2

MENDEL'S PRINCIPLES

STUDY OBJECTIVES

1. To understand that genes are discrete units that control the appearance of an organism 17
2. To understand Mendel's rules of inheritance: segregation and independent assortment 18
3. To understand that dominance is a function of the interaction of alleles; similarly, epistasis is a function of the interaction of nonallelic genes 22
4. To define how genes generally control the production of enzymes and thus the fate of biochemical pathways 37

STUDY OUTLINE

The garden pea plant, *Pisum sativum.*

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Genetics is concerned with the transmission, expression, and evolution of genes, the molecules that control the function, development, and ultimate appearance of individuals. In this section of the book, we will look at the rules of transmission that govern genes and affect their passage from one generation to the next. Gregor Johann Mendel discovered these rules of inheritance; we derive and expand upon his rules in this chapter (fig. 2.1).

In 1900, three botanists, Carl Correns of Germany, Erich von Tschermak of Austria, and Hugo de Vries of Holland, defined the rules governing the transmission of traits from parent to offspring. Some historical controversy exists as to whether these botanists actually rediscovered Mendel's rules by their own research or whether their research led them to Mendel's original paper. In any case, all three made important contributions to the early stages of genetics. The rules had been published previously, in 1866, by an obscure Austrian monk, Gregor Johann Mendel. Although his work was widely available after 1866, the scientific community was not ready to appreciate Mendel's great contribution until the turn of the century. There are at least four reasons for this lapse of thirty-four years.

Figure 2.1 Gregor Johann Mendel (1822–84). (Reproduced by permission of the Moravski Museum, Mendelianum.)

First, before Mendel's experiments, biologists were primarily concerned with explaining the transmission of characteristics that could be measured on a continuous scale, such as height, cranium size, and longevity. They were looking for rules of inheritance that would explain such **continuous variations,** especially after Darwin put forth his theory of evolution in 1859 (see chapter 21). Mendel, however, suggested that inherited characteristics were discrete and constant **(discontinuous):** peas, for example, were either yellow or green. Thus, evolutionists were looking for small changes in traits with continuous variation, whereas Mendel presented them with rules for discontinuous variation. His principles did not seem to apply to the type of variation that biologists thought prevailed. Second, there was no physical element identified with Mendel's inherited entities. One could not say, upon reading Mendel's work, that a certain subunit of the cell followed Mendel's rules. Third, Mendel worked with large numbers of offspring and converted these numbers to ratios. Biologists, practitioners of a very descriptive science at the time, were not well trained in mathematical tools. And last, Mendel was not well known and did not persevere in his attempts to convince the academic community that his findings were important.

Between 1866 and 1900, two major changes took place in biological science. First, by the turn of the century, not only had scientists discovered chromosomes, but they also had learned to understand chromosomal movement during cell division. Second, biologists were better prepared to handle mathematics by the turn of the century than they were during Mendel's time.

MENDEL'S EXPERIMENTS

Gregor Mendel was an Austrian monk (of Brünn, Austria, which is now Brno, Czech Republic). In his experiments, he tried to **crossbreed** plants that had discrete, nonoverlapping characteristics and then to observe the distribution of these characteristics over the next several generations. Mendel worked with the common garden pea plant, *Pisum sativum.* He chose the pea plant for at least three reasons: (1) The garden pea was easy to cultivate and had a relatively short life cycle. (2) The plant had discontinuous characteristics such as flower color and pea texture. (3) In part because of its anatomy, pollination of the plant was easy to control. Foreign pollen could be kept out, and **cross-fertilization** could be accomplished artificially.

Figure 2.2 shows a cross section of the pea flower that indicates the keel, in which the male and female parts develop. Normally, **self-fertilization** occurs when pollen falls onto the stigma before the bud opens. Mendel cross-fertilized the plants by opening the keel of

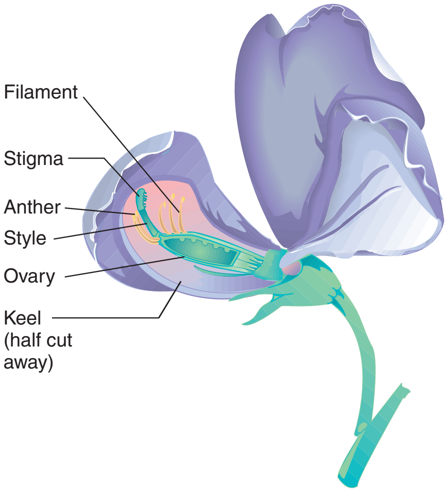


Figure 2.2 Anatomy of the garden pea plant flower. The female part, the pistil, is composed of the stigma, its supporting style, and the ovary. The male part, the stamen, is composed of the pollen-producing anther and its supporting filament.

a flower before the anthers matured and placing pollen from another plant on the stigma. In the more than ten thousand plants Mendel examined, only a few were fertilized other than the way he had intended (either self- or cross-pollinated).

Mendel used plants obtained from suppliers and grew them for two years to ascertain that they were homogeneous, or true-breeding, for the particular characteristic under study. He chose for study the seven characteristics shown in figure 2.3. Take as an example the characteristic of plant height. Although height is often continuously distributed, Mendel used plants that displayed only two alternatives: tall or dwarf. He made the crosses shown in figure 2.4. In the parental, or P_1, generation, dwarf plants pollinated tall plants, and, in a **reciprocal cross,** tall plants pollinated dwarf plants, to determine whether the results were independent of the parents' sex. As we will see later on, some traits follow inheritance patterns related to the sex of the parent carrying the traits. In those cases, reciprocal crosses give different results; with Mendel's tall and dwarf pea plants, the results were the same.

Offspring of the cross of P_1 individuals are referred to as the first **filial generation,** or F_1. Mendel also referred to them as **hybrids** because they were the offspring of unlike parents (tall and dwarf). We will specifically refer to the offspring of tall and dwarf peas as **monohybrids** because they are hybrid for only one characteristic (height). Since all the F_1 offspring plants were tall, Mendel referred to tallness as the **dominant** trait. The alternative, dwarfness, he referred to as **recessive.** Different forms of a gene that exist within a population are termed **alleles.** The terms *dominant* and *recessive* are used to describe both the relationship between the alleles and the traits they control. Thus, we say that both the allele for tallness and the trait, tall, are dominant. Dominance applies to the appearance of the trait when both a dominant and a recessive allele are present. It does not imply that the dominant trait is better, is more abundant, or will increase over time in a population.

When the F_1 offspring of figure 2.4 were self-fertilized to produce the F_2 generation, both tall and dwarf offspring occurred; the dwarf characteristic reappeared. Among the F_2 offspring, Mendel observed 787 tall and 277 dwarf plants for a ratio of 2.84:1. It is an indication of Mendel's insight that he recognized in these numbers an approximation to a 3:1 ratio, a ratio that suggested to him the mechanism of inheritance at work in pea plant height.

SEGREGATION

Rule of Segregation

Mendel assumed that each plant contained two determinants (which we now call **genes**) for the characteristic of height. For example, a hybrid F_1 pea plant possesses the dominant allele for tallness and the recessive allele for dwarfness for the gene that determines plant height. A pair of alleles for dwarfness is required to develop the recessive phenotype. Only one of these alleles is passed into a single **gamete,** and the union of two gametes to form a zygote restores the double complement of alleles. The fact that the recessive trait reappears in the F_2 generation shows that the allele controlling it was hidden in the F_1 individual and passed on unaffected. This explanation of the passage of discrete trait determinants, or genes, comprises Mendel's first principle, the **rule of segregation.** The rule of segregation can be summarized as follows: A gamete receives only one allele from the pair of alleles an organism possesses; fertilization (the union of two gametes) reestablishes the double number. We can visualize this process by redrawing figure 2.4 using letters to denote the alleles. Mendel used capital letters to denote alleles that control dominant traits and lowercase letters for alleles that control recessive traits. Following this notation, T refers to the allele controlling tallness and t refers to the allele controlling shortness (dwarf stature). From figure 2.5, we can see that Mendel's rule of segregation explains the homogeneity of the F_1 generation (all tall) and the 3:1 ratio of tall-to-dwarf offspring in the F_2 generation.

