Appendix Table A, are

Selection for		
	Litter size (X)	Body weight (Y)
i on females	1.271	1.271
i on males	0	1.755
i (mean)	0.6355	1.513

Substitution into [19.9] gives

$$\begin{aligned}\frac{CR}{R} &= 0.43 \times \frac{1.513}{0.6355} \times \sqrt{\left(\frac{0.35}{0.22}\right)} \\ &= 1.29\end{aligned}$$

Selection for body weight is expected to be 29 per cent more effective than selection for litter size, mainly because males can be selected.

81 (1.9) It can easily be shown to be true by 'trial and error' with a small number of alleles. (Calculate the frequency of heterozygotes with three alleles all at the same frequency; then recalculate with unequal frequencies.) A simple general proof comes from consideration of the variance of the allele frequencies. With equal frequencies the variance is zero. Let n be the number of alleles and q the frequency of any allele. Then $\sum q = 1$ and $(\sum q)^2 = 1$. The frequency of homozygotes is $\sum q^2$, and when this is minimal the frequency of heterozygotes is maximal. The variance of q is given by

$$\sigma_q^2 = \frac{1}{n} \left[\sum q^2 - \frac{(\sum q)^2}{n} \right] = \frac{1}{n} \left[\sum q^2 - \frac{1}{n} \right]$$

Rearrangement leads to

$$\sum q^2 = n\sigma_q^2 + \frac{1}{n}$$

Therefore, with any value of n , the frequency of homozygotes is minimal when $\sigma_q^2 = 0$. All alleles then have equal frequencies of $1/n$.

Substituting $\sigma_q^2 = 0$ into the above equation gives the frequency of homozygotes as $1/n$. Therefore the frequency of heterozygotes is $1 - (1/n)$.

Note that the first equation above can be written in the following useful form:

$$\sigma_q^2 = \frac{\sum q^2}{n} - \left[\frac{\sum q}{n} \right]^2 = \bar{q}^2 - (\bar{q})^2$$

i.e., variance = (mean of squares) – (square of mean). This is used in later chapters.

82 (2.8) Because both populations reached the same, intermediate, gene frequency selection must have favoured heterozygotes. This is to be expected because the 'heterozygotes', $so+/+cn$, are wild-type and both homozygotes are mutant. The relative magnitude of the selection coefficients against the two homozygotes can be found by [2.18]:

$$\frac{s_{(so)}}{s_{(cn)}} = \frac{P_{(cn)}}{q_{(so)}} = \frac{0.65}{0.35} = 1.86$$

83 (4.1) The effective population size is given by [4.4b]. Then get ΔF by [4.1] and the inbreeding coefficient by [3.12].

No. of females	10	10	10	10
No. of males	10	5	2	1
N_e	20	13.33	6.67	3.636
ΔF	0.025	0.0375	0.075	0.1375
$F(t = 10)$	0.224	0.318	0.541	0.772

84 (5.9) The incidence in the non-inbred individuals is q^2 , and in the inbred individuals is $q^2(1 - F) + qF$, from the right-hand side of Table 3.1. The overall incidence is therefore

$$I = (1 - y)q^2 + y[q^2(1 - F) + qF]$$

By multiplying out the brackets this reduces easily to

$$(1 - yF)q^2 + yFq = I$$

which can be solved for q if y and F are known.

Note that yF is the average inbreeding coefficient in the population as a whole, and the expression for the overall incidence can be got immediately from Table 3.1 by putting yF in place of F .

The equation can be used to get the exact solution to Problem 5.8, assuming there are no other causes of departure from Hardy-Weinberg proportions. The frequency of cousin marriages varies a lot, but is about 1 per cent in many populations.

85 (15.2) This is rapid inbreeding so we should use column (2) of Table 15.1, with $F = 0.5$, $f = 0.594$ (from Table 5.1). This gives the components on the left below. We need, however, the variance of observed means of lines estimated from four individuals, which is $\sigma_b^2 + \frac{1}{4} \sigma_w^2$ (Table 13.3). This gives the values on the right below.

<i>Components</i>		<i>Variance of observed means</i>	
<i>Genetic</i>	<i>Phenotypic</i>	<i>Genetic</i>	<i>Phenotypic</i>
Between, σ_b^2	2.47	2.47	2.63
Within, σ_w^2	0.65	2.57	—

The heritability of observed line-means is $2.63/3.11 = 0.85$. The intensity of selection for $p = 5$ per cent is $i = 2.063$ from Appendix Table A. The expected response is given by [13.2], the lines being equivalent to families. It is

$$R = 2.063 \times 0.85 \times \sqrt{(3.11)} = 3.1 \text{ bristles.}$$

(If worked as if for slow inbreeding, $R = 2.9$ bristles: not very different.)

86 (7.9) To get the population mean we need the frequencies of the four genotypes as shown in table (i). Multiply the value of each genotype in Example 7.7 by its frequency and add to give the population mean = 1.112. Convert the values to deviations from the mean as in table (ii). These deviations from the mean will now be referred to simply as values. Next, we have to look at each locus separately and find the mean value of each of its two genotypes in this population. These are given in the margins of table (ii); for example, the mean value of the C- genotype is $0.6(0.328) + 0.4(-0.342) = +0.060$. Now get the additive expectations of the combined genotypes as in table (iii). These are the values the combined genotypes would have if the values of the two single-locus genotypes were simply added together. For example, the expectation for the B- C- genotype is 0.228 (for B-) + 0.060 (for C-) = 0.288. Finally, the interaction deviation of each genotype is the difference between the observed value in table (ii) and the additive expectation in table (iii). These are given in table (iv). For example, the interaction deviation of B- C- is $0.328 - 0.288 = +0.04$. To check, see that the mean interaction deviation is zero.

(i) Frequencies

	B-	bb
<i>Freq.</i>	0.6	0.4
C-	0.8	0.48
c ^e c ^e	0.2	0.12

(ii) Observed deviations from mean

	B-	bb	<i>Mean</i>
<i>Freq.</i>	0.6	0.4	
C-	0.8	0.328	+0.060
c ^e c ^e	0.2	-0.172	-0.240
<i>Mean</i>	+0.228	-0.342	0.000

(iii) Additive expectations

	B-	bb
C-	+0.288	-0.282
c ^e c ^e	-0.012	-0.582

(iv) Interaction deviations

	B-	bb
C-	+0.04	-0.06
c ^e c ^e	-0.16	+0.24

The interaction deviations can also be calculated directly from the table of genotypic values as follows. The means in the margins are obtained as in table (ii) above.

	B-	bb	Mean
C-	1.44	0.77	1.172
c ^e c ^e	0.94	0.77	0.872
Mean	1.34	0.77	1.112

Then, taking the B- C- genotype as an example, the steps followed above in calculating the interaction deviation can be summarized as

$$(1.44 - M) - [(1.34 - M) + (1.172 - M)]$$

where M is the population mean = 1.112. The interaction deviation of this genotype then becomes

$$1.44 - 1.34 - 1.172 + 1.112 = 0.04$$

87 (13.2) The responses relative to individual selection, R , are got from the expressions at the right-hand side of Table 13.4. (1) and (2) are family selection; (3) is sib selection; (4) is within-family selection.

$$(1) \quad R_f / R = \frac{1 + (4 \times 0.25)}{\sqrt{5[1 + (4 \times 0.10)]}} = 0.76$$

$$(2) \quad R_f / R = \frac{1 + (4 \times 0.5)}{\sqrt{5[1 + (4 \times 0.36)]}} = 0.86$$

$$(3) \quad R_s / R = \frac{5 \times 0.5}{\sqrt{5[1 + (4 \times 0.36)]}} = 0.72$$

$$(4) \quad R_w / R = (1 - 0.5) \sqrt{\left[\frac{4}{5(1 - 0.36)} \right]} = 0.56$$

88 (10.5) This illustrates some of the difficulties in interpreting twin data. The heritability can be estimated in three ways with different biases, as shown in the table below. All are biased, but in different amounts, by dominance and by epistatic components not shown in the table. (2) and (3) are biased by common environment. The children under 10 make reasonably good sense. The degree of genetic determination is estimated approximately by (1) as 52 per cent. There is resemblance due to common environment, which can be estimated approximately by subtracting (1) from (2), or equivalently by subtracting (2) from (3), as $V_{Ec} = 12$ per cent. The children aged 10–15 do not make good sense. It appears that V_{Ec} does not contribute to their resemblance, because (2) and (3) are less than (1).

		Under 10	10–15
(1)	$2(MZ-DZ) = (V_A + 1\frac{1}{2}V_D)/V_P$	0.52	0.98
(2)	$MZ = (V_A + V_D + V_{Ec})/V_P$	0.64	0.91
(3)	$2DZ = (V_A + \frac{1}{2}V_D + 2V_{Ec})/V_P$	0.76	0.84

89 (14.3) The experiment gave two values, 8.1 and 8.5, for the mean with $F = 0$. The solution will be based on the mean of these, i.e., 8.3. Let D_M and D_L be the depression due to inbreeding in the mothers and the litters respectively when $F = 1$. Then from the third line of the table in Example 14.2

$$\begin{aligned}0.5 D_M &= 8.3 - 6.2 \\D_M &= 4.2\end{aligned}$$

From the second line of the table

$$\begin{aligned}0.5 D_L + 0.375 D_M &= 8.3 - 5.7 \\D_L &= 2.05\end{aligned}$$

Inbreeding in the mothers caused about twice as much depression as inbreeding in the litters. The total depression at $F = 1$ would be

$$D_M + D_L = 4.2 + 2.05 = 6.25$$

and the mean litter size would be $8.3 - 6.25 = 2.05$ young per litter.

90 (19.6) First work out the expected response to selection of females only, which was not calculated in the solution to Problem 19.5. We can assume that 25 per cent are selected out of a large number, so the intensity of selection is taken from Appendix Table A. By [11.3] the response is

$$R = \frac{1}{2} \times 1.271 \times 0.22 \times \sigma_P = 0.140 \sigma_P$$

For the joint selection we calculate the response expected from the direct selection for litter size in females by [11.3] and the correlated response from selection for body weight in males by [19.6], and then add the two expected responses together. This is equivalent to calculating the mean breeding value for litter size of the selected females and males. The units throughout are phenotypic standard deviations of litter size. The intensity of selection on females has to be taken from Appendix Table B because all are selected from small samples, i.e., 1 out of 4. The predicted responses are

$$\begin{aligned}\text{From females: } R &= \frac{1}{2} \times 1.029 \times 0.22 &= 0.113 \sigma_P \\ \text{From males: } CR &= \frac{1}{2} \times 1.271 \times \sqrt{(0.35 \times 0.22)} \times 0.43 &= 0.076 \sigma_P \\ \text{From both: } \text{Joint response} &&= 0.189 \sigma_P\end{aligned}$$

The joint response relative to the response expected from selecting females only is

$$\frac{0.189}{0.140} = 1.35$$

The third procedure would be 35 per cent better than the first.

