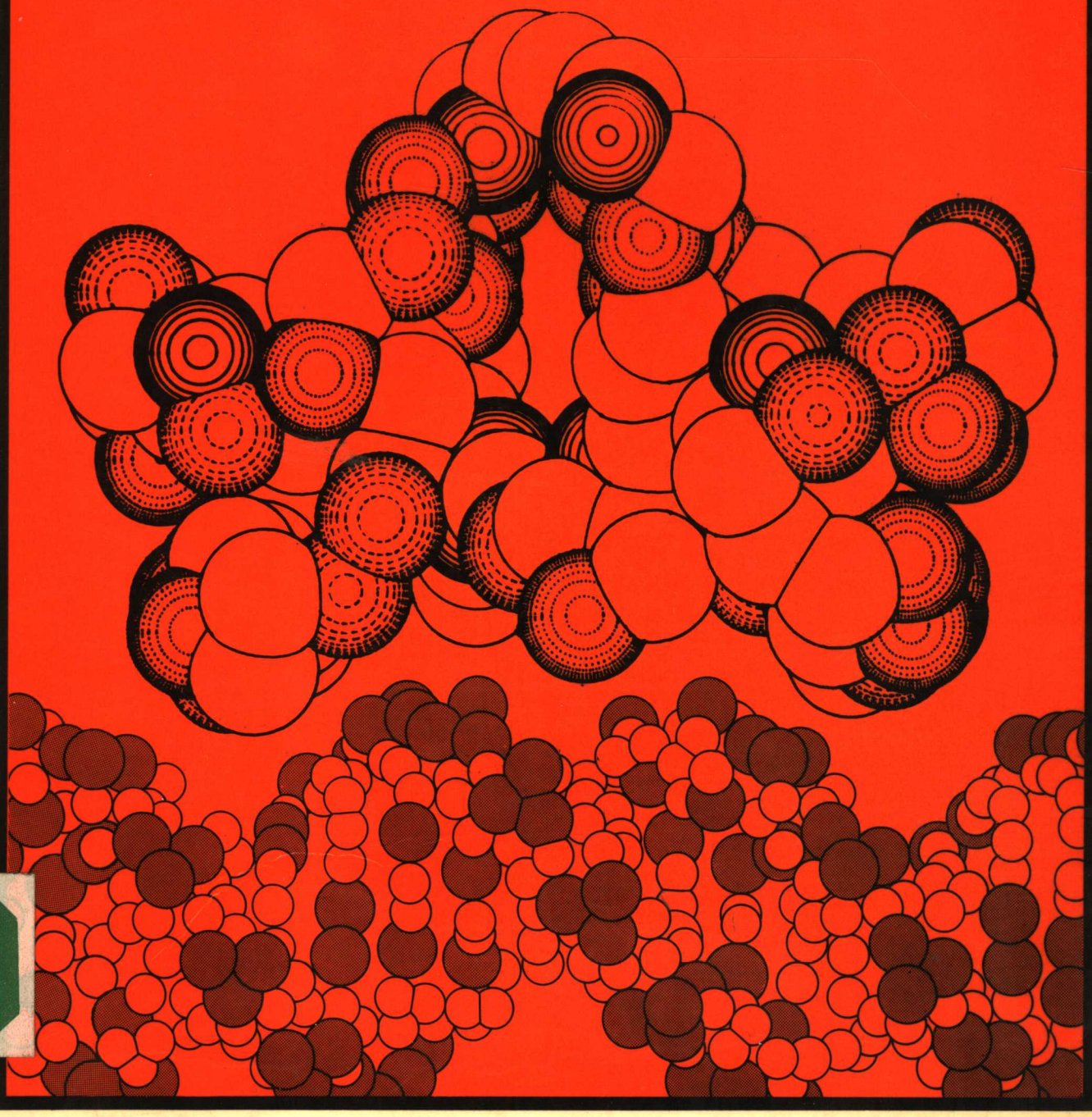
GENETIC MECHANISMS

M. R. INGLE



STUDIES IN ADVANCED BIOLOGY 2

GENETIC MECHANISMS

M. R. INGLE
B.Sc., Ph.D.
Head of Biology, Moreton Hall School,
Oswestry, Shropshire

BASIL BLACKWELL

PREFACE

Most students have access to a general text which provides the framework on which their course is constructed. This series builds on that framework by examining defined areas of the syllabus more closely. It looks especially at those parts of the subject which have recently undergone the most change, and brings together new concepts which are presently widely scattered throughout the available literature. In doing so, it tries to avoid simply substituting new dogmatic assertions for old, and to show how today's concepts have evolved from previous ones.

Whilst it was tempting to follow the vagaries of fashion and adopt a non-historical approach to genetics, it was felt that this would make the volume less useful as an accompaniment to most standard texts. To avoid merely repeating what has already been said so well before, familiar territory is covered by a mix of structured questions and, I hope, less familiar perspectives. Where alternative reading material is at present more difficult to find, a fuller explanation is given. Some aspects of a subject as large as genetics inevitably fall outside the main thrust of the book. The reader must not interpret their omission to mean that they are unimportant; some of the extension projects are designed to allow the student to cover these areas from other sources.

In keeping with the direction the subject has taken, a quantitative and biochemical treatment is used where appropriate. Key words are highlighted in bold type and a glossary is provided to avoid interrupting the text with too many asides.

MRI
1986

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Contents

Part I Classical Genetics

1

Mendel and the Theory of Particulate Inheritance

SUMMARY

The work of Gregor Mendel (1866) suggests that inherited characteristics are determined by discrete (distinct) factors. These pass unaltered from one generation to the next even if the environment modifies the expression of the characteristics.

1.1 MENDELISM

The relationships between the inheritance of characteristics, chromosomal behaviour, and gene action are now so well established that it is easy to be wise after the event. It is simple to forget that Mendel drew major conclusions about inheritance some thirty-four years before meiosis was first described (von Winiwarter, 1900), thirty-seven years before any relationship between inheritance and chromosomes was suggested (Sutton, 1903), and seventy-five years before anyone knew what the inherited material did (Beadle and Tatum, 1941), or what it was made of (Avery, McLeod, and McCarty, 1944).

Mendel succeeded in revealing some of the basic features of inheritance where others before him had failed. His success was partly due to his choice of experimental material: peas are easy to grow, self-fertile and cross-fertile, and there are many constant varieties (Appendix II). Also he chose clearly distinguishable characters such as 'tall' and 'short' which are relatively unaffected by the environment. In addition, much of his success was undoubtedly due to his experimental procedure, the principal features of which are shown in Table 1.1.

1.1.1 The monohybrid experiments

A **monohybrid** is an individual produced by crossing **pure strains** differing by a single character, e.g. tall × short (character = height). After obtaining monohybrids, Mendel selfed them. Figure 1.1 illustrates one such cross and the explanation of it, while Table 1.2 lists the results of this and other crosses. Two features of these crosses were of outstanding importance.