Let us define some terms. The **genotype** of an organism is the gene combination it possesses. In figure 2.5,

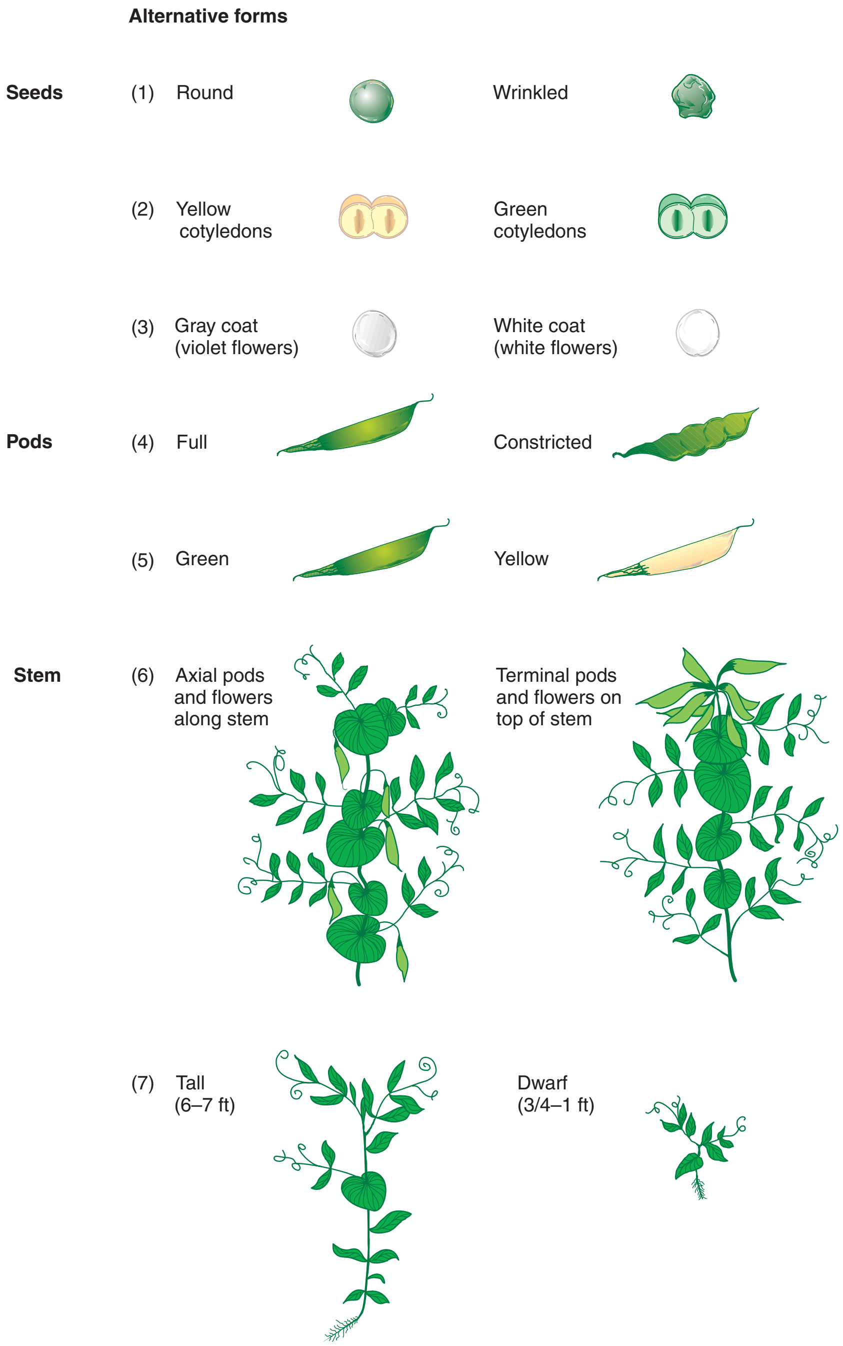


Figure 2.3 Seven characteristics that Mendel observed in peas. Traits in the left column are dominant.

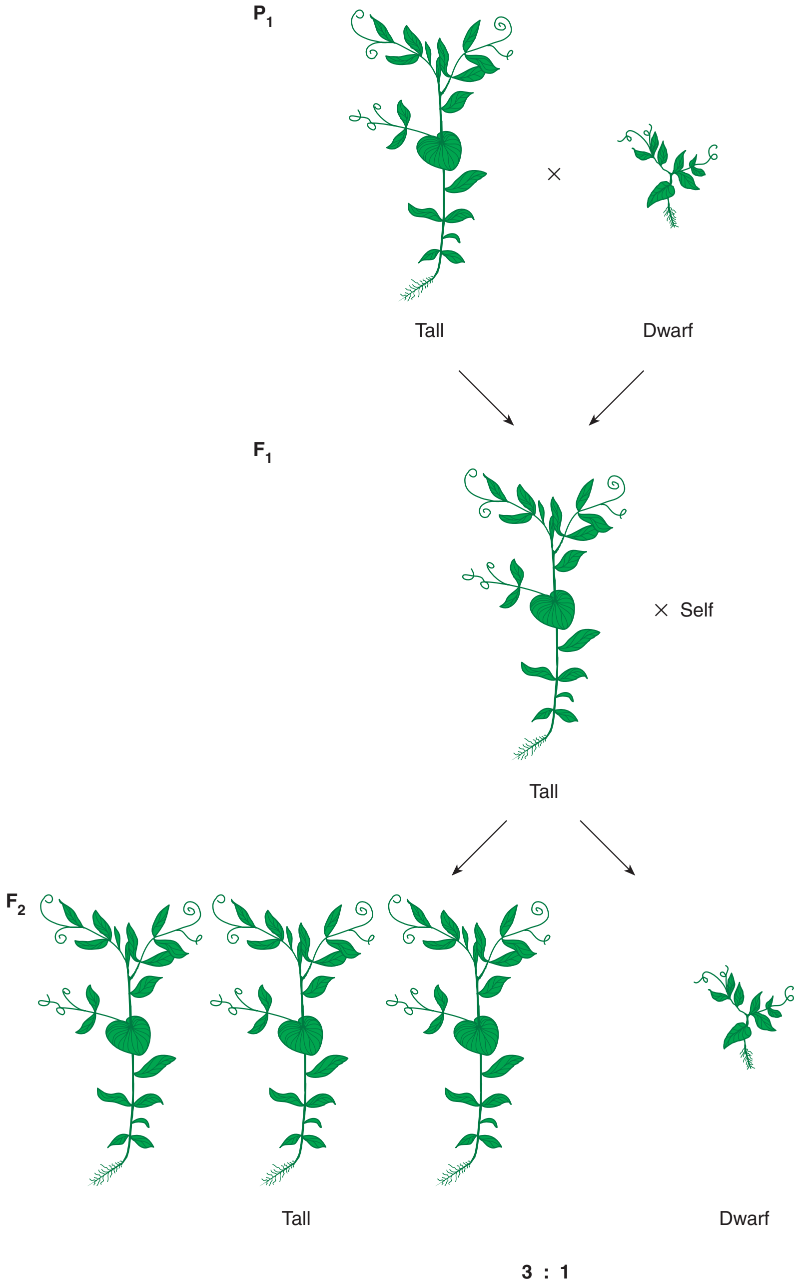


Figure 2.4 First two offspring generations from the cross of tall plants with dwarf plants.

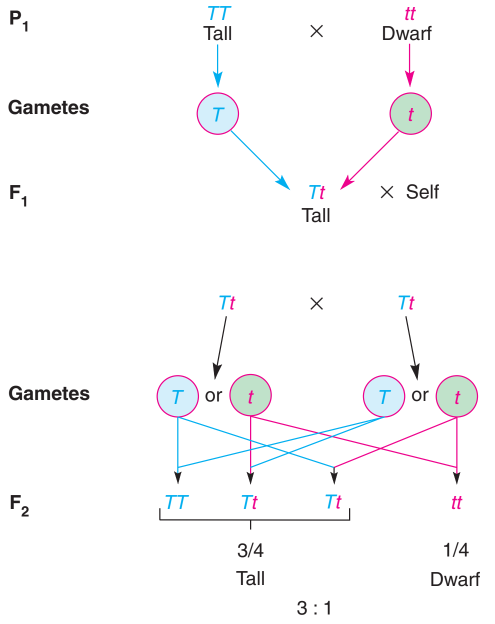


Figure 2.5 Assigning genotypes to the cross in figure 2.4.

the genotype of the parental tall plant is *TT;* that of the F_1 tall plant is *Tt.* **Phenotype** refers to the observable attributes of an organism. Plants with either of the two genotypes *TT* or *Tt* are phenotypically tall. Genotypes come in two general classes: **homozygotes,** in which both alleles are the same, as in *TT* or *tt,* and **heterozygotes,** in which the two alleles are different, as in *Tt.* William Bateson coined these last two terms in 1901. Danish botanist Wilhelm Johannsen first used the word *gene* in 1909.

If we look at figure 2.5, we can see that the *TT* homozygote can produce only one type of gamete, the *T*-bearing kind, and the *tt* homozygote can similarly produce only *t*-bearing gametes. Thus, the F_1 individuals are uniformly heterozygous *Tt,* and each F_1 individual can produce two kinds of gametes in equal frequencies, *T*- or *t*-bearing. In the F_2 generation, these two types of gametes randomly pair during fertilization. Figure 2.6 shows three ways of picturing this process.