- 91 (1.10) The working comes from Table 1.5 and equation [1.5]. AA bb is produced by union of two recombinant gametes of type Ab, whose frequency, s , we therefore have to find. (Ab corresponds to A_1B_2 in Table 1.5.) We need to know the following quantities.

(i) The gene frequencies; these are 0.5 at both loci. (ii) The equilibrium frequency, \hat{s} , of Ab gametes; this is $\hat{s} = p_A q_B = 0.25$. (iii) The disequilibrium measure, D_0 , in generation 0, before any recombination has taken place, and (iv) the disequilibrium, D_2 , in generation 2. The disequilibrium in any generation, calculated from the Ab gamete frequencies, is $-D = s - \hat{s}$. In generation 0, $s = 0$ so $D_0 = \hat{s} = 0.25$. D_2 is got from [1.5]; the generation 2 progeny are the product of 2 generations of recombination, so $t = 2$ and $D_2 = D_0(1 - c)^2$. With free recombination in question (1), $c = 0.5$ and $D_2 = 0.25(0.5)^2 = 0.0625$. With $c = 0.2$ in question (2), $D_2 = 0.25(0.8)^2 = 0.16$. Next we return to the equation $-D = s - \hat{s}$ given above. Writing this as $s = \hat{s} - D_2$ and substituting the values obtained for \hat{s} and D_2 we get for generation 2,

$$(1) s = 0.25 - 0.0625 = 0.1875, \text{ and } (2) s = 0.25 - 0.16 = 0.09.$$

Finally, the frequency of AA bb in the progeny produced by these gametes is s^2 . The answers are therefore (1) 0.0352 and (2) 0.0081.

92 (2.9) Let R be the resistance gene with frequency p , and S the susceptible allele; let s_1 be the selection coefficient against RR, given as $s_1 = 0.63$. To find the proportion of rats that die as a result of the poisoning we have to find s_2 , the selection coefficient against SS. By [2.18]

$$\frac{s_2}{s_1} = \frac{p}{1-p}$$

$$s_2 = 0.63 \times \frac{0.34}{0.66} = 0.32$$

The proportion of deaths is

$$\begin{array}{ll} \text{RR} & \text{SS} \\ s_1 p^2 & + s_2 (1-p)^2 \\ = 0.63(0.34)^2 & + 0.32(0.66)^2 \\ = 0.07 & + 0.14 \\ = 0.21 & \end{array}$$

21 per cent of all rats die. This can be got more directly by [2.21], which gives the total deaths, i.e., the load, as

$$L = 0.63 \times 0.34 = 0.21$$

93 (4.2) Substitute $N_m = N_f/d$ into [4.4a] to give

$$\begin{aligned} \frac{1}{N_e} &= \frac{d}{4N_f} + \frac{1}{4N_f} \\ &= \frac{d+1}{4N_f} \\ N_e &= \frac{4N_f}{d+1} \end{aligned}$$

94 (18.1) The required values of x and i are got from Appendix Table A, with interpolation. The correlations, t , are calculated from the approximate formula [18.1]. The values of r come from Table 9.3. The heritability is estimated by [18.2]. Taking first-degree relatives as an example,

$$t = (3.090 - 2.061)/3.367 = 0.306$$

$$h^2 = 2t = 0.61$$

	$p\%$	x	i	t	r	$h^2\%$
Population	0.1	3.090	3.367	—	—	—
Relatives						
1st degree	1.97	2.061	—	0.306	$\frac{1}{2}$	61
2nd degree	0.34	2.706	—	0.114	$\frac{1}{4}$	46
3rd degree	0.19	2.895	—	0.058	$\frac{1}{8}$	46

The estimate from first-degree relatives is likely to be the most precise, i.e., to have the smallest standard error, because the number of affected relatives is greatest and because the standard error of t is multiplied by 2 rather than by 4 or 8. On the other hand, first-degree relatives may have some environmental correlation through intra-uterine maternal effects. The most reliable estimate is probably that from second-degree relatives. Approximate standard errors can be calculated from the expression for the sampling variance of t given in the paragraph below equation [18.2], the standard error being the square root of the sampling variance. Multiplying the standard error of t by $1/r$ gives the standard errors of the three estimates of h^2 as 4, 10, and 26 per cent respectively. The estimates from first- and second-degree relatives are not significantly different from each other, and the estimate from third-degree relatives is not significantly different from zero.

95 (15.3) The first generation were full sibs, making $F = 0.25$. Assume that there was no further inbreeding and that non-additive genetic variance is negligible. Then rearranging [15.1] leads to

$$h_0^2 = \frac{h_t^2}{1 - F(1 - h_t^2)}$$

Substituting $h_t^2 = 0.34$ gives the heritability in the base population as

$$h_0^2 = \frac{0.34}{1 - (0.25 \times 0.66)} = 0.41$$

96 (16.1) The predicted yield of a three-way cross is the mean of two single crosses. We therefore have to look for the best two single crosses in which three varieties are involved. The single-cross yields, in order of merit, are

Cross	AE	AC	BC	AB	DE	BE
Yield	31.8	22.8	16.5	14.1	13.1	12.4

The best two involve three varieties and so are suitable. The variety appearing in both would have to be used for the second cross, so the cross would be $(C \times E) \times A$, and its predicted yield is $\frac{1}{2}(AC + AE) = 27.3$.

The predicted yield of a four-way cross is the mean of four single crosses. We therefore have to look for the best four single crosses with four varieties each involved in two of the crosses. These are AE, AC, BC and BE. The cross would be made as $(A \times B) \times (C \times E)$, and its predicted yield is $\frac{1}{4}(AC + AE + BC + BE) = 20.9$.

97 (13.3) The index required is for the individual and mean of sibs. The coefficients of the additive and the phenotypic components of the variance of observed family means in Table 13.3 are denoted by k and K respectively.

$$k = \frac{1+(4 \times 0.5)}{5} = 0.600$$

$$K = \frac{1+(4 \times 0.36)}{5} = 0.488$$

The weighting factors in the index are

$$b_1 = \frac{h^2(0.400)}{0.512}; \quad b_2 = \frac{h^2(0.112)}{0.250}$$

and the index is

$$I = h^2(0.781)P_1 + h^2(0.448)P_2$$

where P_1 is the individual's gain and P_2 is the family mean, both being deviations from the population mean.

For convenience in application the index can be rescaled as

$$I' = P_1 + 0.574P_2$$

The rescaled index can also be calculated from [13.8].

Note that if the units of the index are to be units of weight gain, then P_2 in the rescaled index, and both P_1 and P_2 in the unscaled index, must be deviations from the population mean.

98 (10.6) We first have to calculate the observational components as shown in Table 10.3. Putting $d = 3$, $k = 10$, the mean squares of males are

$$3.894 = \sigma_w^2 + 10\sigma_p^2 + 30\sigma_s^2$$

$$2.198 = \sigma_w^2 + 10\sigma_D^2$$

$$1.125 = \sigma_T^2$$

From these equations, and the corresponding ones for females, the observational components and the correlations are as follows.

Components	<i>Males</i>	<i>Females</i>
Between sires, σ_S^2	0.05653	0.0800
Between dams, σ_D^2	0.1073	0.1168
Within dams, σ_w^2	1.125	0.893
Total σ_T^2	1.28883	1.0898
Correlations		
Half-sib, σ_S^2/σ_T^2	0.0439	0.0734
Full-sib, $(\sigma_S^2 + \sigma_D^2)/\sigma_T^2$	0.1271	0.1806

The relationship between observational and causal components is given in Table 10.4. The estimates of the causal components are as follows.

	<i>Bristle units</i>		<i>Per cent of total</i>	
	<i>Males</i>	<i>Females</i>	<i>Males</i>	<i>Females</i>
V_A	$= 4\sigma_S^2$	0.2261	0.3200	17.5
$\frac{1}{4}V_D + V_{Ec}$	$= \sigma_D^2 - \sigma_S^2$	0.0508	0.0368	3.9
$\frac{3}{4}V_D + V_{Ew}$	$= \sigma_w^2 - 2\sigma_S^2$	1.0119	0.7330	78.5
V_P	$= \sigma_T^2$	1.2888	1.0898	99.9
				100.1

Without maternal half sibs V_{Ec} cannot be separated from $\frac{1}{2}V_D$, nor V_{Ew} from $\frac{3}{4}V_D$.

99 (14.4) The predicted depression is $0.56D_M + 0.64D_L$. Taking the values of D_M and D_L calculated in Problem 14.3 for the non-inbred mean of 8.3, this gives the depression as

$$(0.56 \times 4.2) + (0.64 \times 2.05) = 3.66$$

The means in Fig. 14.2(a), read from the graph, are approximately 7.6 at $F = 0$ and 4.2 at the last generation, giving a depression of 3.4 young per litter. This agrees very well with the prediction.