(i) **The F_1 were always identical in appearance to**

Table 1.1 *Mendel's methodology*

Step	Comments
1 Cross-pollination of pure-breeding parents	**Pure breeding** means that the parents produce identical offspring *when selfed*. Using pure strains thus ensures that the offspring (F_1) receive inherited information from parents whose characteristics are *known*. Any difference between the F_1 and the parents (P) must therefore be due to cross-pollination. Mendel controlled pollination by removing unwanted anthers and covering the flowers with muslin bags to prevent the entry of bees. Cross-pollination was done by hand using a small paintbrush.
2 Recording the F_1	The characteristics of the F_1 were noted (see above).
3 Selfing the F_1	The F_1 were allowed to self-pollinate at random. The F_2 (second generation) therefore all received their inherited information from *one* source (the F_1).
4 Recording the F_2	A significant difference between Mendel's procedures and those of earlier workers was that he recorded the *number of each type* amongst the F_2.
5 Reciprocal crosses	To eliminate the possibility that the results could be explained by the source of the male gamete, Mendel performed step 1 in two ways: tall (pollen) × short (stigma), and tall (stigma) × short (pollen). No differences were observed: in marked contrast to some later experiments (see Chapters 2 and 3, sex linkage).

one parent. There were no mixtures, and no intermediate forms.

(ii) **There was always a mixture in the F_2, with one phenotype (form) being about three times as common as the other. The common phenotype always looked identical to the F_1.**

From these two observations several important conclusions can be drawn.

(i) Because the F_2 are a mixture of phenotypes (tall/short), and they all originate from an F_1 consisting of one phenotype (all tall), an inherited factor for 'short' must have been present but not expressed (i.e. it must have been masked) in the F_1. In modern terms the inherited factor governing the character (height) would be called a **gene**, and the possible forms in which it can occur (tall/short) would be called **alleles** of the gene. Mendel described the masked allele (short) in the F_1 as **recessive,** and the one which was expressed (tall) as **dominant**. If we let t = allele for short, and T = allele for tall, the simplest possible way of representing the F_1 genetically would be Tt. The genetic make-up of an organism, whatever its appearance, is called its **genotype**, i.e. F_1 genotype = Tt, even though F_1 **phenotype** = tall. Any organism which contains different alleles of a gene is called a **heterozygote**, whereas if the alleles are the same, it is called a **homozygote.**

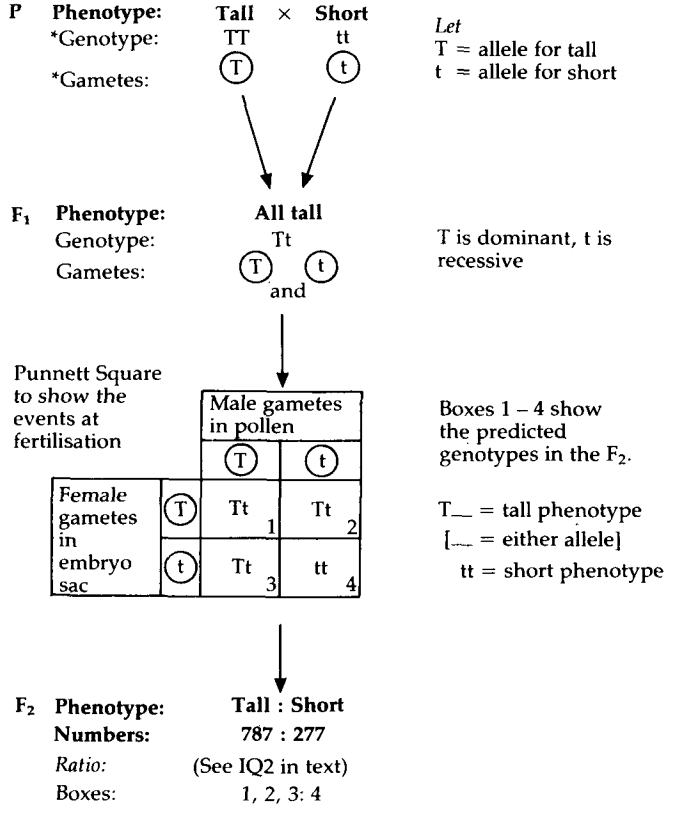


Fig. 1.1 *A worked example of monohybrid inheritance.* Observations are in **bold print**, deductions are in normal print, assumptions are in *italics*. The reader is strongly advised, when explaining genetics problems, to distinguish very clearly between what can be observed and what is deduced, for example, by underlining the former.
*In this and subsequent illustrations, 'genotype' refers to the genotype of the organism, and 'gametes' means the genotype of the gametes.

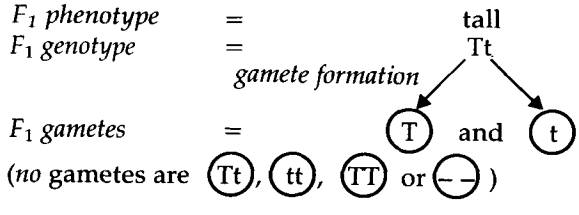
Q1 In Fig. 1.1. name:
(a) a heterozygote
(b) two different homozygotes.

(ii) Mendel then made a very important assumption – that the actual **numbers in the F_2** (Table 1.2) **reflect a simple underlying ratio.**

Q2 Work out the ratios (most common : least common) amongst the F_2 in Table 1.2. Thus for 787 : 277, divide both by the smaller of the two numbers. Round off each ratio to the nearest whole number.

Given that this assumption is reasonable (something we shall examine in a moment), it is now possible to explain the F_2 by making one further assumption, namely that:

(iii) **During gamete formation, one allele (but only one) of every gene will enter each gamete.** This statement is **Mendel's First Law**, or the **Law of Segregation**, and is summarised in the following diagram.



If this law is true, then selfing the F_1 produces an F_2 as indicated by the **Punnett Square** in Fig. 1.1.

Table 1.2 *Summary of Mendel's monohybrid experiments.* (Mendel also performed several other similar experiments, which all gave essentially similar results.)

Character	Parents		Monohybrid (F_1)	F_2 results	Number in F_2
	First	Second			
Stem height	Tall	Short	All tall	Tall : Short	787 : 277
Seed shape	Round	Wrinkled	All round	Round : Wrinkled	5474 : 1850
Seed colour	Yellow	Green	All yellow	Yellow : Green	6022 : 2001

Q3 Use Mendel's Law and work backwards from the F_1 to explain why the genotypes of the parents are as given in Fig. 1.1.

Q4 *Drosophila melanogaster* is a small fruit fly often used in genetics experiments. A fly with a grey body was crossed to one with a dark body to produce an F_1. The F_1 were allowed to interbreed to produce the following F_2:

	Males	Females
Grey bodies	37	42
Dark bodies	13	12

Construct a flow diagram like Fig. 1.1 and explain how body colour is inherited in *Drosophila*. Predict what the phenotype of the F_1 must have been.

1.1.2 The dihybrid experiments

A **dihybrid** is an individual produced by crossing pure strains differing by two characteristics, e.g. yellow/green, round/wrinkled (two characteristics = colour and shape). One such experiment is shown in Fig. 1.2. In the F_2 all combinations of colour and shape are observed, with the four categories of offspring falling into a 9 : 3 : 3 : 1 ratio. Questions 5–8 lead to an explanation of the result.