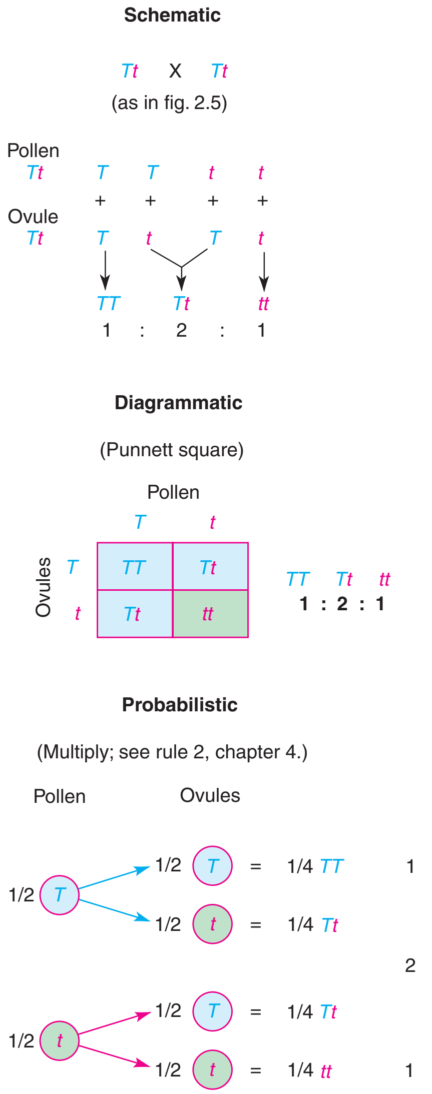


Figure 2.6 Methods of determining F_2 genotypic combinations in a self-fertilized monohybrid. The Punnett square diagram is named after the geneticist Reginald C. Punnett.

Testing the Rule of Segregation

We can see from figure 2.6 that the F_2 generation has a phenotypic ratio of 3:1, the classic Mendelian ratio. However, we also see a genotypic ratio of 1:2:1 for dominant homozygote:heterozygote:recessive homozygote. Demonstrating this genotypic ratio provides a good test of Mendel's rule of segregation.

The simplest way to test the hypothesis is by **progeny testing,** that is, by self-fertilizing F_2 individuals to produce an F_3 generation, which Mendel did (fig. 2.7). Treating the rule of segregation as a hypothesis, it is possible to predict the frequencies of the phenotypic classes that would result. The dwarf F_2 plants should be recessive homozygotes, and so, when **selfed** (self-fertilized), they should produce only *t*-bearing gametes and only dwarf offspring in the F_3 generation. The tall F_2 plants, however, should be a heterogeneous group, one-third of which should be homozygous *TT* and two-thirds heterozygous *Tt.* The tall homozygotes, when selfed, should produce only tall F_3 offspring (genotypically *TT*). However, the F_2 heterozygotes, when selfed, should produce

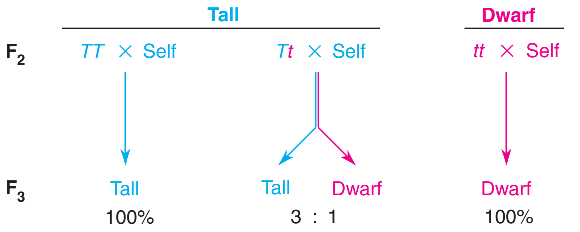


Figure 2.7 Mendel self-fertilized F_2 tall and dwarf plants. He found that all the dwarf plants produced only dwarf progeny. Among the tall plants, 72% produced both tall and dwarf progeny in a 3:1 ratio.

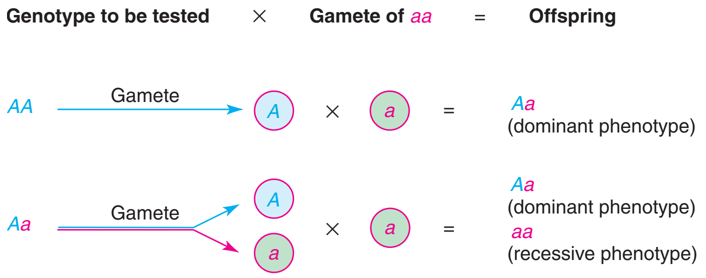


Figure 2.8 Testcross. In a testcross, the phenotype of an offspring is determined by the allele the offspring inherits from the parent with the genotype being tested.

tall and dwarf offspring in a ratio identical to that the selfed F_1 plants produced: three tall to one dwarf offspring. Mendel found that all the dwarf (homozygous) F_2 plants bred true as predicted. Among the tall, 28% (28/100) bred true (produced only tall offspring) and 72% (72/100) produced both tall and dwarf offspring. Since the prediction was one-third (33.3%) and two-thirds (66.7%), respectively, Mendel's observed values were very close to those predicted. We thus conclude that Mendel's progeny-testing experiment confirmed his hypothesis of segregation. In fact, a statistical test—developed in chapter 4—would also the support this conclusion.

Another way to test the segregation rule is to use the extremely useful method of the **testcross,** that is, a cross of any organism with a recessive homozygote. (Another type of cross, a **backcross,** is the cross of a progeny with an individual that has a parental genotype. Hence, a testcross can often be a backcross.) Since the gametes of the recessive homozygote contain only recessive alleles, the alleles that the gametes of the other parent carry will determine the phenotypes of the offspring. If a gamete from the organism being tested contains a recessive allele, the resulting F_1 organism will have a recessive phenotype; if it contains a dominant allele, the F_1 organism will have a dominant phenotype. Thus, in a testcross, the genotypes of the gametes from the organism being tested determine the phenotypes of the offspring (fig. 2.8). A testcross of the tall F_2 plants in figure 2.5 would produce the results shown in figure 2.9. These results further confirm Mendel's rule of segregation.

Tall (two classes)

TT × *tt* = all *Tt*

Tt × *tt* = *Tt* : *tt*

1 : 1

Figure 2.9 Testcrossing the dominant phenotype of the F_2 generation from figure 2.5.

DOMINANCE IS NOT UNIVERSAL

If dominance were universal, the heterozygote would always have the same phenotype as the dominant homozygote, and we would always see the 3:1 ratio when heterozygotes are crossed. If, however, the heterozygote were distinctly different from both homozygotes, we

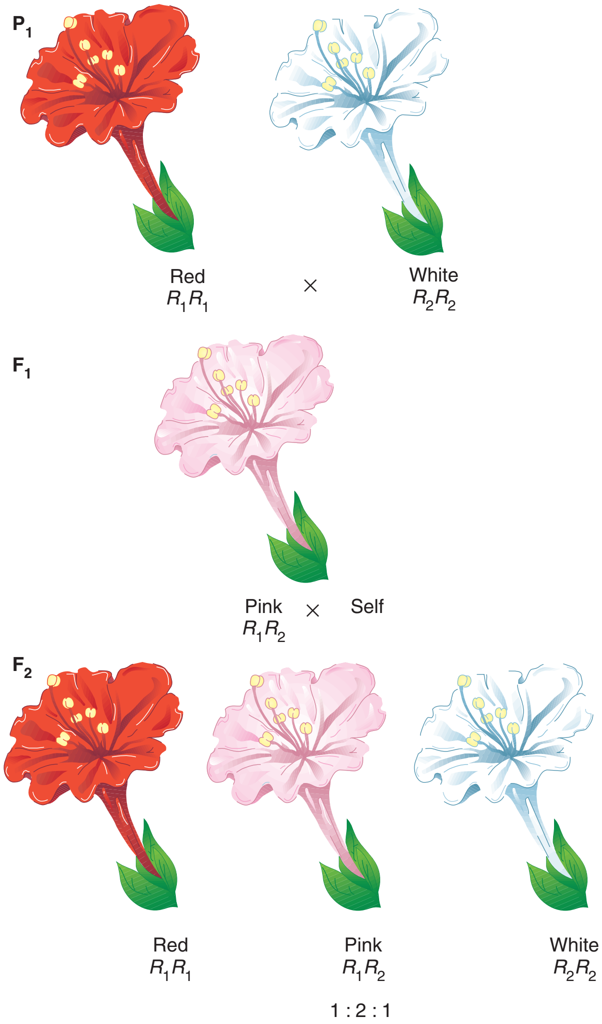


Figure 2.10 Flower color inheritance in the four-o'clock plant: an example of partial, or incomplete, dominance.

would see a 1:2:1 ratio of phenotypes when heterozygotes are crossed. In **partial dominance** (or **incomplete dominance),** the phenotype of the heterozygote falls between those of the two homozygotes. An example occurs in flower petal color in some plants.

Using four-o'clock plants (*Mirabilis jalapa*), we can cross a plant that has red flower petals with another that has white flower petals; the offspring will have pink flower petals. If these pink-flowered F_1 plants are crossed, the F_2 plants appear in a ratio of 1:2:1, having red, pink, or white flower petals, respectively (fig. 2.10). The pink-flowered plants are heterozygotes that have a petal color intermediate between the red and white colors of the homozygotes. In this case, one allele (R_1) specifies red pigment color, and another allele specifies no color (R_2; the flower petals have a white background color). Flowers in heterozygotes (R_1R_2) have about half the red pigment of the flowers in red homozygotes (R_1R_1) because the heterozygotes have only one copy of the allele that produces color, whereas the homozygotes have two copies.

As technology has improved, we have found more and more cases in which we can differentiate the heterozygote. It is now clear that dominance and recessiveness are phenomena dependent on which alleles are interacting and on what phenotypic level we are studying. For example, in Tay-Sachs disease, homozygous recessive children usually die before the age of three after suffering severe nervous system degeneration; heterozygotes seem to be normal. As biologists have discovered how the disease works, they have made the detection of the heterozygotes possible.