100 (19.7) Let subscripts 1 denote growth (G) and 2 denote food consumption (F). The index equations from [19.11] are

$$\begin{aligned} b_1 P_{11} + b_2 P_{12} &= A_{11} \\ b_1 P_{21} + b_2 P_{22} &= A_{21} \end{aligned}$$

Substitute the given parameter estimates into [19.12]:

$$P_{11} = (1.11)^2 = 1.2321$$

$$P_{22} = (2.48)^2 = 6.1504$$

$$P_{12} = P_{21} = 0.83 \times 1.11 \times 2.48 = 2.2848$$

$$A_{11} = 0.52 \times (1.11)^2 = 0.6407$$

$$A_{21} = 0.71 \times \sqrt{(0.52 \times 0.40) \times 1.11 \times 2.48} = 0.8914$$

Substitute these values into the index equations:

$$1.2321 b_1 + 2.2848 b_2 = 0.6407 \quad (1)$$

$$2.2848 b_1 + 6.1504 b_2 = 0.8914 \quad (2)$$

$$(1) \times 6.1504: \quad 7.5779 b_1 + 14.05 b_2 = 3.9406 \quad (3)$$

$$(2) \times 2.2848: \quad 5.2203 b_1 + 14.05 b_2 = 2.0367 \quad (4)$$

$$(3) - (4): \quad 2.3576 b_1 = 1.9039$$

$$b_1 = 0.8076$$

Substitute b_1 into (1):

$$b_2 = -0.1551$$

The index is

$$I = 0.808G - 0.155F$$

Or, rescaled to give unit weight to G, in the form

$$I' = G + WF$$

where $W = b_2/b_1$, it is

$$I' = G - 0.192F$$

101 (1.11) The single-locus genotypes are now not in Hardy–Weinberg proportions in the generation 0 progeny, because the gene frequencies are different in the male and female parents. This affects the disequilibrium in generation 1, which must therefore be worked out first. Recombinant gametes are produced only by the AB/ab genotype. Here all the generation 0 progeny are of this genotype, so s_1 (the frequency of Ab gametes) is $\frac{1}{2}c$. (In Problem 1.10 only half of the generation 0 progeny were AB/ab, so s_1 was half as great.) The rest of the calculation is as follows.

	(1) $c = 0.5$	(2) $c = 0.2$
$s_1 = \frac{1}{2}c$	0.25	0.10
equilibrium, \hat{s}	0.25	0.25
$D_1 = \hat{s} - s_1$	0	0.15
$D_2 = D_1(1 - c)$, by [1.5],	0	0.12
$s_2 = \hat{s} - D_2$	0.25	0.13
s_2^2 (freq. of AA bb)	0.0625	0.0169

There is less disequilibrium following the ‘cross’ than after the ‘mixture’ of the strains in Problem 1.10. With no linkage the two-locus equilibrium frequencies are attained in generation 1, which corresponds with the F_2 of a classical two-factor cross with genotype frequencies of 1/16.

102 (2.10) Genotype frequencies among the parents (both genes) and gene frequency, q_0 , of mutant:

AA	Aa	aa	q_0
0.6	0	0.4	0.4

Gene (a) gamete frequencies:

	A	a	Total
	0.6	0.4×0.5	0.8
Divided by 0.8:	0.75	0.25	1.0

Random union among these gametes gives the genotype frequencies in the progeny:

AA	Aa	aa
0.5625	0.3760	0.0625

The observed gene frequency in the progeny, by [1.1], is $q_1 = 0.25$. This is the same as in the gametes. Hardy–Weinberg expectations based on q_1 are therefore exactly as observed. The progeny alone give no evidence of selection.

Gene (b): gamete frequency of mutant is $q_0 = 0.4$. With random mating the genotype frequencies in the progeny are

	BB	Bb	bb	Total
In zygotes	0.36	0.48	0.16	1.00
In survivors	0.36	0.48	0.08	0.92
Observed	0.391	0.522	0.087	1.000

Observed gene frequency by [1.1]: $q_1 = 0.348$, which gives Hardy–Weinberg expectations

0.425	0.454	0.121
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The observed frequencies have an excess of heterozygotes and a deficiency of both homozygotes, suggesting to the unwary that selection favoured heterozygotes. The progeny alone tell us only that the conditions for Hardy–Weinberg expectations have not all been met. Δq is greater for gene (a) because there were no heterozygotes among the parents and all mutant genes were exposed to selection in homozygotes. With gene (b) many mutant genes were sheltered from selection in heterozygotes.

103 (4.3) Remember that 500 breeding pairs means $N = 1000$.

$$N_e = 253 \text{ by [4.6];}$$

$$\Delta F = 0.20 \text{ per cent by [4.1].}$$

104 (18.2) The required values of x and i from Appendix Table A are given below. The correlations, t , are calculated by [18.1]. The correlations are multiplied by 2 to give the heritability because $r = \frac{1}{2}$. The two estimates agree very well. The 'repeat births' are treated in the same way as relatives to give the correlation which is the repeatability. It is calculated as $(1.812 - 1.282)/2.208 = 0.24$.

	$p\%$	x	i	t	$h^2\%$
Population	3.5	1.812	2.208	—	—
Mothers	4.6	1.685	—	0.0575	12
Daughters	4.8	1.665	—	0.0666	13
Repeat births	10.0	1.282	—	0.24	—

105 (15.4) One-quarter of the mutations occurring will be fixed in a sib-mated line, in which there are 4 gametes per generation. So the number of mutations found is the mutation rate per gamete. The number of generations by which the sublines were separated is $21 + 29 = 50$, and there were 27 characters. Therefore the total mutation rate per gamete per generation per character is

$$\frac{5}{50 \times 27} = 3.7 \times 10^{-3}$$

This is the total mutation rate. If the mutation rate per locus is u and if each character can be affected by mutations at any of n loci, then

$$3.7 \times 10^{-3} = nu$$

We can take our choice as to what is the most credible combination of values for u and n , e.g.,

u	n
3.7×10^{-3}	1
3.7×10^{-4}	10
3.7×10^{-5}	100

106 (16.2) Let A , B , and AB represent the performances of the two lines or breeds and the single cross or F_1 .

<i>Generation</i>	<i>Genotypes crossed</i>		<i>Expected performance of progeny</i>
1	AA	\times BB	AB
2	AB	\times AA	$(AB + A)/2$
3	AB AA	$\left. \right\} \times$ BB	$(3AB + B)/4$
4	3AB BB	$\left. \right\} \times$ AA	$(5AB + 3A)/8$

107 (13.4) We use the rescaled index in which P_1 is the individual weight gain and P_2 is the family mean, which must be expressed as a deviation from the population mean; b_2 is the weighting factor for P_2 . Problem 13.3 gave $b_2 = 0.574$ for families of $n = 5$. For $n = 8$, $k = 0.5625$ and $K = 0.4400$, giving $b_2 = 0.636$. The index values of the individuals are

- A: $1.6 + (0.574 \times -0.2) = 1.485$
- B: $1.5 + (0.574 \times 0.1) = 1.557$
- C: $1.5 + (0.636 \times 0.1) = 1.564$
- D: $1.3 + (0.636 \times 0.2) = 1.427$

The order of merit is C, B, A, D.

(Note: P_2 has to be a deviation from the population mean because its weighting (b_2) is not the same in all individuals. P_1 does not have to be a deviation because its weighting is the same. It is sensible to have an index whose mean is equal to the population mean or to zero. If all measurements in the index are expressed as deviations, then the index itself is a deviation and its mean is zero. If one measurement is in actual units, then all others must be deviations and the index then has a mean equal to the population mean.)

108 (10.7) Consider first the particular case of $t = 0.75$, $h^2 = 0.5$. Let $V_p = 100$. Then $V_A = 50$ and $\text{cov}_{FS} = 75$.

$$\text{cov}_{FS} = \frac{1}{2} V_A + \frac{1}{4} V_D + V_{Ec} = 75$$

Therefore

$$\frac{1}{4} V_D = V_{Ec} = 75 - 25 = 50$$

Now, the phenotypic variance can be written as

$$V_p = V_A + (\frac{1}{4} V_D + V_{Ec}) + \frac{3}{4} V_D + V_{Ew} = 100$$

Therefore

$$\frac{3}{4} V_D + V_{Ew} = 100 - 50 - 50 = 0$$

So h^2 cannot be greater than 0.5 because neither V_D nor V_{Ew} can be less than zero.

To generalize, consider the variance within full-sib families (see Table 10.4), which is

$$\begin{aligned}\frac{1}{2} V_A + \frac{3}{4} V_D + V_{Ew} &= V_p - \text{cov}_{FS} = V_p(1 - t) \\ \frac{1}{2} V_A &= V_p(1 - t) - \frac{3}{4} V_D - V_{Ew}\end{aligned}$$

V_A is therefore maximal when V_D and V_{Ew} are zero. The value of h^2 at its maximum is thus

$$\begin{aligned}\frac{1}{2} h^2 &= 1 - t \\ h^2 &= 2(1 - t)\end{aligned}$$

If the full-sib correlation is 0.8, the maximum possible heritability is

$$h^2 = 2 \times 0.2 = 0.4$$

A character with $V_{Ew} = 0$ is extremely improbable, especially if V_{Ec} is not zero, so in practice the upper limit of h^2 will be substantially lower than $2(1 - t)$.

109 (14.5) We shall calculate the average selection differential on females required per generation. With $N_e = 40$ the rate of inbreeding, by [4.1] was $\Delta F = 0.0125$. The inbreeding coefficient at generation 30, by [3.12], was $F = 0.3143$. With slow inbreeding like this it is a good enough approximation to take the inbreeding coefficient of mothers and litters as being

the same. The depression from mothers and litters together will be taken from the solution to Problem 14.3 as being 6.25 for $F = 1$. Therefore the expected depression at $F = 0.3143$ is $0.3143 \times 6.25 = 1.964$, and the rate per generation is $1.964/30 = 0.065$. Counteracting selection would be required to give a response of 0.065 per generation. Putting $h^2 = 0.22$ into [11.2], this makes $S = 0.065/0.22 = 0.30$. With no selection on males, the selection differential on females would have to be 0.6 mice per litter each generation on average. This means that if, for example, 1 in 5 females in each generation were replacements, subject to selection, they would have had to come from litters averaging $0.6 \times 5 = 3$ mice per litter above their generation mean.

110 (19.8) The predicted response to selection for the index is given by [19.17], but we first need to find the variance of index values by [19.18], for which we need the unscaled values $b_1 = 0.8076$ and $b_2 = -0.1551$. By [19.18]

$$\begin{aligned}\sigma_I^2 &= b_1 A_{11} + b_2 A_{21} \\ &= (0.8076 \times 0.6407) + (-0.1551 \times 0.8914) \\ &= 0.3792 \\ \sigma_I &= 0.6158\end{aligned}$$

The response to selection by the index, by [19.17], is

$$\begin{aligned}R_I &= 1.5775 \times 0.6158 \\ &= 0.971\end{aligned}$$

The units in which the index was calculated in Problem 19.7 were 100 g. Therefore the predicted improvement is 97 g per generation.

The response to selection for growth alone was calculated in Problem 19.3. In 100 g units it is $R = 0.911$. So the relative effectiveness of index selection is

$$\frac{R_I}{R} = \frac{0.971}{0.911} = 1.066$$

The index is expected to be 6.6 per cent better. In this case the use of the secondary character gives little benefit.