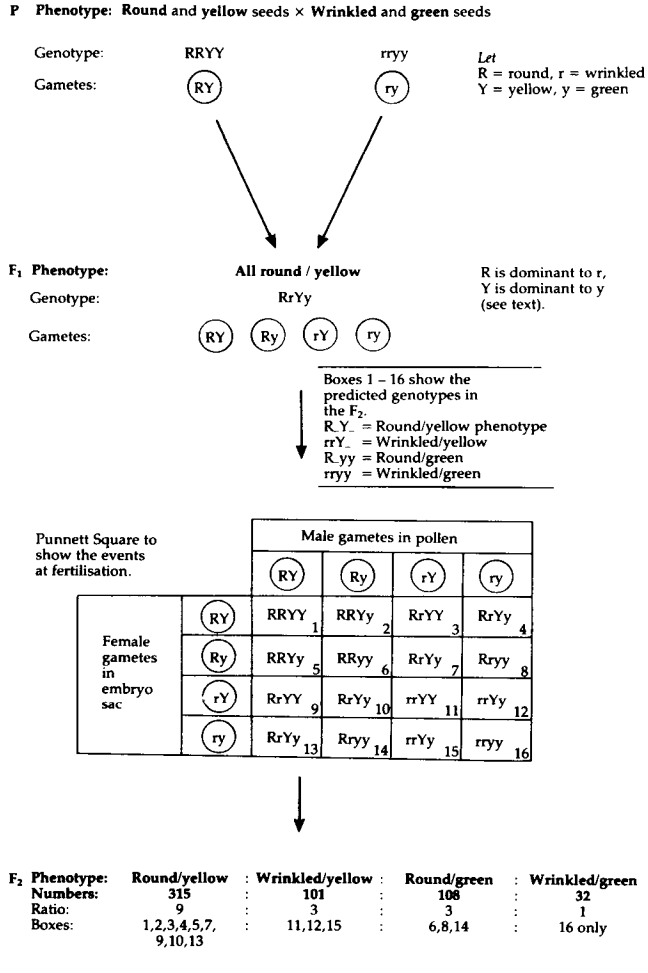


Fig. 1.2 *A worked example of dihybrid inheritance.*

Consider just one characteristic at a time.

Q5 Ignore shape completely. What is the colour of the F_1? Which colour allele is dominant?

Q6 Still ignoring shape, what is the ratio of yellow : green in the F_2?

Q7 Now consider shape and ignore colour. What is the shape of the F_1? Which shape allele is dominant?

Q8 Still ignoring colour, what is the ratio of round : wrinkled in the F_2?

For each character on its own, we clearly have 3 : 1 ratios, but taking the characters together we have a 9 : 3 : 3 : 1 ratio. Now 9 : 3 : 3 : 1 = $(3 : 1)^2$ or (3 : 1) × (3 : 1) and according to the mathematical rules of probability (Section 1.2) this means that each character is behaving **independently** of the other. This independent behaviour of two characters has been called **Mendel's Second Law**, or the **Law of Independent Assortment** (defined below). Let us examine Fig. 1.2.

(i) Since the parents are pure strains for both colour and shape, they must be homozygous:
Parent phenotype: Round/Yellow × Wrinkled/Green
Parent genotype: RR YY rr yy
where R = round; r = wrinkled; Y = yellow; y = green.
(R and Y are clearly dominant: compare the shape and colour of the F_1 to that of the parents.)

(ii) Since one allele of each gene is present in *every* gamete (Mendel's First Law), the parental gametes can be represented thus:
Parent gametes: (RY) (ry)

Q9 Could gametes like (R), (Y), (r), (y), (Ry), or (rY) possibly arise from *these* parents? Explain.

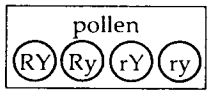
(iii) Given these parental gametes and cross-fertilisation, all the F_1 must be heterozygotes, RrYy.
F_1 genotype: RrYy
A 3 : 1 ratio is produced because *equal numbers* of gametes with contrasting alleles ((T) and (t)) are produced. Since 9 : 3 : 3 : 1 = (3 : 1) × (3 : 1), once again all possible types of gametes must be produced *equally often:*
F_1 gametes: (RY) (Ry) (rY) (ry)
The crux of Mendel's Second Law is therefore that

either allele of one gene has an equal chance of combining with either allele from a second gene. This is not, however, the only requirement for a 9 : 3 : 3 : 1 ratio.

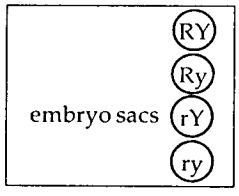
1.1.3 The demands of ratios

Ratios like 3 : 1 and 9 : 3 : 3 : 1 can only be expected if specific conditions are met. For example, in Fig. 1.2

the line



and the row



imply that there is an equal chance of every possible male gamete combining with every possible female gamete. A full list of preconditions for 3 : 1 and 9 : 3 : 3 : 1 ratios is given in Table 1.3. In practice, these requirements may not be fulfilled completely, and consequently deviations from 3 : 1 and 9 : 3 : 3 : 1 ratios are common. Some examples are shown in Table 1.4 and will be examined later. Given the number of preconditions, it is rather odd that no

Table 1.3 *Requirements for a (3 : 1)^n ratio*

1	The characters must be governed by **distinct genes** with distinct alleles, such as A and a (where A/a = alleles of a gene governing *one* character).
2	The generation producing the ratio must be **heterozygous**, i.e. Tt(3 : 1), or RrYy (9 : 3 : 3 : 1).
3	For each gene, one allele must be completely **dominant** over another, i.e. AaBb must have the same phenotype as, say, AABB.
4	Each gamete of the heterozygote must contain one allele of each gene (**Mendel's First Law**).
5	All possible gametes must be produced in equal numbers, i.e. genotype AaBb must yield AB, Ab, aB, and ab gametes equally often (**Mendel's Second Law**).
6	Fertilisation must be **random**, as implied by the Punnett Square. There must be no special tendency of, say, AB gametes to fuse with, say, ab gametes.
7	There must be an **equal chance of survival** amongst all the offspring.
8	There must be a **large number** of offspring. Obviously no ratio can be obtained if, in practice, there is only one offspring. (A ratio might nevertheless be *expected*: see text.)

Table 1.4 *Explanations of commonly-observed results.* Other results may be encountered which reflect **continuous variation** (e.g. intelligence), due to many genes each having small additive effects and/or environmental influences, **cytoplasmic inheritance**, **maternal effects**, and **incomplete penetrance**. (See Chapter 2EQ, and the Index.)

Observed result	Explanation of observed result	
	Parental genotype	Remarks
(i) 1 : 1	Het. × Rec. (Aa × aa)	A is dominant to a
(ii) 2 : 1	Het. × Het. (Aa × Aa)	A is dominant to a; AA dies (**lethal gene**): (Section 4.5.3)
(iii) 3 : 1	Het. × Het. (Aa × Aa)	*A* is dominant to a.
(iv) 1 : 2 : 1	Het. × Het. (Aa × Aa)	**Incomplete dominance** (Section 4.5.1)
All the above possibilities may arise in dihybrid crosses. The most common ones are shown below.		
(v) 9 : 3 : 3 : 1 $=(3:1)^2$	Double het. × Double het. (AaBb) (AaBb)	A is dominant to a, B to b
(vi) 3 : 3 : 1 : 1 $=(3:1)\times(1:1)$	Double het. × Single het. (AaBb) (Aabb)	as above
(vii) 1 : 1 : 1 : 1 $=(1:1)^2$	Double het. × Double rec. (AaBb) (aabb)	as above
Sometimes simple ratios may be obscured by a form of **gene interaction** called **epistasis** (Section 4.5.2). Two common examples are shown in (viii) and (ix).		
(viii) 9 : 7	As (v)	9 : (3 : 3 : 1), but three categories look identical
(ix) 9 : 3 : 4	As (v)	9 : 3: (3 : 1), but two categories look identical
(x) One sex shows one characteristic, the other sex shows a different or both characteristics.		see **sex linkage** (Section 2.2)
(xi) There are two or more categories of offspring, but no simple ratio, i.e. no permutation of (i)–(iv) above.		see **linkage** (Chapter 3)

results like points (ii), (iv), (viii), (ix), and (xi) in Table 1.4, were reported by Mendel. (He would not have been expected to observe (x) since peas are hermaphrodite.)