As with many genetic diseases, the culprit is a defective **enzyme** (protein catalyst). Afflicted homozygotes have no enzyme activity, heterozygotes have about half the normal level, and, of course, homozygous normal individuals have the full level. In the case of Tay-Sachs disease, the defective enzyme is hexoseaminidase-A, needed for proper lipid metabolism. Modern techniques allow technicians to assay the blood for this enzyme and to identify heterozygotes by their intermediate level of enzyme activity. Two heterozygotes can now know that there is a 25% chance that any child they bear will have the disease. They can make an educated decision as to whether or not to have children.

The other category in which the heterozygote is discernible occurs when the heterozygous phenotype is not on a scale somewhere between the two homozygotes, but actually expresses both phenotypes simultaneously. We refer to this situation as **codominance.** For example, people with blood type AB are heterozygotes who express both the *A* and *B* alleles for blood type (see the section entitled "Multiple Alleles" for more information about blood types). Electrophoresis (a technique described in chapter 5) lets us see proteins directly and also gives us many examples of codominance when we can see the protein products of both alleles.

NOMENCLATURE

Throughout the last century, botanists, zoologists, and microbiologists have adopted different methods for naming alleles. Botanists and mammalian geneticists tend to prefer the capital-lowercase scheme. *Drosophila* geneticists and microbiologists have adopted schemes that relate to the **wild-type.** The wild-type is the phenotype of the organism commonly found in nature. Though other naturally occurring phenotypes of the same species may also be present, there is usually an agreed-upon common

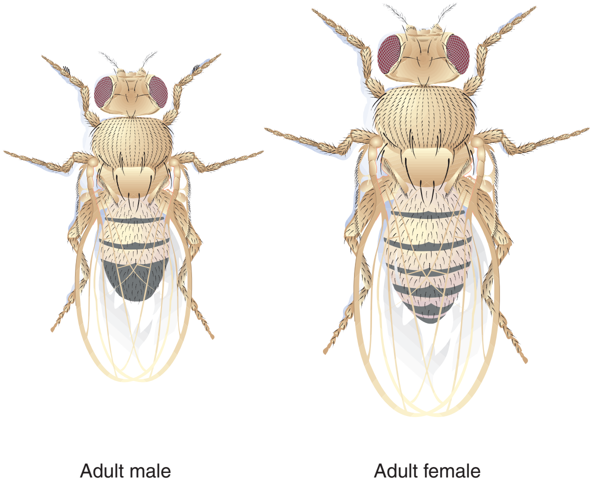


Figure 2.11 Wild-type fruit fly, *Drosophila melanogaster.*

Table 2.1 Some Mutants of *Drosophila*

Mutant Designation	Description	Dominance Relationship to Wild-Type
abrupt (*ab*)	Shortened, longitudinal, median wing vein	Recessive
amber (*amb*)	Pale yellow body	Recessive
black (*b*)	Black body	Recessive
Bar (*B*)	Narrow, vertical eye	Dominant
dumpy (*dp*)	Reduced wings	Recessive
Hairless (*H*)	Various bristles absent	Dominant
white (*w*)	White eye	Recessive
white-apricot (w^a)	Apricot-colored eye (allele of white eye)	Recessive

phenotype that is referred to as the wild-type. For fruit flies (*Drosophila*), organisms commonly used in genetic studies, the wild-type has red eyes and round wings (fig. 2.11). Alternatives to the wild-type are referred to as **mutants** (fig. 2.12). Thus, red eyes are wild-type, and white eyes are mutant. Fruit fly genes are named after the mutant, beginning with a capital letter if the mutation is dominant and a lowercase letter if it is recessive. Table 2.1 gives some examples. The wild-type allele often carries the symbol of the mutant with a + added as a superscript; by definition, every mutant has a wild-type allele as an alternative. For example, *w* stands for the white-eye allele, a recessive mutation. The wild-type (red eyes) is thus assigned the symbol w^+. Hairless is a dominant allele with the symbol *H.* Its wild-type allele is denoted as H^+. Sometimes geneticists use the + symbol alone for the wild-type, but only when there will be no confusion about its use. If we are discussing eye color only, then + is clearly the same as w^+: both mean red eyes. However, if we are discussing both eye color and bristle morphology, the + alone could refer to either of the two aspects of the phenotype and should be avoided.

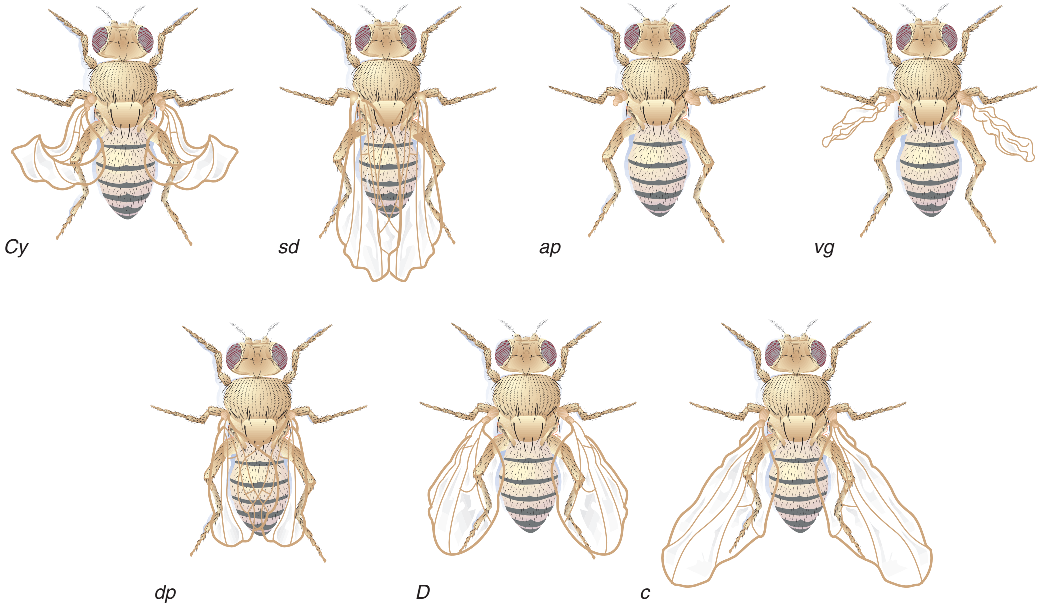


Figure 2.12 Wing mutants of *Drosophila melanogaster* and their allelic designations: *Cy,* curly; *sd,* scalloped; *ap,* apterous; *vg,* vestigial; *dp,* dumpy; *D,* Dichaete; *c,* curved.

Table 2.2 ABO Blood Types with Immunity Reactions

Blood Type Corresponding to Antigens on Red Blood Cells	Antibodies in Serum	Genotype	Reaction of Red Cells to Anti-A Antibodies	Reaction of Red Cells to Anti-B Antibodies
O	Anti-A and anti-B	ii	–	–
A	Anti-B	I^AI^A or I^Ai	+	–
B	Anti-A	I^BI^B or I^Bi	–	+
AB	None	I^AI^B	+	+

MULTIPLE ALLELES

A given gene can have more than two alleles. Although any particular individual can have only two, many alleles of a given gene may exist in a population. The classic example of multiple human alleles is in the ABO blood group, which Karl Landsteiner discovered in 1900. This is the best known of all the red-cell antigen systems primarily because of its importance in blood transfusions. There are four blood-type phenotypes produced by three alleles (table 2.2). The I^A and I^B alleles are responsible for the production of the A and B antigens found on the surface of the erythrocytes (red blood cells). Antigens are substances, normally foreign to the body, that induce the immune system to produce antibodies (proteins that bind to the antigens). The ABO system is unusual because antibodies can be present (e.g., anti-B antibodies can exist in a type A person) without prior exposure to the antigen. Thus, people with a particular ABO antigen on their red cells will have in their serum the antibody against the other antigen: type A persons have A antigen on their red cells and anti-B antibody in their serum; type B persons have B antigen on their red cells and anti-A antibody in their serum; type O persons do not have either antigen but have both antibodies in their serum; and type AB persons have both A and B antigens and form neither anti-A or anti-B antibodies in their serum.