111 (11.7) Both the intensity of selection and the generation length are now different for males and females. Assume that the numbers of males and females are equal at maturity. The average number of lambs per ewe per season is 1.2 as stated in Problem 11.6. The number of male lambs per male parent per season is therefore $\frac{1}{2} \times 1.2 \times 10 = 6$. The males are bred for 2 seasons, so each has on average 12 male offspring from which 1 must be selected, giving $i = 1.840$. The selection intensity on females for female replacements is $i = 0.704$ as calculated in Problem 11.6. The generation length is 2.5 years for males and 3 years for females. The mean intensity of selection per year is therefore

$$\frac{\frac{1}{2}(1.840+0.704)}{\frac{1}{2}(2.5+3)} = 0.463$$

The effectiveness relative to the optimal procedure in Problem 11.6 is $0.463/0.274 = 1.69$. It would be 69 per cent better.

The reason why there is an optimal age for discarding parents is that L increases by equal steps but i increases by diminishing steps. The reason for the optimal age being lower is the greater intensity of selection on males. The optimal age for discarding both sexes depends on the mean i and the mean L , not on the ratio of i to L in each sex separately.

112 (2.11) The effect of selection in males and females is different and has to be worked out separately. The heterogametic sex will be referred to as male. Let q be the initial frequency of the recessive gene. The genotypes and their initial frequencies are shown below, with the gene frequencies among the survivors and in the next generation. For the gene frequency among surviving females see the derivation of [2.9].

<i>Males</i>		<i>Females</i>		
A	a	AA	Aa	aa
p	q	p^2	$2pq$	q^2
Gene frequency in survivors	0		$q/(1+q)$	
in next generation	$q/(1+q)$		$\frac{1}{2}q(1+q)$	

The overall gene frequency among survivors of both sexes is

$$q_1 = \frac{2q}{3(1+q)} \quad (\text{see [1.4]}).$$

In the zygotes of the next generation the gene frequency is no longer the same in the two sexes, but the overall gene frequency is not further changed. We can therefore take the above expression for q_1 as the overall gene frequency after one generation of selection. The change of gene frequency is then

$$\Delta q = \frac{2q}{3(1+q)} - q$$

which simplifies to

$$\Delta q = \frac{q(1+3q)}{3(1+q)}$$

113 (4.4) The self-fertile variety breeds as an idealized population, for which $N_e = N$; $\Delta F = 1/2N_e = 2.50$ per cent. With the self-fertile variety $\Delta F = 2.44$ per cent by [4.2b]. Exclusion of self-fertilization makes little difference, and even less with larger N .

114 (18.3) This form of analysis is equivalent to working on the '0, 1' scale. It makes no difference if the values assigned to individuals are 0 and 1 rather than 1 and 2. Each half-sib family has a mean which, with values 0, 1, is the proportion of its members that have twins. The covariance of half sibs is thus the variance of the proportion among half-sib families. On the 0, 1 scale, then, the heritability is $4 \times 0.0058 = 2.32$ per cent. This can be converted to the liability scale by [18.4]. We need the population incidence and the corresponding i , which from Problem 18.2 are $p = 0.035$, $i = 2.208$. The heritability of liability is then

$$h^2 = \frac{2.32 \times 0.965}{(2.208)^2 \times 0.035} \text{ per cent} = 13 \text{ per cent}$$

which agrees very closely with the estimate obtained by the analysis of liability in Problem 18.2.

115 (15.5) The component of variance between crosses, σ_x^2 , comes directly from [15.4]. The total variance is the same as that of the base population, so the component within

crosses, σ_w^2 , is the difference from V_p . The component of variance between crosses, σ_x^2 , is the variance of the true means of crosses. The variance of observed means, σ_M^2 , is $\sigma_x^2 + \frac{1}{20} \sigma_w^2$. (See Table 13.3.)

<i>F</i>	<i>Between crosses</i>	<i>Within crosses</i>	<i>Observed means</i>
	$FV_A + F^2V_D = \sigma_x^2$	$\sigma_w^2 = V_p - \sigma_x^2$	$\sigma_M^2 = \sigma_x^2 + \frac{1}{20} \sigma_w^2$
(1) 0.5	$432 + 47 = 479$	5319	745
(2) 1.0	$864 + 188 = 1052$	4746	1289

116 (16.3) Let *A*, *B*, and *C* represent the purebred performances, and *AB*, *AC*, *BC* the single-cross performances.

<i>Generation</i>	<i>Genotypes crossed</i>		<i>Expected performance of progeny</i>
1	AA	× BB	<i>AB</i>
2	AB	× CC	$(AC + BC)/2$
3	AC	}	$(2AC + AB + A)/4$
	BC		
4	2AC	}	$(5AB + 2BC + B)/8$
	AB		
	AA		
5	5AB	}	$(9BC + 5AC + 2C)/16$
	2BC		
	BB		

117 (13.5) For calculating the efficiency we need the coefficients of the unscaled index. These were found in Problem 13.3 to be

$$b_1 = 0.781h^2; \quad b_2 = 0.448h^2$$

It is not necessary to know h^2 because it will cancel out when the comparison with individual selection is made.

Next we need the variance of the index given by [13.12]. In this, $A_{11} = \sigma_A^2$; A_{21} , the additive covariance of an individual with its family mean, is equal to the additive variance of observed family means, which is $k\sigma_A^2$. Substitution into [13.12] then gives

$$\begin{aligned}\sigma_I^2 &= (b_1 + b_2 k)h^2\sigma_A^2 \\ &= 1.050 h^2\sigma_A^2\end{aligned}$$

The expected response to selection by the index is given by [13.15] as

$$R_I = i\sigma_I = i(1.025)h\sigma_A$$

This is directly comparable with the expected response to individual selection, *R*, in [11.4], and, provided the intensity of selection, *i*, is the same

$$R_I/R = 1.025$$

Index selection would be 2.5 per cent better than individual selection. The benefit is small because *t* is not very different from *r*.

118 (10.8) All three regressions and the full-sib correlation are significantly different from zero but, with the large standard errors, the partitioning of the variance can only be tentative. The regression of offspring on mid-parent estimates the heritability without bias from the assortative mating, giving $h^2 = 0.82$. Correcting the regressions on one parent for the bias caused by the assortative mating ($r = 0.33$) by equation (14) of Table 10.6 gives $h^2 = 2b/(1 + r) = 0.71$ and 0.72 respectively. These are not inconsistent with the estimate from the mid-parent regression. To deal with the effect of assortative mating on the sib correlation we need to know the correlation of breeding values, m . Not knowing this, we might take $m = r$ as an approximation. Then the correlation of full sibs in respect of breeding values, from equation (15) of Table 10.6, and taking $h^2 = 0.82$, is $t = 0.41 \times 1.33 = 0.55$. The observed correlation is higher than this, though not significantly, suggesting that there may be some environmental variance common to full sibs, or some dominance variance, amounting to $0.71 - 0.55 = 16$ per cent of the total variance.

119 (14.6) Let \bar{P} be the mean yield of the two parents and let F_1, F_2, F_3 represent the yields of these generations. Then the predicted yields are

$$\begin{aligned}F_2 &= \frac{1}{2}(\bar{P} + F_1) \\F_3 &= \frac{1}{2}(\bar{P} + F_2)\end{aligned}$$

giving

Cross	<i>Observed</i>		<i>Predicted</i>	
	\bar{P}	F_1	F_2	F_3
(1)	1.40	1.41	1.405	1.40
(2)	1.08	1.42	1.25	1.165

The reasons for these expectations may be made clearer by consideration of the heterosis, H . By definition, $H_{F_1} = F_1 - \bar{P}$. By [14.10], $H_{F_2} = \frac{1}{2}H_{F_1}$. The expected yield of the F_2 is

$$\bar{P} + H_{F_2} = \bar{P} + \frac{1}{2}(F_1 - \bar{P}) = \frac{1}{2}(\bar{P} + F_1)$$

Each generation of selfing halves the frequency of heterozygotes (Table 5.1), so the expected heterosis in the F_3 is half that of the F_2 . Thus the predicted yield of the F_3 is

$$\bar{P} + \frac{1}{2}(F_2 - \bar{P}) = \frac{1}{2}(\bar{P} + F_2).$$

120 (19.9) The correlated response is given by [19.19], but we first need to get the additive genetic covariance of character 2 with the index. The covariance of character 1 with the index is given by [19.20]. The covariance of character 2 with the index, which is given in Example 19.5, is

$$\text{cov}_{2I} = b_2 A_{22} + b_1 A_{21}$$

A_{22} was not calculated in Problem 19.7. It is $0.40 \times (2.48)^2 = 2.4602$.

$$\begin{aligned}\text{cov}_{2I} &= (-0.1551 \times 2.4602) + (0.8076 \times 0.8914) \\&= 0.3383\end{aligned}$$

To get the response from [19.19] we need $i = 1.5775$ and $\sigma_i = 0.6158$, both coming from Problem 19.8. The correlated response of food consumption is then

$$CR_2 = 1.5775 \times \frac{0.3383}{0.6158}$$

$$= 0.87 \text{ (in 100 g units)}$$

The food consumption would be expected to increase by 87 g per generation.

121 (11.8) Let n be the number of litters on which selection is based, and let t be the generation length in years. Let R and R_n be the responses when selection is based on 1 and on n litters respectively. The responses can be compared by [11.3], $R = ih^2\sigma_p$, but it is simpler to do so by [11.4], $R = ih\sigma_A$, because σ_A does not change with the number of litters. We do not need to evaluate the actual responses because the optimal value of n will be the number that gives the maximal value of the ratio

$$\frac{R_n/t_n}{R/t} = \frac{i_n h_n}{i h} \frac{t}{t_n}$$

The calculations are shown below. Note that the expected number of females in each litter is 4, so the proportion of sows that must be selected is 1/4 with $n = 1$, 1/8 with $n = 2$ etc. The ratio h_n^2/h^2 was calculated in Problem 8.6 for the repeatability of 0.409. The values of i are found from Appendix Table A.

n	t	$p\%$	i	h_n^2/h^2	i_n/i	h_n/h	t/t_n	$\frac{R_n/t_n}{R/t}$
1	1	25	1.271	—	—	—	—	—
2	1.5	12.5	1.647	1.42	1.296	1.192	0.667	1.03
3	2	8.33	1.840	1.65	1.448	1.285	0.500	0.93

The optimal number of litters is 2.