1.1.4 The test cross

A genotype cannot be seen. It is not possible to see that there is a mixture of TT and Tt in the F_2 (Fig. 1.1) because they all look the same (tall) due to the presence of at least one 'T'. The only thing of which we can be certain is that the tall F_2 = T_ where _ = t or T. It is, however, possible to deduce accurately the genotype of any individual by using a test cross. A **test cross** is a cross between a **homozygous recessive and a dominant *phenotype*** with the purpose of revealing the latter's genotype. Thus:

	Parent 1 homozygous recessive		*Parent 2* dominant phenotype **(tall)**
Genotype:	tt	×	T_ (_ is unknown)
Gametes:	(t)		(T) and (_)

At fertilisation:	*dominant phenotype (Parent 2)*	
	(T)	(_)
homozygous recessive (Parent 1) (t)	Tt	_t

The importance of using a homozygous recessive is now revealed. If all the offspring are tall, then _ =T, but if there is a 1 : 1 ratio of tall : short, then _ = t. We have no way of knowing in advance what result we shall get, but as soon as we see the result, we can accurately decide whether Parent 2 (the unknown) is TT or Tt.

Similarly in dihybrid crosses we can find the genotype of double dominants like round/yellow (R_ Y_) by test-crossing against double recessives.

	Parent 1 homozygous recessive		*Parent 2* double dominant phenotype (round/yellow)
Genotype:	rryy	×	R_Y_
Gametes:	(ry)		(RY) (R_) (_Y) (__)

At fertilisation:	*dominant phenotype (Parent 2)*			
	(RY)	(R_)	(_Y)	(__)
homozygous recessive (Parent 1) (ry)	RrYy	Rry_	r_Yy	r_y_

Q10 In this test cross, what would be the genotype of Parent 2 in each of the following cases?

Offspring produced from test cross

(i) all round/yellow
(ii) ½ round/yellow: ½ wrinkled/yellow
(iii) ½ round/yellow: ½ round/green
(iv) round/yellow: round/green: wrinkled/yellow: wrinkled/green in a 1 : 1 : 1 : 1 ratio.

1.2 PROBABILITY AND CHANCE

A Punnett Square like that shown in Fig. 1.1 does not mean that there will be three tall and one short offspring. It means that, on average, 75% of the offspring will be tall and 25% short. Clearly if offspring are only produced one at a time, as in many large mammals, it does not even mean that. In such cases it means that the chance of getting, say, a dominant phenotype is 75%. Similarly, in Fig. 1.2 the chance of getting rryy is 6·25% (1/16). The law of probability states that the chance of several independent events occurring together is $p_1 \times p_2 \ldots p_n$, where p_1, p_2, p_n are the chances of each occurring separately. Thus the chance of getting *two* rryy genotypes in Fig. 1.2, *and no others*, is 1/16 × 1/16 = 0·0039 (0·39%).

Q11 In a cross Rr × Rr (R is dominant) what are the chances of obtaining:
(i) A heterozygote, if only one offspring is produced?
(ii) Three heterozygotes, if only three offspring are produced?
(iii) One dominant phenotype and one recessive phenotype, if two offsprings are produced. (In this last question, note that they could be produced in *two* ways: dominant first/recessive second, or *vice versa*.)

Since we are talking in terms of chance, not certainty, this implies that 'real' results will not always correspond precisely with expected results. In a cross AaBb × AaBb, we might expect a 9 : 3 : 3 : 1 ratio, but in fact obtain:

Genotype:	A_B_	A_bb	aaB_	aabb	
Observed numbers:	55 :	15 :	25 :	5	(Total 100)
Expected ratio:	9 :	3 :	3 :	1	

Given 100 offspring, a perfect 9 : 3 : 3 : 1 ratio ought to give us:

Expected numbers	56.25	18.75	18.75	6.25	(Total 100)

(This example also highlights the fact that we may be expecting the impossible: 6¼ offspring may make sense mathematically, but it makes little sense biologically.) How far from a theoretically expected result can real results be, before we need to ask awkward questions about the theory? To answer this question the **χ^2 test** is applied. (χ^2 = chi squared, pronounced kai to rhyme with 'sky'; Gk.).

$$\chi^2 = \frac{\Sigma(O-E)^2}{E}$$

where O = Observed results
E = Expected results
Σ = 'the sum of'

This test involves three steps:

(i) *Forming the null hypothesis*
We have already done this. In the above example we have calculated the 'expected' numbers on the assumption that the observed numbers are 'really' in the ratio 9 : 3 : 3 : 1. We have therefore assumed that *there is **no** significant difference between the observed numbers and our expected ratio (9 : 3 : 3 : 1 in this example).*

(ii) *Calculating χ^2*

> **WARNING:** The χ^2 test can only be used if all *expected* numbers exceed 5. Since in this example our smallest 'expected' number is 6.25, we can use the test.

Using the above formula:

$$\chi^2 = \frac{(55-56.25)^2}{56.25} + \frac{(15-18.75)^2}{18.75} + \frac{(25-18.75)^2}{18.75} + \frac{(5-6.25)^2}{6.25}$$

$$\chi^2 = 3.11.$$

(iii) *Finding p (the probability) in the table of χ^2*
An abbreviated form of a table of χ^2 is given below (Table 1.5). It is used as follows:

(a) *Degrees of freedom (d.f.)*
It is necessary to look along the correct row of **degrees of freedom** to find out what $\chi^2 = 3.11$ means. Degrees of freedom (n) is calculated from the formula $(x-1)$, where x = number of categories. In our example there are four categories (9, 3, 3, 1) hence 4−1 = 3 d.f. In this example, therefore, we look along the *third* row until we come to a number that is close to 3.11 (see the horizontal arrow).

(b) *Probability (p)*
By looking up the column nearest to 3.11 (vertical arrow) we can see the likelihood (probability) of obtaining these observed results on the basis of chance. By common agreement, if $p \geq 0.05$ (5%) we accept the results as 'fitting' the ratio (we accept the null hypothesis). If $p < 0.05$ we assume that there *is* a significant difference between the observed results and the expected results (we reject the null hypothesis).

> **Q12** In our example, $\chi^2 = 3.11$ at 3 d.f. What is the value of p (convert to %)?
>
> **Q13** Should the null hypothesis be accepted or not? Explain your answer.

1.2.1 A cautionary tale

There are two rather peculiar features of Mendel's results which have caused a considerable amount of speculation.

(i) *Are the numbers too good to be true?*
If similar crosses are made a large number of times, then on average one would expect to obtain $p > 0.5$ in half of them, and $p < 0.5$ in the remaining 50%. Altogether Mendel presented the results of seven monohybrid crosses, of which three are shown in Table 1.2.

> **Q14** Calculate χ^2 for each of the three crosses shown in Table 1.2.
>
> **Q15** For the remaining crosses, $\chi^2 = 0.39$, 0.06, 0.45, and 0.36. What are the p values for all seven crosses? (When calculating n, remember that these are monohybrid crosses, so there are only *two* categories.)

In not one of the above results is $p < 0.5$ (50%), and taking all Mendel's results together, including the dihybrid crosses, the chances of getting such good figures are about 1 in 14 300!