The I^A and I^B alleles, coding for glycosyl transferase enzymes, each cause a different modification to the terminal sugars of a mucopolysaccharide (H structure) found on the surface of red blood cells (fig. 2.13). They are codominant because both modifications (antigens) are present in a heterozygote. In fact, whichever enzyme (product of the I^A or I^B allele) reaches the H structure first will modify it. Once modified, the H structure will not respond to the other enzyme. Therefore, both A and B antigens will be produced in the heterozygote in roughly equal proportions. The i allele causes no change to the H structure: because of a mutation it produces a nonfunctioning enzyme. The i allele and its phenotype are recessive; the presence of the I^A or I^B allele, or both,

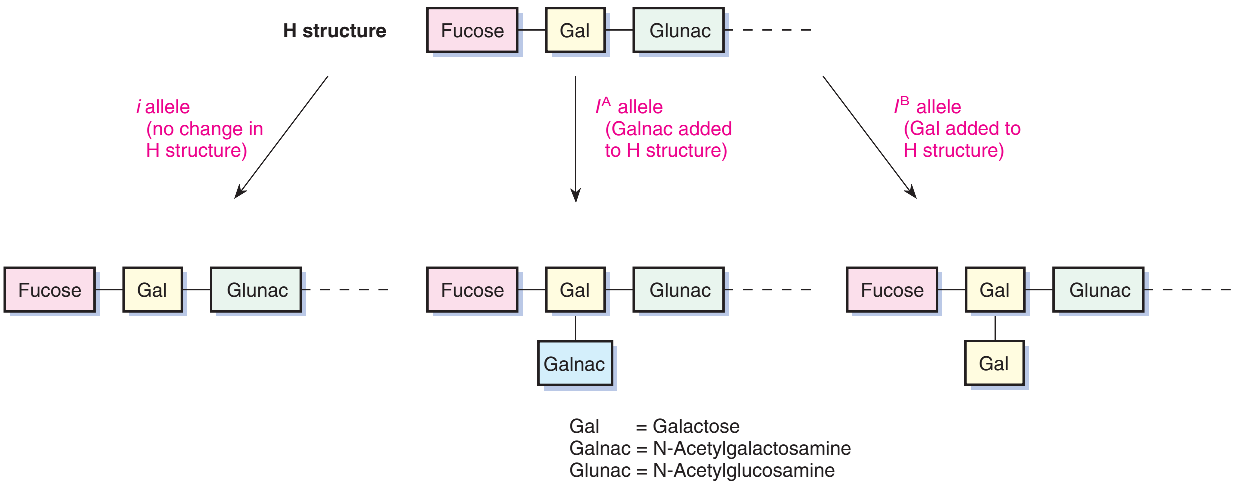


Figure 2.13 Function of the I^A, I^B, and *i* alleles of the ABO gene. The gene products of the I^A and I^B alleles of the ABO gene affect the terminal sugars of a mucopolysaccharide (H structure) found on red blood cells. The gene products of the I^A and I^B alleles are the enzymes alpha-3-N-acetyl-D-galactosaminyltransferase and alpha-3-D-galactosyltransferase, respectively.

will modify the H product, thus masking the fact that the *i* allele was ever there.

Adverse reactions to blood transfusions primarily occur because the antibodies in the recipient's serum react with the antigens on the donor's red blood cells. Thus, type A persons cannot donate blood to type B persons. Type B persons have anti-A antibody, which reacts with the A antigen on the donor red cells and causes the cells to clump.

Since both I^A and I^B are dominant to the *i* allele, this system not only shows multiple allelism, it also demonstrates both codominance and simple dominance. (As with virtually any system, intense study yields more information, and subgroups of type A are known. We will not, however, deal with that complexity here.) According to the American Red Cross, 46% of blood donors in the United States are type O, 40% are type A, 10% are type B, and 4% are type AB.

Many other genes also have multiple alleles. In some plants, such as red clover, there is a gene, the S gene, with several hundred alleles that prevent self-fertilization. This means that a pollen grain is not capable of forming a successful pollen tube in the style if the pollen grain or its parent plant has a self-incompatibility allele that is also present in the plant to be fertilized. Thus, pollen grains from a flower falling on its own stigma are rejected. Only a pollen grain with either a different self-incompatibility allele or from a parent plant with different self-incompatibility alleles is capable of fertilization; this avoids inbreeding. Thus, over evolutionary time, there has been selection for many alleles of this gene. Presumably, a foreign plant would not want to be mistaken for the same plant, providing the selective pressure for many alleles to survive in a population. Recent research has indicated that the products of the *S* alleles are ribonuclease enzymes, enzymes that destroy RNA. Researchers are interested in discovering the molecular mechanisms for this pollen rejection.

In *Drosophila,* numerous alleles of the white-eye gene exist, and people have numerous hemoglobin alleles. In fact, multiple alleles are the rule rather than the exception.

INDEPENDENT ASSORTMENT

Mendel also analyzed the inheritance pattern of traits observed two at a time. He looked, for instance, at plants that differed in the form and color of their peas: he crossed true-breeding (homozygous) plants that had seeds that were round and yellow with plants that produced seeds that were wrinkled and green. Mendel's results appear in figure 2.14. The F_1 plants all had round, yellow seeds, which demonstrated that round was dominant to wrinkled and yellow was dominant to green. When these F_1 plants were self-fertilized, they produced an F_2 generation that had all four possible combinations of the two seed characteristics: round, yellow seeds; round, green seeds; wrinkled, yellow seeds; and wrinkled, green seeds. The numbers Mendel reported in these categories were 315, 108, 101, and 32, respectively. Dividing each number by 32 gives a 9.84 to 3.38 to 3.16 to 1.00 ratio, which is very close to a 9:3:3:1 ratio. As you will see, this is the ratio we would expect if the genes governing these two traits behaved independently of each other.

In figure 2.14, the letter *R* is assigned to the dominant allele, round, and *r* to the recessive allele, wrinkled; *Y* and *y* are used for yellow and green color, respectively. In figure 2.15, we have rediagrammed the cross in figure 2.14. The P_1 plants in this cross produce only one type of gamete each, *RY* for the parent with the dominant traits and *ry* for the parent with the recessive traits. The resulting F_1 plants are heterozygous for both genes **(dihybrid).** Self-fertilizing the dihybrid (*RrYy*) produces the F_2 generation.

In constructing the **Punnett square** in figure 2.15 to diagram the F_2 generation, we make a critical assumption: The four types of gametes from each parent will be produced in equal numbers, and hence every offspring category, or "box," in the square is equally likely. Thus, because sixteen boxes make up the Punnett square (named after its inventor, Reginald C. Punnett), the ratio of F_2 offspring should be in sixteenths. Grouping the F_2 offspring by phenotype, we find there are 9/16 that have round, yellow seeds; 3/16 that have round, green seeds; 3/16 that have wrinkled, yellow seeds; and 1/16 that have wrinkled, green seeds. This is the origin of the expected 9:3:3:1 F_2 ratio.

Reginald C. Punnett (1875–1967).
From *Genetics,* 58 (1968): frontispiece. Courtesy of the Genetics Society of America.

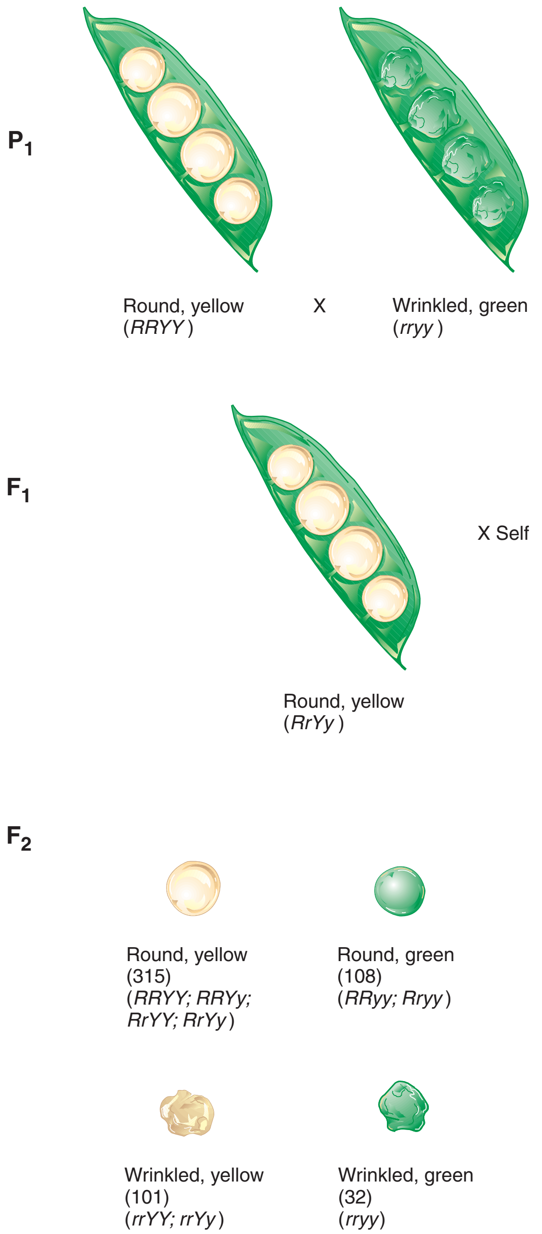
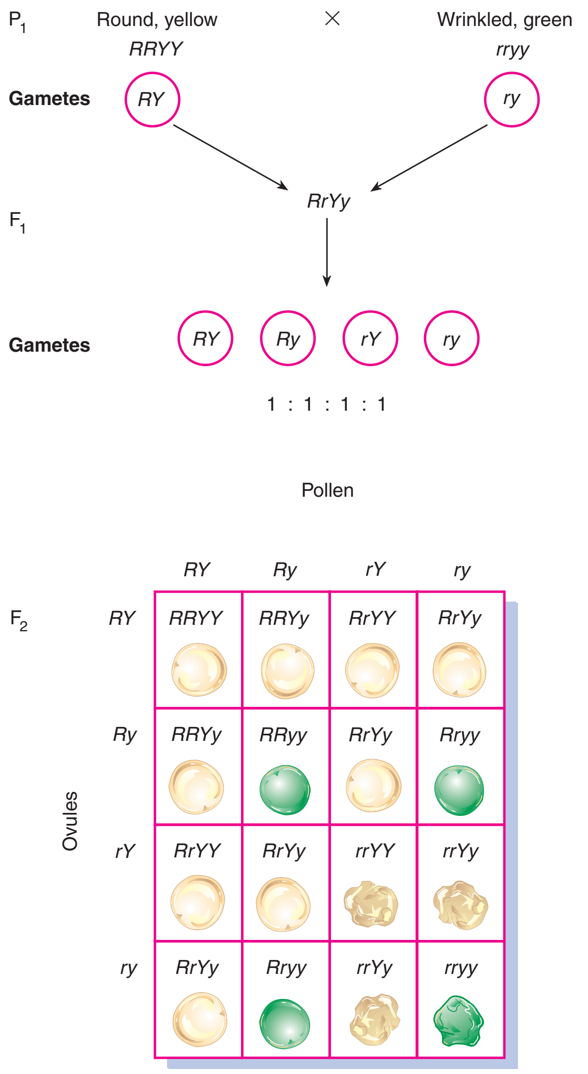