122 (2.12) Assume that the gene frequency will be low enough for females homozygous for the deleterious gene to be ignored, as an approximation. Elimination of the gene by selection then takes place only in males. One-third of the genes are in males, so the proportion $sq/3$ of the genes are eliminated by selection in each generation, where s is the coefficient of selection. At equilibrium these are replaced by mutation, so $sq/3 = u$, and $q = 3u/s$.

The muscular dystrophy data fit this expectation very well with $s = 1$ and no selection against heterozygous females. The gene frequency, neglecting the male-female difference, is the incidence in males, which is almost exactly three times the estimated mutation rate, as expected.

123 (4.5) Let k = number of offspring used, i.e. family size, as given. The actual number of parents, including the sterile pair, is $N = 16$. To get N_e from [4.7] we need to calculate the variance of k . The mean is $\bar{k} = 2$, and the deviations ($k - \bar{k}$) are: $-2, -1, -1, 0, 0, +1, +1, +2$, from which $\sum(k - \bar{k})^2 = 12$ and $V_k = 12/8 = 1.5$. (Divided by 8, not 7, because this is the whole ‘population’ in the statistical sense, not a sample.) Then by [4.7] $N_e = 64/3.5 = 18.3$. N_e is still a little larger than N in spite of the failure to equalize family size.

124 (18.4) Care is needed with the signs of x and i . Here x will denote the population mean as a deviation from the threshold so that, with incidences less than 50 per cent, x is negative. The mean of affected individuals, i_A , is a deviation from the population mean and is positive. We shall need also the mean of unaffected individuals, i_N , and this is negative. Appendix Table A provides values of i_A for the incidence p , from which i_N is got as $i_N = -i_A p/(1-p)$. The two generations have to be worked out separately because the change of incidence resulting from the first selection changes the selection differential in the second selection.

Selection for reduced incidence will be explained first because it is simpler. The working is shown below. Since more than 50 per cent of individuals are normal all selected individuals of both sexes will be normal and the selection differential in standard deviation units will be $S = i_N$. The response is $R = h^2 S$, and the new mean liability is $x_1 = x_0 + R$. To get the new incidence we have to find the value of p corresponding to x_1 in Appendix Table A. The values given were obtained by interpolation, but it will make little difference if the nearest tabulated value of p is taken. For the second generation the calculation is repeated using p_1 and x_1 in place of p_0 and x_0 . The prediction is that the incidence will be reduced to 17 per cent.

Selection for reduced incidence

<i>First selection</i>	<i>Second selection</i>
p_0	23%
x_0	-0.739
i_A	1.320
$S = i_N$	-0.394
$R = 0.3S$	-0.118
$x_1 = x_0 + R$	-0.857
p_1	19.6%
p_1	19.6%
x_1	-0.857
i_A	1.411
$S = i_N$	-0.344
$R = 0.3S$	-0.103
$x_2 = x_1 + R$	-0.960
p_2	16.9%

The calculation of selection for increased incidence, shown below, is the same as before except that the selection differential is more complicated. Since the proportion of selected males is less than the incidence, all selected males will be affected and the selection differential on males will be $S_\delta = i_A$. The selected females, however, will have to include some normals because fewer than 50 per cent are affected. In the first selection, the proportion of the selected females that are affected will be $0.23/0.5 = 0.46$, and the proportion that are normal will be 0.54. The selection differential on females will thus be $S_\varphi = 0.46i_A + 0.54i_N$. Or, in terms of the incidence, $S_\varphi = 2pi_A + (1 - 2p)i_N$. The combined selection on both sexes will be $\frac{1}{2}(S_\delta + S_\varphi)$. The rest of the calculation needs no further explanation. After the second selection the incidence will be increased to 41 per cent. The much greater response to selection for increased incidence results from the larger selection differential.

Selection for increased incidence

<i>First selection</i>	<i>Second selection</i>
p_0	23%
x_0	-0.739
i_A	1.320
i_N	-0.394
$S_\delta = i_A$	1.320
$S_\varphi = 2pi_A + (1 - 2p)i_N$	0.3944
$S = \frac{1}{2}(S_\delta + S_\varphi)$	0.8572
$R = 0.3S$	0.257
x_1	-0.482
p_1	31.5%
p_1	31.5%
x_1	-0.482
i_A	1.128
i_N	-0.519
S_δ	1.128
S_φ	0.5186
S	0.8233
R	0.247
x_2	-0.235
p_2	40.7%

125 (15.6) Let X be the true mean and M the observed mean of a cross. Selecting 1 out of 50 gives $i = 2.249$ from Appendix Table B. The deviation of the best cross from the mean of all the crosses is therefore $i\sigma_M$, where σ_M is the standard deviation of observed means. σ_M^2

was calculated in Problem 15.5. The expected mean of all crosses is the original population mean, which was 308. Adding 308 to $i\sigma_M$ gives the predicted observed mean of the best cross.

	F	σ_X^2	σ_M^2	σ_M	$i\sigma_M$	$M, \text{predicted}$
(1)	0.5	479	745	27.3	61.4	369.4
(2)	1.0	1052	1289	35.9	80.7	388.7

The prediction of future performance was explained in Chapter 8 in connection with repeatability. The expected mean of the repeated cross, the future performance, is the true mean of the cross. To predict the true mean we need to know the regression of the true means on observed means. The observed mean is $M = X + E$, where E is the deviation due to sampling error. Now,

$$\text{cov}_{XM} = \text{cov}_{X(X+E)} = \text{cov}_{XX} + \text{cov}_{XE}$$

$\text{cov}_{XX} = \sigma_X^2$ and $\text{cov}_{XE} = 0$ because X and E are uncorrelated. Thus $\text{cov}_{XM} = \sigma_X^2$. The required regression is $b_{XM} = \text{cov}_{XM}/\sigma_M^2 = \sigma_X^2/\sigma_M^2$. The rest of the calculation is as follows.

	$b_{XM} = \sigma_X^2/\sigma_M^2$	<i>Predicted true mean of best cross</i>
(1)	0.643	$308 + 0.643(61.4) = 347.5$
(2)	0.816	$308 + 0.816(80.7) = 373.9$

126 (16.4) In each case the right-hand column of the table in the solution represents the proportion of each genotype in the progeny. It is simplest to consider the proportion of homozygotes, which is the inbreeding coefficient, F , relative to the first generation, in which there are no homozygotes. Then the amount of heterosis relative to that of the single crosses is $H_t = 1 - F_t$.

<i>Generation</i> (t)	<i>Two lines</i>		<i>Three lines</i>	
	F_t	H_t	F_t	H_t
1	0	1	0	1
2	1/2	0.5	0	1
3	1/4	0.75	1/4	0.75
4	3/8	0.625	1/8	0.875
5	5/16	0.6875	2/16	0.875
Many	1/3	0.667	1/7	0.857

If the series of generations were continued the heterosis would be found to settle down after a few cycles to 2/3 in the case of two lines and 6/7 in the case of three lines. The general formula for the final level of inbreeding relative to the first cross is $1/(2^n - 1)$, where n is the number of lines.

127 (13.6) The index required is for mother and mean of half sisters. The index equations are

$$b_2P_{22} + b_3P_{23} = A_{21}$$

$$b_2P_{32} + b_3P_{33} = A_{31}$$

Subscript 1 refers to the individual to be selected, which is not measured; 2 refers to the mother and 3 refers to the mean of the half sisters. $P_{22} = \sigma^2$ (i.e., the phenotypic variance);

$P_{23} = P_{32} = 0$; $P_{33} = K\sigma^2$, where $K = [1 + (n - 1)t]/n$, as before. A_{21} is the additive covariance of the individual with its mother $= r_2\sigma_A^2 = r_2h^2\sigma^2$, where $r_2 = \frac{1}{2}$. A_{31} is the additive covariance of the individual with the mean of its half sisters in which the individual is not included; this is the covariance relevant to sib selection, and this is not affected by the number of half sibs, for the reason explained in the paragraph following equation [9.2]. Thus $A_{31} = r_3h^2\sigma^2$, where $r_3 = \frac{1}{4}$. Substituting these values in the index equation gives

$$\begin{aligned} b_2\sigma^2 + 0 &= r_2h^2\sigma^2 \\ 0 + b_3K\sigma^2 &= r_3h^2\sigma^2 \end{aligned}$$

from which

$$\begin{aligned} b_2 &= r_2h^2 = \frac{1}{2}h^2 \\ b_3 &= r_3h^2/K = \frac{1}{4}h^2/K \end{aligned}$$

Now evaluate K . Because there is no environmental resemblance between half sisters, $t = \frac{1}{4}h^2 = 0.0875$. With $n = 10$ this gives

$$K = \frac{1 + (9 \times 0.0875)}{10} = 0.17875$$

Substituting for K and for $h^2 = 0.35$ gives the unscaled index

$$I = 0.175P_2 + 0.490P_3$$

128 (10.9) The equations in Table 10.6 provide the solutions. Because the choice of mates is purely phenotypic, $m = rh^2$. Then equation (15) is $t = \frac{1}{2}h^2(1 + rh^2)$, where h^2 is the heritability in the population mating assortatively. Rearranging gives $\frac{1}{2}rh^4 + \frac{1}{2}h^2 - t = 0$, which has the solution

$$h^2 = [-\frac{1}{2} \pm \sqrt{(\frac{1}{4} + 2rt)}/r$$

Substituting the values of r and t gives only one possible solution, which is $h^2 = 0.50$. The heritability in the same population if it mated at random, h_0^2 , is given by equation (9). Substituting $h^2 = 0.5$ and $m = rh^2 = 0.2$ gives

$$h_0^2 = 0.5 (0.8/0.9) = 0.44$$

129 (14.7) It follows from [14.10] that the difference between the F_1 and the F_2 is half the heterosis, i.e., $F_1 - F_2 = \frac{1}{2}H$, from which $H = -0.24$. But the difference between the F_1 and F_2 was very small and non-significant, so this small amount of heterosis deduced is not significantly different from zero. In fact the means of the parental varieties were 17.88 ± 0.24 and 15.00 ± 0.19 , making $\bar{P} = 16.44 \pm 0.20$, and the observed heterosis was $H = -0.72 \pm 0.28$.