Table 1.5 *An abbreviated table of χ^2.* The numbers in bold type are those which the reader is most likely to use in the application of χ^2 to genetics problems. (The use of the table and the significance of the arrows is described in the text.)

Degrees of freedom, n	Probability, P (to convert to %, multiply by 100)															
	0.99	0.98	0·95	0.90	0.80	0.75	0.70	0.50	0.30	0.25	0.20	0.10	**0.05**	0.02	0.01	0.001
1	0.00	0.00	0.004	0.016	0.064	0.10	0.15	0.45	1.07	1.32	1.64	2.71	**3.84**	5.41	6.64	10.83
2	0.02	0.04	0.10	0.21	0.45	0.58	0.71	1.39	2.41	2.77	3.22	4.61	**5.99**	7.82	9.21	13.82
→ 3	0.12	0.18	0.35	0.58	1.00	1.21	1.42	2.37	3.66	4.11	4.64	6.25	**7.82**	9.84	11.34	16.27
4	0.30	0.43	0.71	1.06	1.65	1.92	2.20	3.36	4.88	5.39	5.99	7.78	**9.49**	11.67	13.28	18.46

(ii) *$(3 : 1)^n$ is only one of several possible patterns of inheritance*

This fact was mentioned briefly in Section 1.1.3. Even if the reader is unfamiliar with **incomplete dominance, multiple-factor inheritance, lethal genes, epistasis,** and **linkage** (see Table 1.4 for cross references), the terms do at least indicate that there are many possible patterns of inheritance in addition to $(3 : 1)^n$.

Did Mendel (or an associate) bias the numbers, either deliberately or unconsciously? Did he stumble across other patterns of inheritance but, for whatever reason, either ignore them or fail to report them? Extensive research by scientific historians has produced no conclusive answers to either of these questions. Many of the original manuscripts were destroyed soon after Mendel's death, and the answers may never be known.

Despite these uncertainties, the principles of inheritance which Mendel established have been substantiated by countless experiments, and undoubtedly form the basis of modern genetics (Section 1.3). Whether or not Mendel was entirely honest is a different issue, and the two must not be confused.

1.3 THE THEORY OF PARTICULATE INHERITANCE

One of the most important features of Mendel's work is the implication that inherited characteristics are determined by discrete (distinct) structures or particles which are passed from one generation to the next without being affected by the environment. Each particle (gene) is represented twice in each somatic cell, but only once in a gamete (First Law). During gamete formation the gene may combine randomly with other particles (Second Law). This idea, **particulate inheritance**, diametrically opposed the popular nineteenth-century idea of blending inheritance. The latter proposed that inherited characters were strongly influenced by the environment, so that an organ which was well developed in an individual would be strongly inherited by its offspring. Blending inheritance also proposed that the inherited factors from each parent would blend together to produce not just an intermediate phenotype but an intermediate genotype.

Study guide

Vocabulary

Distinguish between the following pairs of terms:

allele and gene
genotype and phenotype
monohybrid and dihybrid
dominant and recessive
homozygote and heterozygote

Review Questions

1 In swallowtail butterflies the normal background wing colour is deep yellow. A rare form exists in which deep yellow is replaced by pale yellow. A female with deep yellow wings, captured from the wild, produced offspring with similar deep yellow markings. When these were allowed to breed amongst themselves, they produced an F_2 in which some butterflies had deep yellow and some had pale yellow wings. A single female from this F_2 with deep yellow wings was mated to a male with pale yellow markings, and produced an F_3 in which seven offspring had pale yellow wings and thirteen had deep yellow wings. Explain the genetics of these results, giving reasons for all the conclusions you draw. (*Modified from Oxford Local Examining Board.*)

2 A Jimson weed with white flowers and smooth pods (A), was crossed with two different plants, B and C, which had purple flowers and spiny pods. In the cross A × B, all the F_1 had purple flowers and spiny pods. In the cross A × C, the F_1 consisted of equal numbers of four different phenotypes, one of which D was crossed to the F_1 of the cross A × B. This final cross yielded purple/spiny: white/spiny: purple/smooth: white/smooth in the ratio 3 : 3 : 1 : 1. Find the genotypes of A, B, C and D, and explain the ratio in the last cross.

Extension Questions

1 An inbred barley plant, susceptible to mildew, was cross-pollinated with a homozygous mildew-resistant plant. The F_1, which were all mildew resistant, were allowed to self-pollinate, and the seeds were collected and sown to produce an F_2. 512 F_2 plants were grown but as there was no mildew attack that year, no observations could be made. The F_2 were allowed to self-pollinate to produce an F_3. Amongst the F_3, 586 were found to be susceptible to mildew, and 1014 were mildew resistant. Explain the genetics of this cross, and comment on its implications for agriculture and plant breeding. (*Modified from Oxford and Cambridge Examinining Board.*)

2 If n = 1 or 2, then $(3 : 1)^n$ produces a 3 : 1 or 9 : 3 : 3 : 1 ratio respectively. What ratio would be expected if n = 3?

2

The Chromosome Theory

SUMMARY

The chromosome theory asserts that Mendelian genes are located on chromosomes in the nucleus. (A few genes are not Mendelian, these are located in cytoplasmic structures like mitochondria, chloroplasts and plasmids.)

2.1 MEIOSIS AND MENDELISM

Sutton (1903) first drew attention to the close correspondence between the behaviour of Mendelian genes and the behaviour of chromosomes at meiosis and fertilisation (Table 2.1). He concluded that this correspondence provided at least circumstantial evidence that Mendelian genes were carried on chromosomes. Figure 2.1 illustrates this idea for an AaBb individual with just two pairs of homologous (similar) chromosomes. In this figure, the two genes A/a and B/b are on different (non-homologous) chromosomes. As we shall see later (Fig. 2.4) this need not necessarily be the case.

The critical features of Fig. 2.1 are as follows:

(i) If one allele is on one chromosome, the other allele of the same gene will be at the same position on the **homologous** chromosome.

(ii) During the preceding interphase each strand of each chromosome made a replica of itself. Consequently every allele is actually present twice, and hence prophase$_I$ is drawn as AAaaBBbb, although by convention the genotype is simply given as AaBb.

(iii) At metaphase$_I$ non-homologous chromosomes act independently (like genes), so that 50 per cent will be like (a) and 50 per cent will be like (b).