Figure 2.14 Independent assortment in garden peas.



	RY	*Ry*	*rY*	*ry*
RY	*RRYY*	*RRYy*	*RrYY*	*RrYy*
Ry	*RRYy*	*RRyy*	*RrYy*	*Rryy*
rY	*RrYY*	*RrYy*	*rrYY*	*rrYy*
ry	*RrYy*	*Rryy*	*rrYy*	*rryy*

Figure 2.15 Assigning genotypes to the cross in figure 2.14.

Rule of Independent Assortment

This ratio comes about because the two characteristics behave independently. The F_1 plants produce four types of gametes (check fig. 2.15): *RY, Ry, rY,* and *ry.* These gametes occur in equal frequencies. Regardless of which seed shape allele a gamete ends up with, it has a 50:50 chance of getting either of the alleles for color—the two genes are segregating, or assorting, independently. This is the essence of Mendel's second rule, the **rule of independent assortment,** which states that alleles for one gene can segregate independently of alleles for other genes. Are the alleles for the two characteristics of color and form segregating properly according to Mendel's first principle?

If we look only at seed shape (see fig. 2.14), we find that a homozygote with round seeds was crossed with a homozygote with wrinkled seeds in the P_1 generation ($RR \times rr$). This cross yields only heterozygous plants with round seeds (*Rr*) in the F_1 generation. When these

BOX 2.1

Historical Perspectives

Excerpts from Mendel's Original Paper

In February and March of 1865, Mendel delivered two lectures to the Natural History Society of Brünn. These were published as a single forty-eight-page article handwritten in German. The article appeared in the 1865 *Proceedings of the Society,* which came out in 1866. It was entitled "*Versuche über Pflanzen-Hybriden,*" which means "Experiments in Plant Hybridization." Following are some paragraphs from the English translation to give us some sense of the original.

In his introductory remarks, Mendel writes:

> That, so far, no generally applicable law governing the formation and development of hybrids has been successfully formulated can hardly be wondered at by anyone who is acquainted with the extent of the task, and can appreciate the difficulties with which experiments of this class have to contend. A final decision can only be arrived at when we shall have before us the results of detailed experiments made on plants belonging to the most diverse orders.
>
> Those who survey the work done in this department will arrive at the conviction that among all the numerous experiments made, not one has been carried out to such an extent and in such a way as to make it possible to determine the number of different forms under which the offspring of hybrids appear, or to arrange these forms with certainty according to their separate generations, or definitely to ascertain their statistical relations. . . .
>
> The paper now presented records the results of such a detailed experiment. This experiment was practically confined to a small plant group, and is now, after eight years' pursuit, concluded in all essentials. Whether the plan upon which the separate experiments were conducted and carried out was the best suited to attain the desired end is left to the friendly decision of the reader.

After discussing the origin of his seeds and the nature of the experiments, Mendel discusses the F_1, or hybrid, generation:

> This is precisely the case with the Pea hybrids. In the case of each of the seven crosses the hybrid-character resembles that of one of the parental forms so closely that the other either escapes observation completely or cannot be detected with certainty. This circumstance is of great importance in the determination and classification of the forms under which the offspring of the hybrids appear. Henceforth in this paper those characters which are transmitted entire, or almost unchanged in the hybridization, and therefore in themselves constitute the characters of the hybrid, are termed the *dominant,* and those which become latent in the process, *recessive.* The expression "recessive" has been chosen because the characters thereby designated withdraw or entirely disappear in the hybrids, but nevertheless reappear unchanged in their progeny, as will be demonstrated later on.

He then writes about the F_2 generation:

> In this generation there reappear, together with the dominant characters, also the recessive ones with their peculiarities fully developed, and this occurs in the definitely expressed average proportion of three to one, so that among each four plants of this generation three display the dominant character and one the recessive. This relates without exception to all the characters which were investigated in the experiments. The angular wrinkled form of the seed, the green colour of the albumen, the white colour of the seed-coats and the flowers, the constrictions of the pods, the yellow colour of the unripe pod, of the stalk, of the calyx, and of the leaf venation, the umbel-like form of the inflorescence, and the dwarfed stem, all reappear in the numerical proportion given, without any essential alteration. *Transitional forms were not observed in any experiment. . . .*

F_1 plants are self-fertilized, the result is 315 + 108 round seeds (*RR* or *Rr*) and 101 + 32 wrinkled seeds (*rr*) in the F_2 generation. This is a 423:133 or a 3.18:1.00 phenotypic ratio—very close to the expected 3:1 ratio. So the gene for seed shape is segregating normally. In a similar manner, if we look only at the gene for color, we see that the F_2 ratio of yellow to green seeds is 416:140, or 2.97:1.00—again, very close to a 3:1 ratio. Thus, when two genes are segregating normally according to the rule of segregation, their independent behavior demonstrates the rule of independent assortment (box 2.1).

From the Punnett square in figure 2.15, you can see that because of dominance, all phenotypic classes except the homozygous recessive one—wrinkled, green

> Expt. 1. Form of seed.—From 253 hybrids 7,324 seeds were obtained in the second trial year. Among them were 5,474 round or roundish ones and 1,850 angular wrinkled ones. Therefrom the ratio 2.96 to 1 is deduced.
>
> If *A* be taken as denoting one of the two constant characters, for instance the dominant, *a* the recessive, and *Aa* the hybrid form in which both are conjoined, the expression
>
> $$A + 2Aa + a$$
>
> shows the terms in the series for the progeny of the hybrids of two differentiating characters.

Mendel used a notation system different from ours. He designated heterozygotes with both alleles (e.g., *Aa*) but homozygotes with only one allele or the other (e.g., *A* for our *AA*). Thus, whereas he recorded $A + 2Aa + a$, we would record $AA + 2Aa + aa$. Mendel then went on to discuss the dihybrids. He mentions the genotypic ratio of 1:2:1:2:4:2:1:2:1 and the principle of independent assortment:

> The fertilized seeds appeared round and yellow like those of the seed parents. The plants raised therefrom yielded seeds of four sorts, which frequently presented themselves in one pod. In all, 556 seeds were yielded by 15 plants, and of those there were:
>
> 315 round and yellow,
> 101 wrinkled and yellow,
> 108 round and green,
> 32 wrinkled and green.
>
> Consequently the offspring of the hybrids, if two kinds of differentiating characters are combined therein, are represented by the expression
>
> $$AB + Ab + aB + ab + 2ABb + 2aBb + 2AaB + 2Aab + 4AaBb.$$

(In today's notation, we would write: $AABB + AAbb + aaBB + aabb + 2AABb + 2aaBb + 2AaBB + 2Aabb + 4AaBb$.)