130 (19.10) The index equations from [19.15] are

$$\begin{aligned} b_1P_{11} + b_2P_{12} &= a_1A_{11} + a_2A_{12} \\ b_1P_{21} + b_2P_{22} &= a_1A_{21} + a_2A_{22} \end{aligned}$$

The left-hand sides, being phenotypic parameters, are the same as in Problem 19.7. For the right-hand sides we need $A_{11} = 0.6407$ and $A_{12} = A_{21} = 0.8914$, both also from Problem 19.7. $A_{22} = 2.4602$ as calculated in Problem 19.9. The economic values are already in the 100 g units used for the other parameters in the equations, so $a_1 = 8$ and $a_2 = -2$. The index equations with the values entered are

$$\begin{aligned}1.2321 b_1 + 2.2848 b_2 &= (8 \times 0.6407) + (-2 \times 0.8914) = 3.3428 \\2.2848 b_1 + 6.1504 b_2 &= (8 \times 0.8914) + (-2 \times 2.4602) = 2.2108\end{aligned}$$

Eliminating b_2 as in Problem 19.7 gives

$$\begin{aligned}2.3576 b_1 &= 20.5596 - 5.0512 \\b_1 &= 6.578 \\b_2 &= -2.084\end{aligned}$$

The index for selection is

$$I = 6.578G - 2.084F$$

or, more conveniently,

$$I' = G - 0.317F$$

131 (11.9) We have first to get the coefficient of selection, s , acting on the gene by [11.8]. Substituting $2a = 0.3$, $\sigma_p = 2.0$ and $i = 1.755$ gives $s = 0.2633$. The gene frequency after one generation of selection is then given by line (1) of Table 2.2. The gene frequency q in the formula is that of the allele selected against, so we must put $q = 0.6$. The formula can be rewritten in a form that makes the substitutions simpler:

$$\begin{aligned}q_1 &= q[1 - \frac{1}{2}s(1 + q)]/(1 - sq) \\&= 0.6[1 - 0.1316(1.6)]/(1 - 0.1580) \\&= 0.5625\end{aligned}$$

For the second generation, put q_1 in place of q , giving

$$q_2 = 0.5245$$

The frequency of the increasing allele will therefore be 0.4755.

132 (2.13) Initial gene frequency of red, $q_0 = \sqrt{0.01} = 0.10$. (1) By [2.9], $q_2 = 0.1/1.2 = 0.0833$. Frequency of red calves = $q_2^2 = 0.0069$. (2) This is tricky because more selection is applied to bulls than to cows. Consequently, after selection the gene frequency is not the same in the male and female parents and the genotypes in the progeny are not in Hardy–Weinberg frequencies. The change of gene frequency has to be worked out separately for each sex. The frequency of heterozygotes before selection is 0.18. The proportion of heterozygous bulls that will escape detection by having no red progeny in the test is $(\frac{3}{4})^6 = 0.178$. The proportion of all bulls that are undetected heterozygotes is therefore $0.18 \times 0.178 = 0.0320$.

	<i>Bulls</i>				<i>Cows</i>			
<i>First generation Before</i>	RR	Rr	rr	Total	RR	Rr	rr	Total
selection	0.81	0.18	0.01	1.00	0.81	0.18	0.01	1.00
After selection	{ 0.81 0.9620	{ 0.0320 0.0380	{ 0 0	{ 0.8420 1.0000	{ 0.81 0.8182	{ 0.18 0.1818	{ 0 0	{ 0.99 1.0000
	$q_{1m} = \frac{1}{2} \times 0.0380 = 0.0190$				$q_{1f} = \frac{1}{2} \times 0.1818 = 0.0909$			

Now make a table of gamete frequencies, like Table 1.2, and get the genotype frequencies in the progeny.

		<i>Male gametes</i>	
		R	r
		0.9810	0.0190
<i>Female gametes</i>	R	0.9091	0.0173
	r	0.0909	0.0017

<i>Second generation</i>	<i>Bulls</i>				<i>Cows</i>			
	RR	Rr	rr	Total	RR	Rr	rr	Total
Before selection	0.8918	0.1065	0.0017	1.0000	0.8918	0.1065	0.0017	1.0000
After selection	{ 0.8918 0.9792	0.0190 0.0208	0 0	0.9108 1.0000	0.8918 0.8933	0.1065 0.1067	0 0	0.9983 1.0000
	$q_{2m} = 0.0104$				$q_{2f} = 0.05335$			

The frequency of red calves in the progeny is $q_{2m}q_{2f} = 0.06$ per cent.

(Note: q_{1f} can be got more easily by [2.9], but q_{2f} cannot be got this way because the genotypes before the second selection are not in Hardy-Weinberg frequencies.)

133 (4.6) The breeding plan was minimal inbreeding with $N = 16$, so by [4.9], $N_e = 31$.

The data led to the inbreeding coefficient at generation 27 being $F(t = 27) = 0.447$. By [3.12]

$$(1 - \Delta F)^{27} = 1 - 0.447 = 0.553$$

$$27 \log(1 - \Delta F) = -0.2573$$

$$1 - \Delta F = 0.9783$$

$$\Delta F = 0.0217$$

$$N_e = 1/(2\Delta F) = 23.0$$

134 (18.5) Here x is the deviation of the threshold from the population mean. The values of x and i needed are as follows.

<i>Class</i>	<i>Threshold</i>	<i>p%</i>	<i>x</i>	<i>i</i>
<i>N</i>	T_1	20	-0.842	-1.400
$H + F$	T_1	80	-0.842	+1.400 \times 20/80 = +0.350
<i>F</i>	T_2	30	+0.524	+1.159

The value of i for $p = 80$ per cent is the value for $p = 20$ per cent multiplied by $(1 - p)/p$, as stated at the head of Appendix Table A.

(1) Difference between thresholds

$$= 0.524 - (-0.842) = 1.366\sigma$$

$$1 \text{ t.u.} = 1.366\sigma; \sigma = 0.732 \text{ t.u.}$$

(2) Population mean as deviation from lower threshold

$$= +0.842\sigma = (0.842 \times 0.732) \text{ t.u.} = +0.616 \text{ t.u.}$$

$$(3) \bar{N} = -1.400\sigma = -1.025 \text{ t.u.}$$

$$\bar{F} = +1.159\sigma = +0.848 \text{ t.u.}$$

$$(\bar{H} + \bar{F}) = +0.350\sigma = +0.256 \text{ t.u.}$$

$(\bar{H} + \bar{F})$ is the mean of all individuals above the lower threshold, made up of 50/80 H and 30/80 F . Therefore

$$(\bar{H} + \bar{F}) = \frac{50}{80} \bar{H} + \frac{30}{80} \bar{F}$$

$$0.256 = 0.625 \bar{H} + (0.375 \times 0.848)$$

$$\bar{H} = -0.099 \text{ t.u.}$$

To check, see that the mean of N , H , and F , each weighted by its frequency, sums to zero as the mean deviation from the population mean.

$$N: -1.025 \times 0.2 = -0.2050$$

$$H: -0.099 \times 0.5 = -0.0495$$

$$F: +0.848 \times 0.3 = +0.2544$$

$$\Sigma = \underline{\underline{0.000}}$$

135 (15.7) The working follows exactly that of Example 15.2 and will not be explained in detail. The varieties themselves, whose yields are on the diagonal of the table, must be excluded because combining ability refers to performance in crosses. The values of T and G are on the right of the table below. G is the general combining ability of the variety indicated on the left of the table. As examples,

$$T_B = 14.1 + 16.5 + 6.2 + 12.4 = 49.2$$

$$G_B = \frac{49.2}{3} - \frac{302.6}{5 \times 3} = -3.77$$

The G 's are deviations from the mean; to check, see that $\Sigma G = 0$.

The expected value of, for example, the cross A \times B is

$$\bar{X} + G_A + G_B$$

$$= 15.13 + 8.36 - 3.77$$

$$= 19.72$$

The deviation (SCA + error) is therefore $14.1 - 19.72 = -5.62$. To check, see that the deviations sum to zero. The deviations are given in the table below.

	B	C	D	E	T	G
A	-5.62	+0.55	-1.25	+6.32	85.6	+8.36
B	—	+6.38	+0.18	-0.95	49.2	-3.77
C	—	—	-0.25	-6.68	56.8	-1.24
D	—	—	—	+1.32	44.5	-5.34
E	—	—	—	—	66.5	+1.99
Σ	—	—	—	—	302.6	0.00
\bar{X}	$302.6/20 = 15.13$					

136 (16.5) To avoid confusion, designate the breeds by letters to correspond with those used in Problem 16.3, as shown below. In calculating the expectations for each generation, remember that the formula for any generation applies to W in that generation and to N in the next. The required total litter weight is $W \times N$.

Breed or cross Designation	Y A	C B	D C	YC AB	YD AC	CD BC
W	84	78	88	90	96	92
N	7.9	6.6	6.3	8.2	7.3	7.4
Generation	Genotypes		Expectations			
	W	N	W	N	W × N	
1	AB	A	90	7.9	711	
2	X ₁ × C	AB	94	8.2	771	
3	X ₂ × A	X ₁ × C	91.5	7.35	673	
4	X ₃ × B	X ₂ × A	89	7.675	683	
5	X ₄ × C	X ₃ × B	92.75	7.8	723	

Note that the crossbred performance fluctuates and none is better than the three-way cross in generation 2.

137 (13.7) The two intensities of selection cannot be combined because the standard deviation of the index is not the same as that of yield. The response has to be got from the predicted breeding values of males and of females. First, from [13.12]

$$\begin{aligned}
 \sigma_i^2 &= b_2 A_{21} + b_3 A_{31} \\
 &= b_2 r_2 h^2 \sigma^2 + b_3 r_3 h^2 \sigma^2 \\
 &= (b_2 r_2 + b_3 r_3) h^2 \sigma^2 \\
 &= [(0.175 \times 0.5) + (0.490 \times 0.25)] \times 0.35 \times \sigma^2 \\
 &= 0.0735 \sigma^2 \\
 \sigma_i &= 0.2711 \times 696 \\
 &= 188.59
 \end{aligned}$$

Selecting 5 per cent of bulls gives $i = 2.063$, from Appendix Table A. The expected breeding value of the selected bulls is given by [13.15]:

$$\text{Bulls' breeding value} = i\sigma_i = 2.063 \times 188.69 = 389.3$$

Selecting 50 per cent of cows gives $i = 0.798$, and the predicted breeding value is given by [11.3] as:

$$\text{Cows' breeding value} = ih^2\sigma_p = 0.798 \times 0.35 \times 696 = 194.4$$

Both breeding values are deviations from the population mean and the expected response is the mean of the two:

$$R = \frac{1}{2} (389.3 + 194.4) = 292 \text{ kg}$$

138 (10.10) In all cases we need to know both N , the number of families, and n , the number of offspring or of sibs per family. The one of these that is not given has to be deduced from $T = 400$. The relationships of N and n to T are as follows.