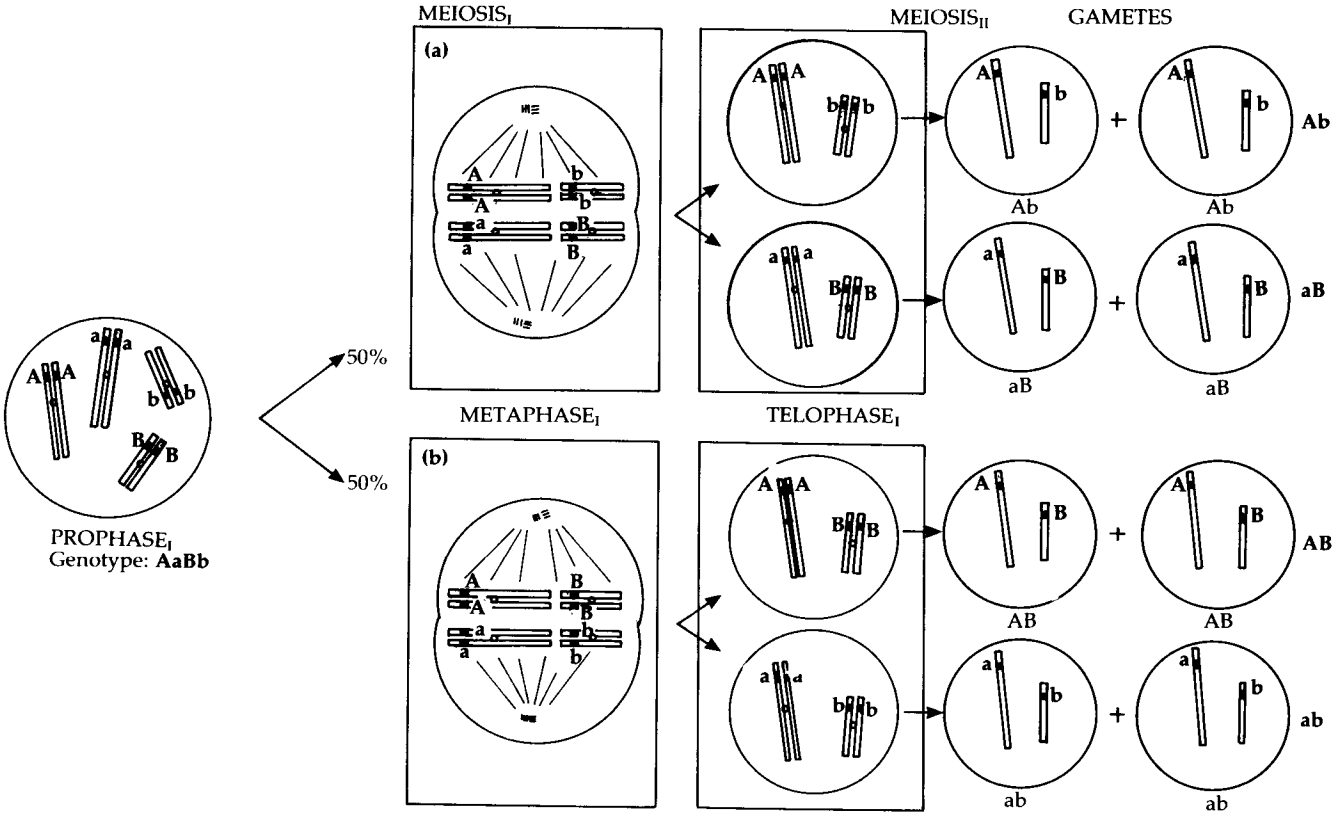


Fig. 2.1 *Meiosis and Mendelian genes.* The figure includes some details, such as the time of chromosome replication (preceding interphase), which were not known when Sutton proposed the chromosome theory. The illustrations are not the only possible arrangements of the genes and alleles (see text).

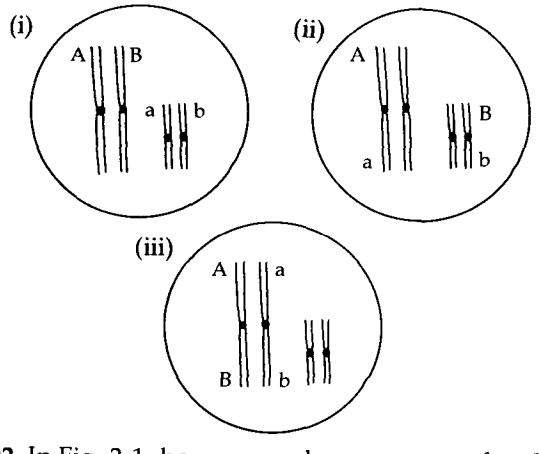
(iv) During anaphase$_I$ entire chromosomes move apart to form daughter cells as shown in telophase$_I$.
(v) During meiosis$_{II}$ the chromosomes split, so that each daughter cell receives single-stranded structures as shown in the gametes.

As a consequence of the combined effects of points (i) to (v), equal numbers of gametes AB, Ab, aB and ab will be produced, as required by Mendel's Second Law.

Table 2.1 *Correlation between Mendelian genes and events at meiosis and fertilisation* (Sutton, 1903). Items 5–7, not known at the time, further support the idea that genes are present on chromosomes.

1	Both chromosomes and Mendel's factors are paired in the organism.
2	Both separate during meiosis, so that there is only one chromosome and one allele of each type in a single gamete.
3	Non-homologous chromosomes and different (unlinked) genes segregate independently during meiosis.
4	Fertilisation restores both the number of genes and the number of chromosomes.
Later evidence:	
5	Sex linkage (Section 2.2).
6	Chemicals and radiations (mutagens) which alter the genes often cause chromosomal rearrangements (Chapter 5).
7	DNA, which is the genetic material, is largely confined to chromosomes (Chapter 5).

Q1 Two of the following diagrams are incorrect, whilst the third is possible but will not give rise to equal numbers of AB, Ab, aB, and ab gametes. Which is which? Explain your answer.



Q2 In Fig. 2.1, how many chromosomes of each type are present at the end of meiosis$_I$? Are these cells haploid or diploid?

2.2 SEX LINKAGE

More direct evidence associating Mendelian genes with chromosomes came with the observation (Wilson, 1905, and others) that the sex of various insects depended upon the chromosomes they inherited. A similar situation was found in other animals, such as humans, where males are XY and females are XX. X and Y are the symbols for chromosomes called the **sex chromosomes**; all other chromosomes are called **autosomes**.

Strictly Mendelian genetics requires pairs of alleles, and thus pairs of chromosomes. However, since the X and Y chromosomes do not carry the same genes, it follows that characters determined by genes on the sex chromosomes will not show the same pattern of inheritance as those determined by genes on the autosomes. Examples are shown in Figs 2.2 and 2.3. The unequal distribution of a character between the

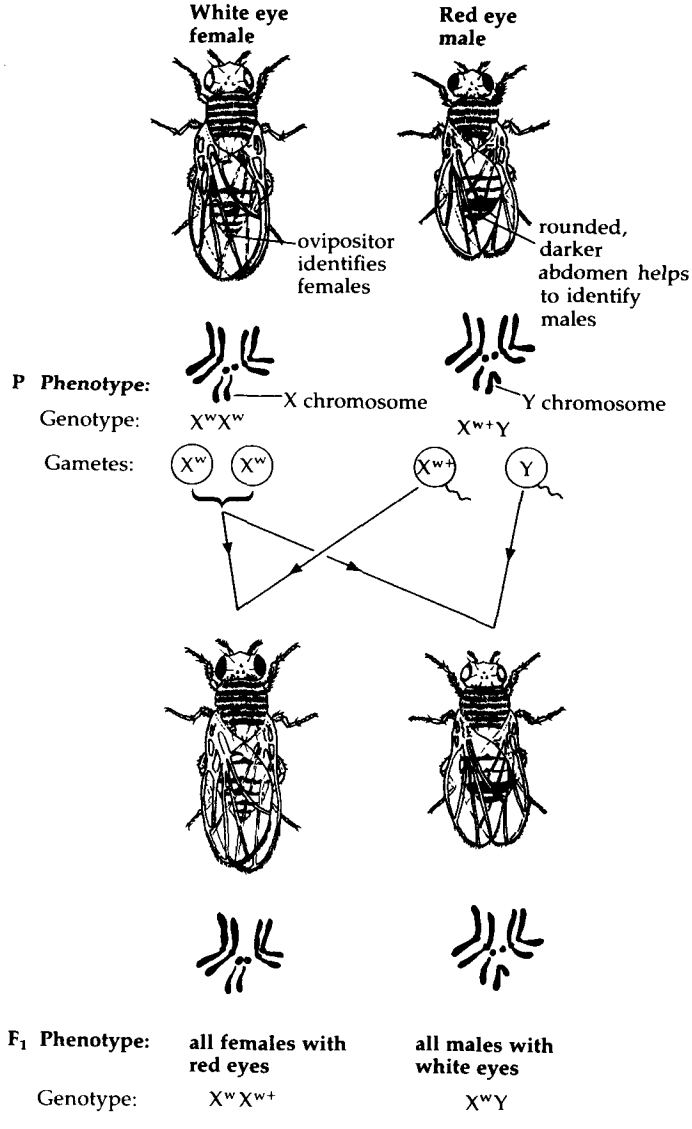


Fig. 2.2 *Inheritance of white eye in Drosophila melanogaster (from Morgan, 1910).* The pattern of inheritance suggests that the recessive allele, w (white eye), is carried on the X-chromosome. Most sex-linked genes are transmitted in this way: cases of inheritance transmitted through the Y chromosome are very rare.