> This expression is indisputably a combination series in which the two expressions for the characters *A* and *a*, *B* and *b* are combined. We arrive at the full number of the classes of the series by the combination of the expressions
>
> $$A + 2Aa + a$$
>
> $$B + 2Bb + b$$

(In today's notation we would write

$$AA + 2Aa + aa$$

$$BB + 2Bb + bb.)$$

> There is therefore no doubt that for the whole of the characters involved in the experiments the principle applies that *the offspring of the hybrids in which several essentially different characters are combined exhibit the terms of a series of combinations, in which the developmental series for each pair of differentiating characters are united.* It is demonstrated at the same time that *the relation of each pair of different characters in hybrid union is independent of the other differences in the two original parental stocks.*

Table 1 is a summary of all the data Mendel presented on monohybrids (the data from only one dihybrid and one trihybrid cross were presented):

Table 1 **Mendel's Data**

	Dominant Phenotype	Recessive Phenotype	Ratio
Seed form	5,474	1,850	2.96:1
Cotyledon color	6,022	2,001	3.01:1
Seed coat color	705	224	3.15:1
Pod form	882	299	2.95:1
Pod color	428	152	2.82:1
Flower position	651	207	3.14:1
Stem length	787	277	2.84:1
Total	14,949	5,010	2.98:1

Source: Copyright The Royal Horticultural Society. Taken from the *Journal of the Royal Horticultural Society*, vol. 26. Pg. 1–32. 1901.

seeds—are actually genetically heterogeneous, with phenotypes made up of several genotypes. For example, the dominant phenotypic class, with round, yellow seeds, represents four genotypes: *RRYY, RRYy, RrYY,* and *RrYy.* When we group all the genotypes by phenotype, we obtain the ratio shown in figure 2.16. Thus, with complete dominance, a self-fertilized dihybrid gives a 9:3:3:1 phenotypic ratio in its offspring (F_2). A 1:2:1:2:4:2:1:2:1 genotypic ratio also occurs in the F_2 generation. If the two genes exhibited incomplete dominance or codominance, the latter would also be the phenotypic ratio. What ratio would be obtained if one gene exhibited dominance and the other did not? An example of this case appears in figure 2.17.

BOX 2.2

Historical Perspectives

Did Mendel Cheat?

Overwhelming evidence gathered during this century has proven the correctness of Mendel's conclusions. However, close scrutiny of Mendel's paper has led some to suggest that (1) Mendel failed to report the inheritance of traits that did not show independent assortment and (2) Mendel fabricated numbers. Both these claims are, on the surface, difficult to ignore; both have been countered effectively.

The first claim—that Mendel failed to report crosses involving traits that did not show independent assortment—arises from the observation that all seven traits that Mendel studied do show independent assortment and that the pea plant has precisely seven pairs of chromosomes. For Mendel to have chosen seven genes, one located on each of the seven chromosomes, by chance alone seems extremely unlikely. In fact, the probability would be

$$7/7 \times 6/7 \times 5/7 \times 4/7 \times 3/7 \times 2/7 \times 1/7 = 0.006$$

That is, Mendel had less than one chance in one hundred of randomly picking seven traits on the seven different chromosomes. However, L. Douglas and E. Novitski in 1977 analyzed Mendel's data in a different way. To understand their analysis, you have to know that two genes sufficiently far apart on the same chromosome will appear to assort independently (to be discussed in chapter 6). Thus, Mendel's choice of characters showing independent assortment has to be viewed in light of the lengths of the chromosomes. That is, Mendel could have chosen two genes on the same chromosome that would still show independent assortment. In fact, he did. For example, stem length and pod texture (wrinkled or smooth) are on the fourth chromosome pair in peas. In their analysis, Douglas and Novitski report that the probability of randomly choosing seven characteristics that appear to assort independently is actually between one in four and one in three. So it seems that Mendel did not have to manipulate his choice of characters in order to hide the failure of independent assortment. He had a one in three chance of naively choosing the seven characters that he did, thereby uncovering no deviation from independent assortment.

The second claim—that Mendel fabricated data—comes from a careful analysis of Mendel's paper by R. A. Fisher, a brilliant English statistician and population geneticist. In a paper in 1936, Fisher pointed out two problems in Mendel's work. First, all of Mendel's published data taken together fit their expected ratios better than chance alone would predict. Second, some of Mendel's data fit incorrect expected ratios. This second "error" on Mendel's part came about as follows.

Testcrossing Multihybrids

A simple test of Mendel's rule of independent assortment is the testcrossing of the dihybrid plant. We would predict, for example, that if we crossed an *RrYy* F_1 individual with an *rryy* individual, the results would include four phenotypes in a 1:1:1:1 ratio, as shown in figure 2.18. Mendel's data verified this prediction (box 2.2). We will proceed to look at a **trihybrid** cross in order to develop general rules for **multihybrids.**

A trihybrid Punnett square appears in figure 2.19. From this we can see that when a homozygous dominant and a homozygous recessive individual are crossed in the P_1 generation, plants in the F_1 generation are capable of producing eight gamete types. When these F_1 individuals are selfed, they in turn produce F_2 offspring of twenty-seven different genotypes in a ratio of sixty-fourths. By extrapolating from the monohybrid through the trihybrid, or simply by the rules of probability, we can construct table 2.3, which contains the rules for F_1 gamete production and F_2 zygote formation in a multihybrid cross. For example, from this table we can figure out the F_2 offspring when a dodecahybrid (twelve segregating genes: *AA BB CC . . . LL* × *aa bb cc . . . ll*) is selfed. The F_1 organisms in that cross will produce gametes with 2^{12}, or 4,096, different genotypes. The proportion of homozygous recessive offspring in the F_2 generation is $1/(2^n)^2$ where $n = 12$, or 1 in 16,777,216. With complete dominance, there will be 4,096 different phenotypes in the F_2 generation. If dominance is incomplete, there can be 3^{12}, or 531,441, different phenotypes in the F_2 generation.

GENOTYPIC INTERACTIONS

Often, several genes contribute to the same phenotype. An example occurs in the combs of fowl (fig. 2.20). If we cross a rose-combed hen with a pea-combed rooster (or vice versa), all the F_1 offspring are walnut-combed. If we

Mendel determined whether a dominant phenotype in the F_2 generation was a homozygote or a heterozygote by self-fertilizing it and examining ten offspring. In an F_2 generation composed of 1*AA*:2*Aa*:1*aa,* he expected a 2:1 ratio of heterozygotes to homozygotes within the dominant phenotypic class. In fact, this ratio is not precisely correct because of the problem of misclassification of heterozygotes. It is probable that some heterozygotes will be classified as homozygotes because all their offspring will be of the dominant phenotype. The probability that one offspring from a selfed *Aa* individual has the dominant phenotype is 3/4, or 0.75: the probability that ten offspring will be of the dominant phenotype is $(0.75)^{10}$ or 0.056. Thus, Mendel misclassified heterozygotes as dominant homozygotes 5.6% of the time. He should have expected a 1.89:1.11 ratio instead of a 2:1 ratio to demonstrate segregation. Mendel classified 600 plants this way in one cross and got a ratio of 201 homozygous to 399 heterozygous offspring. This is an almost perfect fit to the presumed 2:1 ratio and thus a poorer fit to the real 1.89:1.11 ratio. This bias is consistent and repeated in Mendel's trihybrid analysis.

Fisher, believing in Mendel's basic honesty, suggested that Mendel's data do not represent an experiment but more of a hypothetical demonstration. In 1971, F. Weiling published a more convincing case in Mendel's defense. Pointing out that the data of Mendel's rediscoverers are also suspect for the same reason, he suggested that the problem lies with the process of pollen formation in plants, not with the experimenters. In an *Aa* heterozygote, two *A* and two *a* cells develop from a pollen mother cell. These cells tend to stay together on the anther. Thus, pollen cells do not fertilize in a strictly random fashion. A bee is more likely to take equal numbers of *A* and *a* pollen than chance alone would predict. The result is that the statistics Fisher used are not applicable. By using a different statistic, Weiling showed that, in fact, Mendel need not have manipulated any numbers (nor would have his rediscoverers) in order to get data that fit the expected ratios well. By the same reasoning, very little misclassification of heterozygotes would have occurred.

More recently, Weiling and others have made several additional points. First, for Mendel to be sure of ten offspring, he probably examined more than ten, and thus he probably kept his misclassification rate lower than 5.6%. Second, despite Fisher's brilliance as a statistician, several have made compelling arguments that Fisher's statistical analyses were incorrect. In other words, for subtle statistical reasons, many of his analyses involved methods and conclusions that were in error.

We conclude that there is no compelling evidence to suggest that Mendel in any way manipulated his data to demonstrate his rules. In fact, taking into account what is known about him personally, it is much more logical to believe that he did not "cheat."

cross the hens and roosters of this heterozygous F_1 group, we will get, in the F_2 generation, walnut-, rose-, pea-, and single-combed fowl in a ratio of 9:3:3:1. Can you figure out the genotypes of this F_2 population before reading further? An immediate indication that two allelic pairs are involved is the fact that the 9:3:3:1 ratio appeared in the F_2 generation. As we have seen, this ratio comes about when we cross dihybrids in which both genes have alleles that control traits with complete dominance.