- (1) $T = N(n + 1)$. $N = 200$, $n = 1$.
- (2) $T = N(n + 2)$. $n = 3$, $N = 80$.
- (3) $T = Nn$. $n = 5$, $N = 80$.
- (4) $T = Nn$. $N = 20$, $n = 20$.

In the case of (1) and (2) the number of individuals measured per family is the number of

offspring, n , plus one parent in (1) and two parents in (2).

Equation [10.6] gives the sampling variance of the regression in (1) and (2), and [10.10] gives the sampling variance of the correlation in (3) and (4). In cases (1) and (4), however, the designs are optimal and there is a shorter way of getting the standard error of the heritability.

- (1) The design is optimal because $n = 1$. With one parent measured ($k = 1$), [10.6] reduces to the s.e. of h^2 given in [10.7].

$$\text{s.e.}(h^2) = 2/\sqrt{200} = 0.14$$

- (2) $k = 2$; $t = \frac{1}{2} h^2 = 0.3$ (neglecting dominance); $N = 80$; $n = 3$.

$$\sigma_b^2 = \frac{2[1+(2 \times 0.3)]}{3 \times 80} = 0.0133$$

$$\sigma_b = 0.115$$

The heritability is estimated by b , so

$$\text{s.e.}(h^2) = \sigma_b = 0.115$$

(Note: The approximation here is not very good. The exact formula gives $\sigma_b^2 = 0.0091$; $\text{s.e.}(h^2) = 0.095$.)

- (3) $t = \frac{1}{2} h^2 = 0.2$ (neglecting dominance); $N = 80$; $n = 5$.

$$\sigma_t^2 = \frac{2[1+(4 \times 0.2)]^2(0.8)^2}{5 \times 4 \times 79} = 0.00262$$

$$\sigma_t = 0.051$$

h^2 is estimated as $2t$, so

$$\text{s.e.}(h^2) = 2\sigma_t = 0.10$$

- (4) $N = 20$; $n = 20$.

This is the optimal design for half sibs because $n = 4/h^2$, and the sampling variance of the heritability is given approximately by [10.13].

$$\begin{aligned}\sigma_{h^2}^2 &= (32 \times 0.2)/400 = 0.0160 \\ \text{s.e.}(h^2) &= 0.13\end{aligned}$$

The exact formula, [10.10], gives $\text{s.e.}(h^2) = 0.12$.

139 (20.3) All that is needed before plotting the graph is to convert mortality to survival and, perhaps, to express birth weights as deviations from the mean in standard deviation units. For example

<i>Birth weight (kg)</i>	<i>Deviation in σ</i>	<i>Survival (%)</i>
1.3	-4.24	38.8
1.8	-3.25	66.7
etc.		

Note the flat-topped nature of the curve: 97 per cent of babies have survival probabilities within the narrow range of 97 to 99 per cent. The data give no grounds for believing that small babies die because they are small; they may be small because they have some other disability from which they die.

140 (19.11) The calculation follows that of Problem 19.8. The variance of the index, by [9.18], is

$$\sigma_I^2 = (6.578 \times 3.3428) + (-2.084 \times 2.2108) = 17.3816$$

$$\sigma_I = 4.169$$

The intensity of selection was found in Problem 19.3 to be $i = 1.5775$. Therefore the expected response to selection for the index is

$$R_I = 1.5775 \times 4.169$$

$$= 6.58$$

The predicted improvement in economic value is 6.58 cents per bird per generation.

When selection is made for growth alone, growth will increase as a direct response, giving an economic gain, and food consumption will increase as a correlated response, giving an economic loss. The responses were calculated in Problem 19.3. Converted to 100 g units the direct response of growth is +0.911 and the correlated response of food consumption is +1.268. The economic gain is therefore

From growth:	0.911×8	= 7.29 cents
From food consumption:	$1.268 \times (-2)$	= <u>-2.54 cents</u>
Net economic gain		<u>4.75 cents</u>

The relative effectiveness of the index for improving economic value is thus $6.58/4.75 = 1.39$. The index would be 39 per cent better.

141 (21.1) The difference between the parental lines is the effect of the whole of Chromosome 3; the difference for Interval 1 is the homozygous effect of any QTL in the interval. The differences are as follows:

	<i>Abdominal bristles</i>	<i>Sternopleural bristles</i>
Whole chromosome	13.7	4.6
Interval 1	2.4	2.8
% of whole chromosome	17.5%	60.9%

To test the significance of each difference, calculate its standard error and then t as follows.

	<i>Abdominal bristles</i>	<i>Sternopleural bristles</i>
$\sigma_d^2 = \frac{SS_H + SS_L}{n_H + n_L - 2} \times \frac{n_H + n_L}{n_H n_L}$	$\frac{651.8}{42} \times \frac{44}{403}$	$\frac{28.6}{42} \times \frac{44}{403}$
	= 1.694	= 0.074
σ_d	1.30	0.272
$t = d/\sigma_d$	1.85	10.3
$d.f. = n_H + n_L - 2$	42	42
	$P \sim 0.07$	$P < 0.001$

The presence of a QTL affecting sternopleural bristles is proved, but the effect on abdominal bristles is not significant at the 0.05 level, though nearly so. (A more sensitive test applied in the paper proved the abdominal bristle effect to be highly significant.) The very high variance of abdominal bristle number within marker classes is due to segregation of QTLs on the rest of the chromosome. The much lower variance of sternopleural bristle number was probably due to the QTL alleles that affect only sternopleural bristles being in dispersion, as would be expected from a correlated response.

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Index

Characters are indexed under the relevant organism

- Adaptive value, 25
- Additive
 - combination of loci, 111
 - gene action, 118
 - variance, 123, 125, 154
- Association, loci in, 360
- Assortative mating, 19, 174, 179
- Asymmetry of selection response, 211, 294
- Average effect, 112, 117
- Backcrosses, *see* Crosses
- Base population, *see* Population
- Bean (*Phaseolus*), 363
- BLUP, 244, 328
- Bottle-neck, 77
- Breeding value, 114, 154
- Bulmer effect, 201
- Canalization, 345
- Carriers, frequency of 9
- Cats, 15
- Cattle 138, 142, 162, 248, 314, 357
- Clines, 44
- Coadaptation, 260
- Coancestry, 85, 273
- Coefficient
 - of consanguinity, 85
 - of inbreeding, 58, 71
 - of kinship, 85
 - of relationship, 153
 - of selection, 26
- Coheritability, 317
- Combining ability 274
 - estimation of, 276
 - selection for, 283
- Competition, 157
- Competitive index, 337
- Components
 - of fitness, 335
 - of variance, *see* Variance
- Consanguinity, coefficient of, 85
- Continuous variation, 100
- Controls, 195, 210
- Corn, *see* Maize
- Correlation
 - between characters, 104, 312
 - genetic, 312
 - changes of, 318, 332, 344
 - estimation of, 315, 317
 - examples of, 314
 - and G × E interaction, 221
 - and repeatability, 315
 - between genotype and environment, 131
 - between mates, 174
 - between relatives, 145, *see also*
 - Covariance
 - environmental, 155
 - genetic, 146
 - phenotypic, 157
 - 'theoretical', 153, 163
 - between repeated measurements, 137
 - intraclass, 145–6
- Covariance
 - of gene effects, 130
 - of relatives
 - full sibs, 151
 - general, 152
 - half sibs, 151
 - offspring-parent, 147–50
 - twins, 152, 171
 - with assortative mating, 174–7
 - . with epistasis, 154
- Crossbreeding in animals, 285
- Crosses
 - diallel, 276–8
 - heterosis in
 - backcrosses, 284
 - F1, F2, 254–9
 - wide crosses, 260

- 3-way, 4-way, 284
- inbreeding coefficient after backcrosses, 91
 - 2-way, 4-way, 92
- uniformity, 269, 282
- variance
 - genetic, 272
 - environmental, 267–8
- Degree of genetic determination, 123
- Developmental variation, 135, 268
- Deviation
 - dominance, 116
 - environmental, 108
 - interaction (epistatic), 119
- Diallels, 276–8
- Discontinuous variation, 299
- Dispersion, loci in, 360
- Dispersive process, 48
- Dogs, 217
- Dominance
 - degree of 26, 109, 373
 - deviation, 116
 - directional, 250
 - overdominance, 26, *see also Overdominance*
 - variance, 125
- Drift, *see* Random drift
- Drosophila melanogaster*
 - abdominal bristles
 - components of variance, 129
 - fitness relationship, 348
 - frequency distributions, 103, 221
 - heritability, 162, 164
 - mutation, 222
 - number of loci, 104, 371
 - random drift, 265
 - repeatability, 138–41
 - responses to selection, 187, 189, 216, 218, 221
 - bar-eye facet number, 103
 - effective population size, 69
 - egg number, 129, 162
 - genetic assimilation, 309
 - genetic correlations, 314, 318
 - inbreeding depression, 248
 - lethal genes, 30–2, 225
 - ovary size, 129, 139, 162
 - random drift, 53
 - sternopleural bristles, fitness relationship, 348
- mutation, 222
- QTLs, 103–4, 366, 371, 373
- stabilizing selection, 346
- thorax length, 124, 129, 217–8
- transposable elements, 350
- wing length, 164–5, 268, 318
- Drosophila subobscura*, 251
- Effective factors, 225
- Effective population size, 65
 - ratio of, to actual, 68
- Environment, *see also* Variance
 - common, 155
 - general, 137
 - heterogeneous, 44
 - selection in different, 321–3
 - special, 137
- Environmental sensitivity, 133, 345
 - and selection, 324, 345
- Epistasis, *see* Interaction (epistatic)
- Equilibrium
 - Hardy–Weinberg, 5
 - with assortative mating, 175–6
 - with mutation and selection, 34, 351
 - with natural selection, 342
 - with selection for heterozygotes, 38
- Eugenics, 33
- Family size
 - and heritability estimates, 178–81
 - and inbreeding, 67
 - and selection, 233
- Fisher's fundamental theorem, 339
- Fitness, 25, 335
 - components of, 41, 335
 - of genotypes, 26
 - measurement of, 337
 - 'profiles', 338
 - relative, 26, 335, 339
 - response to selection, 339
- Fixation, 54
 - by close inbreeding, 90
 - with selection, 218
- Founder effect, 78
- Gametes
 - from inbred lines, 93, 272
 - random union, 7
- Gametic phase disequilibrium, 16, 130
 - by selection, 202
 - and overdominance, 41