sexes usually indicates that the gene involved is being transmitted by the sex chromosomes, a phenomenon called **sex-linkage**.

Given that the parents are pure strains, Fig. 2.2 shows a significant difference from Mendel's results in two ways:

(i) Both phenotypes (red and white eye) are expressed in the F_1.

(ii) All members of one sex show one colour; all members of the other sex show a different colour. As indicated in Fig. 2.2, this is best explained by assuming that the eye-colour gene is carried on the X chromosome.

Q3 Study Fig. 2.2. What results would be expected if the F_1 interbred? How would this differ from a strictly Mendelian (autosomal) cross?

Figure 2.2 is not intended to imply that in all cases of sex linkage differences between the sexes will appear in the F_1. They may appear in the F_2, and the actual result will depend on whether the **homogametic sex** (XX) or the **heterogametic sex** (XY) carries the recessive alleles. (To convince yourself, try RQ1.)

Q4 Red-green colour blindness and haemophilia are probably the best known examples of sex-linked human diseases, and show a pattern of inheritance exactly like that for white eye in *Drosophila*.

(i) By means of a flow chart (like Fig. 2.2) illustrate the genetics of the family inside the dotted line in Fig. 2.3.

(ii) Explain why the disease appears to have 'died out' in the British Royal family.

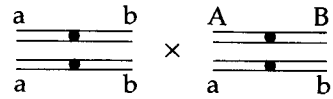
Sex determination

Figures 2.2 and 2.3 touch on something which has nothing to do with the chromosome theory of inheritance as such, but is nonetheless important. The sex chromosomes carry some genes, white eye in *Drosophila* for example, that may have nothing to do with sex determination. Conversely, some genes which have a marked influence on sexual development are carried on the autosomes. In humans, and probably all mammals, fertilised eggs will develop into females unless there is a Y chromosome present: they are said to be **constitutive females**. Thus XX = normal female; XXX (rare) = phenotypically normal female; XO (very rare; Turner's syndrome) = infertile female. It seems that soon after development begins the Y chromosome regulates the production of a hormone called the H-Y antigen. This hormone reprograms the 'presumptive ovaries', causing them to develop into testes instead. The testes subsequently produce at least two hormones which together prevent the embryonic tissues forming female structures, and promote development of the male apparatus. Not all animals show this pattern of sex determination (see the Extension Project).

2.3 OBJECTIONS

Whilst chromosomes seemed to be promising candidates for the location of Mendelian genes, even by 1903 it was clear that there were far more genes than chromosomes. Sutton argued that there must therefore be many genes on each chromosome. In such cases, a dihybrid AaBb could be illustrated as in Q1 (iii). In modern terminology, these genes would be described as **linked**, i.e. on the same or homologous chromosome.

Sutton's theory seemed to predict that in the cross



only two types of offspring ought to be produced (Fig. 2.4a). In practice, at least some offspring of all four classes were always produced (Fig. 2.4b), though not necessarily in a Mendelian ratio of 1 : 1 : 1 : 1. The recovery of all four phenotypes implied the production of all four types of gametes by the heterozygote (AB, aB, Ab, ab). De Vries (1903) argued that this could happen if **crossing-over** (Fig.

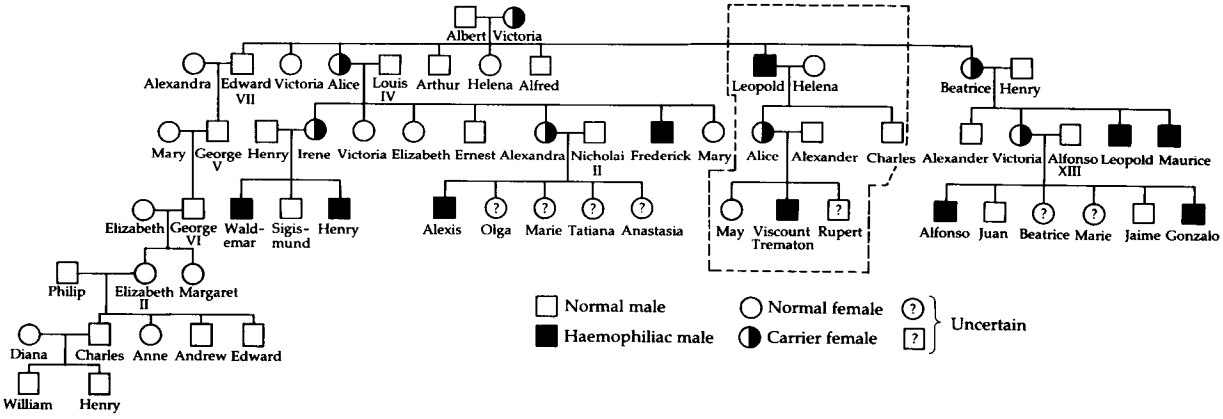


Fig. 2.3 *Inheritance of haemophilia in European royal families.* This disease is transmitted on the X chromosome. In both *Drosophila* and humans, sex linkage can almost always be attributed to the alleles carried on the X chromosome, and the Y chromosome can be virtually ignored.

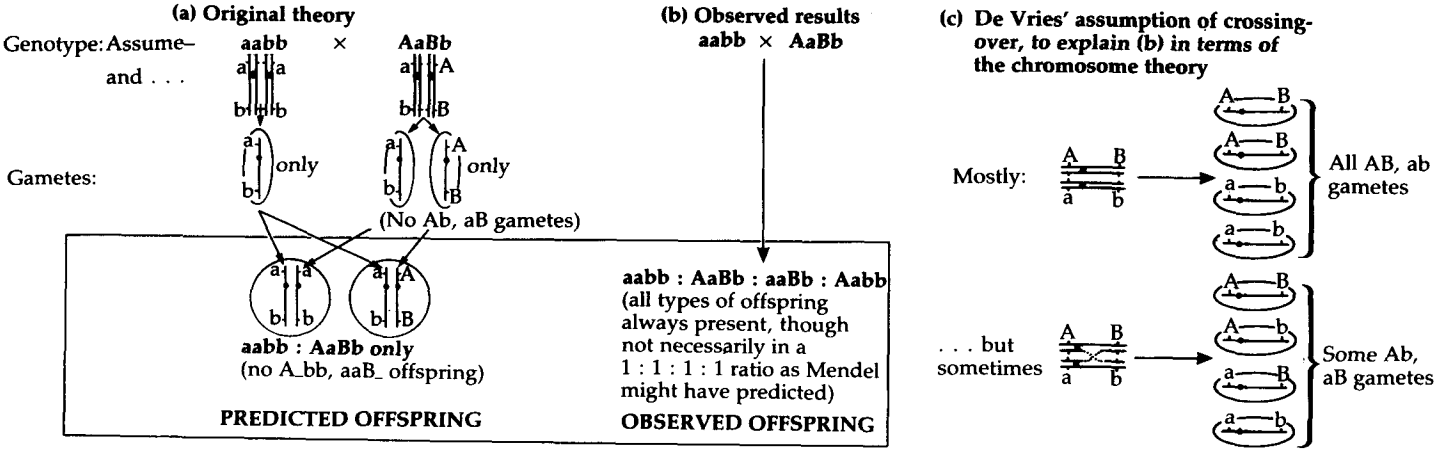


Fig. 2.4 *Flaws and solutions for the chromosome theory?*

2.4c) sometimes occurred between linked genes during meiosis. As Fig. 2.4c suggests, crossing-over means the mutual exchange of genetic material between homologous chromosomes. It was another eight years, however, before convincing evidence was provided to support De Vries' idea and, as a result, the chromosome theory was slow to gain widespread acceptance.

Study guide

Vocabulary

Explain the differences between the following pairs of terms:
autosome and sex-chromosome
meiosis$_I$ and meiosis$_{II}$
homologous and non-homologous chromosomes
linkage and sex-linkage

Review Questions

1 A female *Drosophila* with normal wings was crossed to a male with miniature wings. All the F_1 had normal wings. When allowed to interbreed, the F_1 produced an F_2 as shown below.

	Normal wings	*Miniature wings*
Females	229	0
Males	101	98

(a) Explain these results.
(b) Given the numbers of female/male offspring, predict what results would have been expected if this character had been inherited in a strictly Mendelian manner.

2 About 1/20 males are red-green colour blind, and about $(1/20)^2$ females. How would you explain this mathematical relationship between the sexes?

Extension Project

Some aspects of genetics, not directly related to the general theme developed in the following chapters, have been omitted from the text. Five such topics are listed below. Use library resources to make short notes on each.

Topic	*Comments*
Sex-determination	In mammals and some insects, e.g. *Drosophila*, ♂ = XY (heterogametic sex) and ♀ = XX (homogametic sex). The opposite is true in birds and butterflies. Hormones, genetic and environmental factors may strongly influence the development of normal physical characteristics (ref. testicular feminisation, bees, and some amphibia respectively).
Cytoplasmic inheritance	Some genes are found in the cytoplasm and hence they do not follow the Mendelian laws. Principal examples include: mitochondrial and chloroplast genes; plasmids; κ-particles (kappa, Gk). Are they all cases of degenerate bacteria or viruses?
Multiple-factor inheritance	Some characters are governed by two or more genes with additive effects. The classic experiment is Nilsson-Ehle's work (1909) on the colour of wheat grains.
Sex-limited inheritance	Some genes are expressed more in one sex than another; baldness is an example. Distinguish clearly between sex-linked and sex-limited inheritance. Define the term *incomplete penetrance.*
Heritability	Some characteristics are markedly affected by environmental factors such as diet: weight in humans is a classic example. Other characteristics are principally determined by the genes: eye colour is an example. What are the implications of heritability to, say, an animal or plant breeder? What are the evolutionary implications of environmental and genetic variation?

3

Linkage and Chromosome Mapping

SUMMARY

If two genes are on the same chromosomes they will tend to be inherited together (**linkage**), and Mendelian ratios will not then be obtained. Analysis of linked genes enables geneticists to arrange genes on chromosomes.

Figure 2.2 was a simplified half-truth. In fact the 'experiment' illustrated was part of a much larger series of experiments involving not only eye colour, but also wing shape. These dihybrid crosses not only confirmed the chromosome theory but also produced the first convincing evidence to support De Vries' theory of crossing-over.

Q1 What prompted De Vries to propose the idea of crossing-over in the first place?

3.1 EVIDENCE FOR LINKAGE AND CROSSING-OVER

Morgan (1911) crossed two pure strains differing in eye colour and wing shape, to produce an F_1 (Fig. 3.1). Since the F_1 ♂s had different eye colours/wing shapes from the F_1 ♀s, he concluded that both genes were sex-linked, i.e., carried on the X-chromosomes which they inherited from the P ♀s.

Q2 Morgan also concluded that red eye was dominant to white eye, and long wings were dominant to miniature wings. What justification did he have for this conclusion?

Morgan then allowed the F_1 to interbreed to produce an F_2. The numbers amongst the latter proved to be decisive.

Q3 Predict what the F_2 will be like assuming the chromosomes remain unaltered. (Your prediction does, in fact, turn out to be wrong: the actual results are shown in Fig. 3.2. Consequently, you *cannot* assume that the chromosomes remain unaltered).

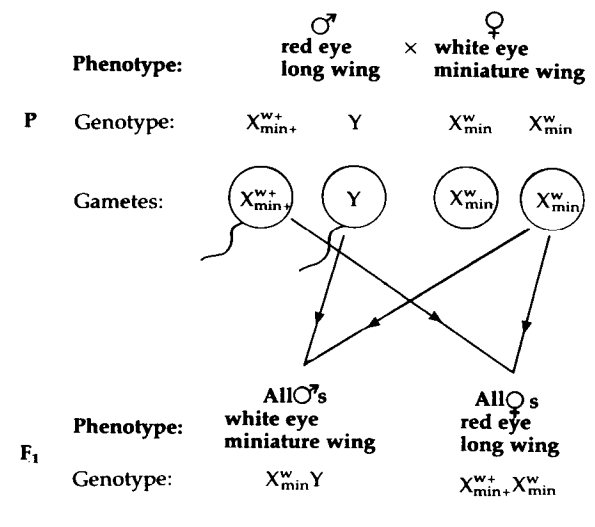


Fig. 3.1 *Morgan's experiment: P and F_1 (continued in Fig. 3.2)*

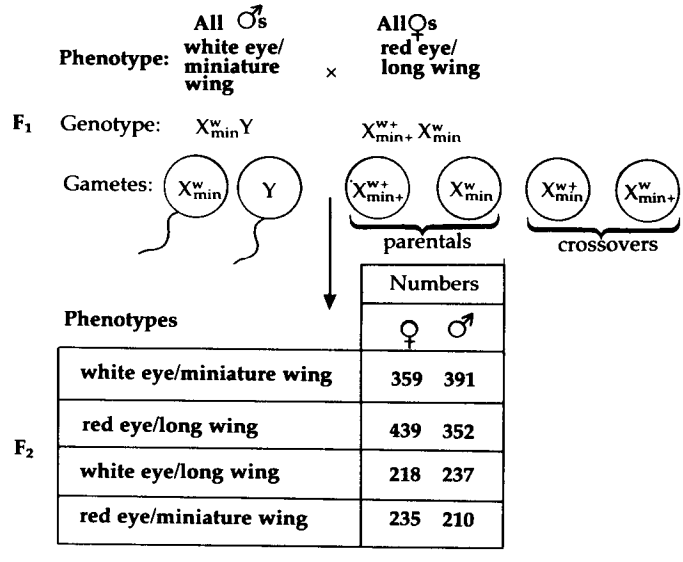


Fig. 3.2 *Morgan's experiment: F_1 and F_2 (continued from Fig. 3.1)*