- Gene frequency, 2
 change of, 4, 23, 199
 distributions of, 53, 75, 77
 variance of, 51, 61, 70
- Gene substitution
 average effect of, 113
 by neutral mutation, 73
- Generation interval, 192
- Generations
 number required, 32
 overlapping, 69, 192
- Genetic assimilation, 309
- Genetic deaths, 34
- Genetic variation, nature of, 3
- Genotype–environment
 correlation, 131
 interaction, 132, 321
- Genotype frequencies, 1
 with inbreeding, 56, 61
 with random mating, 5, 8
 within lines, 62
- Genotypic value, 108, 118
- Hardy–Weinberg law, 5, 11
 test of, 10, 39
 uses of, 9
- Heritability ('broad sense'), 123, 172
- Heritability ('narrow sense'), 123, 160
 with assortative mating, 176
 estimation
 from human data, 171
 from relatives, 163
 from selection, 197, 208–11
 precision, 177
 examples of, 162
 of family means, 232–5
 after inbreeding, 266
 realized, 197
 sampling variance of, 210
- of threshold characters, 301
- of within family deviations, 232–5
- Heterosis, 253, *see also* Crosses
 causes of, 254–7
 examples of, 258
 uses of, 281
- Heterozygosity, 42
- Heterozygote advantage, *see*
 Overdominance
- Heterozygotes, frequency of
 with inbreeding, 56, 62
 with random mating, 8–10
- Homeostasis
 developmental, 268
 genetic, 343
- Hybrids, *see* Crosses
- Hybrid vigour, *see* Heterosis
- Idealized population, 49
- Identical by descent (alleles), 58
- Inbred strains, 252, 269
 experimental use, 269
 sub-line differentiation, 271
 uniformity, 269
- Inbreeding
 coefficient of, 58, 82
 with close inbreeding, 88
 from heterozygosity, 62
 in pedigrees, 82
 close (regular systems), 88
 computations exemplified, 70–2
 depression, 247
 examples of, 248
 in selection responses, 212
 minimal, 69
 mixed with crossing, 93
 rate of, 60, 65
 variances affected
 genetic, 264
 environmental, 267
- Index for selection
 with values of relatives, 240
 with correlated characters, 325
- Intensity of selection, *see* Selection
- Interaction
 between loci (epistatic), 119, 373
 and covariances of relatives, 154
 and heterosis, 257–8, 275, 285–6
 and inbreeding, 250
 and scale 294
 deviation, 119
 genotype × environment, 132, 321
 and selection, 324
- Island model, 75
- Isolation by distance, 75
- Liability, 299
- heritability of, 301
- relation to incidence, table of, 379
- selection for, 308
- Life-history traits, 343
- Limits, *see under* Selection

- Line, 49
Linkage
 and backcrossing, 92
 and correlation
 between characters, 312
 between relatives, 155
 disequilibrium, *see* Gametic phase
 disequilibrium
 and effective factors, 225
 and overdominance, 41
 and stabilizing selection, 345
Load, 34, 36, 38
Logarithmic transformation, 103, 291–4
Maize
 combining ability, 276, 283
 diallel cross, 276
 inbred vs hybrid variability, 268
 inbreeding depression, 248, 251
 QTLs, 370, 372
 responses to selection, 216, 223, 283
 wide crosses, 260–1
Man
 albinism, 33
 birth weight, 136
 blood groups, 1, 2, 10, 13
 diabetes, 372
 diseases, 303
 dwarfism, 35
 finger ridges, 173, 348
 immunoglobulins, 162, 314
 IQ, 131, 173, 248, 340–1
 PKU, 9
 sickle-cell anaemia, 39
 stature (height), 162, 173, 248
 twins, 171
Mapping, 359
Marker loci, 359–60
Maternal effects, 134
 and correlations of relatives, 156
 and crossing, 259
 and inbreeding, 250–2
 and selection response, 199, 212
Mating
 assortative, 19, 174, 179
 frequencies of types, 12
 non-random, 19
 random, 5
Merit, in index selection, 326, 327
Metric character, 100
Migration, 23, 73
Mouse
 body weight
 and fitness, 196–7, 346
 heritability, 162, 165–6
 inbreeding depression, 248
 maternal effect, 156, 199, 212
 repeatability, 138
 responses to selection, 194–8, 209,
 217, 218, 320, 329
 variance components, 169
 variance and scale, 292
 fitness components, 336
 generation interval, 193
 genetic correlations, 314, 324
 growth, 103, 324, 357
 inbred vs hybrid variability, 268
 inbreeding calculations, 70–2
 litter size
 distribution, 103
 heritability, 162
 heterosis, 254
 inbreeding depression, 248, 251
 repeatability, 138
 response to selection, 199, 218
 nursing ability, 320
 pigment granules, 111, 119
 pygmy gene
 under selection, 224
 as test of scale, 295
 values (weight), 109, 111, 114, 295
 variances, 127
 sub-line divergence, 272
 tail length, 156, 162, 314, 329
 vertebra number, 306
Multiple alleles, 13, 115
Multiple measurements, *see*
 Repeatability
Mutation
 balanced by selection, 34, 351
 change of gene frequency, 24
 and inbreeding, 72, 96
 neutral, 45, 78, 269, 351
 non-recurrent, 24, 72
 and origin of variation, 269, 348
 rate of, 25
 recurrent, 24, 73
Natural selection, 335
 response to, 339

- strength of, 345
- Neighbourhood model, 75
- Neutral theory, 78
- Nicotiana*, 133, 258
- Non-additive
 - combination of genes, 119
 - variance, 128–9
- Overdominance, 26
 - causes of, 40
 - and gene frequency, 38
 - and heterosis, 287
 - and inbreeding, 96, 253
 - marginal, 41
 - and natural selection, 347
 - and polymorphism, 43
 - and selection limits, 224
- Panmictic index, 60
- Panmixia, 5
- Pedigrees and inbreeding, 82
- Pigs, 162, 168, 248, 303, 314, 357
- Pleiotropy, 41, 312
- Polycross, 276
- Polygenes, polygenic, 102
- Polymorphism, 42, 78
- Population
 - base-, 49, 58, 94–5
 - effective size, 65
 - mean, 108
 - pedigreed, 82
 - size, 4, 51
 - structured, 94
 - subdivided, 49–50
 - synthetic, 284
- Poultry, 162, 287, 314, 357
- Prediction
 - of cross performance, 274, 277–8, 284–5
 - of future performance, 142
 - of response to selection, 187, 232, 328
- Premisses, xvi
- Progeny test, 321
- Quantitative character, 100
- Quantitative trait loci (QTLs), 103, 356
 - major genes, 356
 - mapping, 359
- Quantitative variation, genes causing, 356, 375
- Random drift, 48
 - in natural populations, 76
- in selection responses, 209
- Random mating, 5
- Range, 110, 216
- Rats, 41, 268, 294
- Reaction norm, 133
- Recombinant lines, 288, 368
- Regression, offspring on parents, 146–50
- Relatives, resemblance of, *see*
 - Correlation
- REML, 171, 198, 244
- Repeatability, 136
 - clonal, 125
 - examples of, 138
- Response, *see* Selection
- Scale
 - effects, 290
 - transformations, 102–3, 290, 304
 - underlying, 299
- Selection
 - accuracy of, 243
 - antagonistic, 324
 - change of gene frequency by, 27, 38, 199
 - coefficient of, 26, 199
 - combined, 235
 - differential, 185
 - correlated, 313, 340
 - effective (realized), 196–7, 224
 - weighted, 196, 339
 - disruptive, 347
 - divergent, 195
 - effects on
 - genetic correlations, 332, 344
 - heritability estimation, 181
 - inbreeding depression, 252
 - random drift, 75
 - variance, 201, 221, 292, 345
 - family, 230
 - frequency-dependent, 43
 - gradient, 341
 - index, 240, 325
 - indirect, 319
 - individual, 230
 - intensity of, 189
 - relation to coefficient of, 200
 - tables of, 379–80
 - limits, 215
 - causes of, 223
 - theory of, 218

- mass, 230
- multiple-trait, 325, 327
- natural, 197, 224, 335
- reciprocal-recurrent, 286
- response, 185
 - asymmetry, 211, 294
 - correlated, 317, 340
 - duration (half life), 216
 - measurement, 194
 - to natural selection, 339
 - prediction, 187, 232
 - repeatability, 208
 - total, 215–6
- sib, 231, 234
- stabilizing, 345, 352
- strength of, 341
- synergistic, 324
- tandem, 325
- truncation, 188
- within-family, 232
- Selective value, 25
- Self-fertilization, 66, 88
- Self-fertilizing plants, 288
- Sex-linked genes, 13, 89
- Sheep, 138, 248, 286, 357
- Sib-analysis, 166
- Standardized effect, 201, 218, 225, 371
- Systematic processes, 23
 - in small populations, 72
- Threshold, 299
 - characters, 299
 - heritability of, 301
 - selection for, 308
 - unit, 305
- Tobacco (*Nicotiana*), 133, 258
- Tomatoes, 258, 372, 374
- Top-cross, 276
- Transformation of scale, 290
- Tribolium*, 52, 223
- True mean, 145
- Twins, 171
- Uniformity
 - in inbred lines, 269
 - in hybrids, 268
- Value
 - breeding, 114
 - economic, 327
 - genotypic, 108
 - phenotypic, 108
- Variable, underlying, 299
- Variance
 - components, 122
 - additive, 125
 - causal, 145, 167
 - environmental, 134, 155
 - epistatic (interaction), 129
 - disequilibrium, 130
 - dominance, 125
 - genotypic, 123, 126
 - mutational, 269, 349
 - observational, 145, 166, 233
 - of family size, 67
 - of gene frequency, 51, 71
 - of observed family-means, 233–4
 - partitioning, 122
 - methods summarized, 143
 - in crosses, 272
 - with inbreeding, 264
- Weighting
 - in heritability estimation, 179
 - selection differential, 196, 339
- Wright's *F*-statistics, 96
- Zygotes, 7

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