Figure 2.21 shows the analysis of this cross. When dominant alleles of both genes are present in an individual (*R- P-*), the walnut comb appears. (The dash indicates any second allele; thus, *R- P-* could be *RRPP, RrPP, RRPp,* or *RrPp.*) A dominant allele of the rose gene (*R-*) with

Table 2.3 **Multihybrid Self-Fertilization, Where *n* Equals Number of Genes Segregating Two Alleles Each**

	Monohybrid $n = 1$	Dihybrid $n = 2$	Trihybrid $n = 3$	General Rule
Number of F_1 gametic genotypes	2	4	8	2^n
Proportion of recessive homozygotes among the F_2 individuals	1/4	1/16	1/64	$1/(2^n)^2$
Number of different F_2 phenotypes, given complete dominance	2	4	8	2^n
Number of different genotypes (or phenotypes, if no dominance exists)	3	9	27	3^n

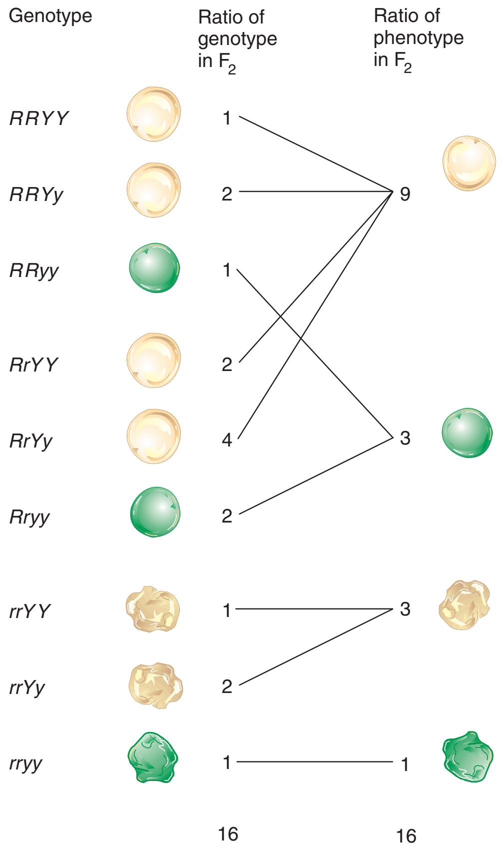


Figure 2.16 The phenotypic and genotypic ratios of the offspring of dihybrid peas.

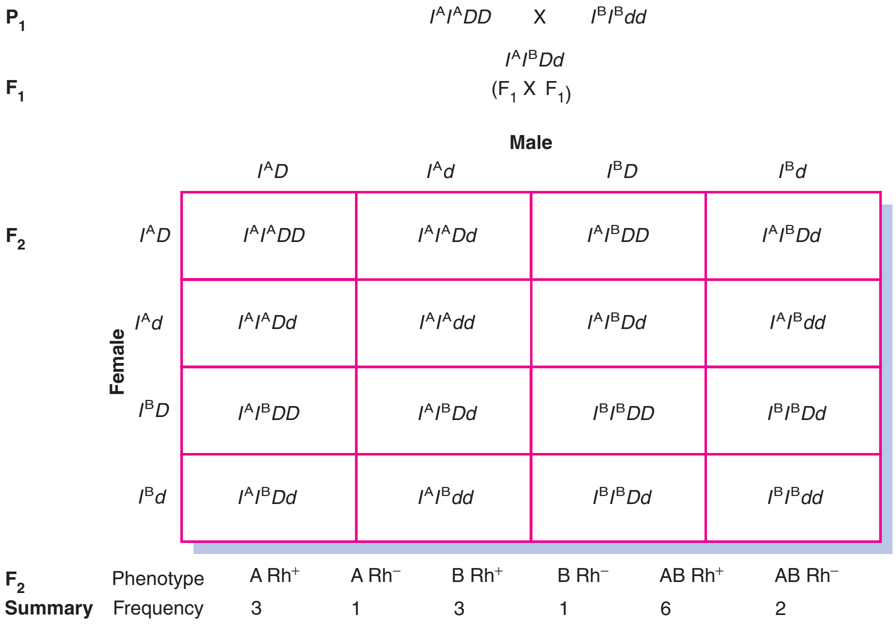
recessive alleles of the pea gene (*pp*) gives a rose comb. A dominant allele of the pea gene (*P-*) with recessive alleles of the rose gene (*rr*) gives pea-combed fowl. When both genes are homozygous for the recessive alleles, the fowl are single-combed. Thus, a 9:3:3:1 F_2 ratio arises from crossing dihybrid individuals even though different expressions of the same phenotypic characteristic, the comb, are involved. In our previous 9:3:3:1 example (see fig. 2.15), we dealt with two separate characteristics: shape and color of peas.

In corn (or maize, *Zea mays*), several different field varieties produce white kernels on the ears. In certain crosses, two white varieties will result in an F_1 generation with all purple kernels. If plants grown from these purple kernels are selfed, the F_2 individuals have both purple and white kernels in a ratio of 9:7. How can we explain this? We must be dealing with the offspring of dihybrids with each gene segregating two alleles, because the ratio is in sixteenths. Furthermore, we can see that the F_2 9:7 ratio is a variation of the 9:3:3:1 ratio. The 3, 3, and 1 categories here are producing the same phenotype and thus make up 7/16 of the F_2 offspring. Figure 2.22 outlines the cross. We can see from this figure that the purple color appears only when dominant alleles of both genes are present. When one or both genes have only recessive alleles, the kernels will be white.

Epistasis

The color of corn kernels illustrates the concept of **epistasis,** the interaction of nonallelic genes in the formation

Figure 2.17 Independent assortment of two blood systems in human beings. In the ABO system, the I^A and I^B alleles are codominant. In a simplified view of the Rhesus system, the Rh$^+$ phenotype (*D* allele) is dominant to the Rh$^-$ phenotype (*d* allele).



P_1 $I^{A}I^{A}DD$ X $I^{B}I^{B}dd$

F_1 $I^{A}I^{B}Dd$
(F_1 X F_1)

F_2

Male

Female	$I^{A}D$	$I^{A}d$	$I^{B}D$	$I^{B}d$
$I^{A}D$	$I^{A}I^{A}DD$	$I^{A}I^{A}Dd$	$I^{A}I^{B}DD$	$I^{A}I^{B}Dd$
$I^{A}d$	$I^{A}I^{A}Dd$	$I^{A}I^{A}dd$	$I^{A}I^{B}Dd$	$I^{A}I^{B}dd$
$I^{B}D$	$I^{A}I^{B}DD$	$I^{A}I^{B}Dd$	$I^{B}I^{B}DD$	$I^{B}I^{B}Dd$
$I^{B}d$	$I^{A}I^{B}Dd$	$I^{A}I^{B}dd$	$I^{B}I^{B}Dd$	$I^{B}I^{B}dd$

F_2 Summary						
Phenotype	A Rh$^+$	A Rh$^-$	B Rh$^+$	B Rh$^-$	AB Rh$^+$	AB Rh$^-$
Frequency	3	1	3	1	6	2

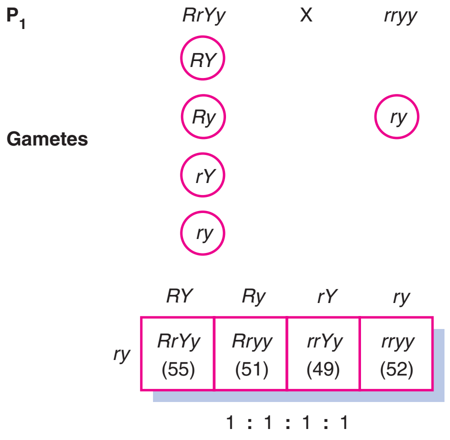


Figure 2.18 Testcross of a dihybrid. A 1:1:1:1 ratio is expected in the offspring.

of the phenotype. This is a process analogous to dominance among alleles of one gene. For example, the recessive apterous (wingless) gene in fruit flies is epistatic to any gene that controls wing characteristics; hairy wing is hypostatic to apterous (that is, the recessive apterous gene, when homozygous, masks the presence of the hairy wing gene, because, obviously, without wings, no wing characteristics can be expressed). Note that the genetic control of comb type in fowl does not involve epistasis. There are no allelic combinations at one locus that mask genotypes at another locus: the 9:3:3:1 ratio is not an indication of epistasis. To illustrate further the principle of epistasis, we can look at the control of coat color in mice.

In one particular example, a pure-breeding black mouse is crossed with a pure-breeding albino mouse (pure white because all pigment is lacking); all of the offspring are agouti (the typical brownish-gray mouse color). When the F$_1$ agouti mice are crossed with each other, agouti, black, and albino offspring appear in the F$_2$ generation in a ratio of 9:3:4. What are the genotypes in this cross? The answer appears in figure 2.23. By now it should be apparent that the F$_2$ ratio of 9:3:4 is also a variant of the 9:3:3:1 ratio; it indicates epistasis in a dihybrid cross. What is the mechanism producing this 9:3:4 ratio? Of a potential 9:3:3:1 ratio, one of the 3/16 classes and the 1/16 class are combined to create a 4/16 class. Any genotype that includes $c^a c^a$ will be albino, masking the A gene, but as long as at least one dominant *C* allele is present, the A gene can express itself. Mice with dominant alleles of both genes (*A-C-*) will have the agouti color, whereas mice that are homozygous recessive at the A gene (*aaC-*) will be black. So, at the A gene, *A* for agouti

P$_1$ *AA BB CC* × *aa bb cc*

F$_1$ *Aa Bb Cc* × Self

	A B C	*A B c*	*A b C*	*A b c*	*a B C*	*a B c*	*a b C*	*a b c*
A B C	*AA BB CC*	*AA BB Cc*	*AA Bb CC*	*AA Bb Cc*	*Aa BB CC*	*Aa BB Cc*	*Aa Bb CC*	*Aa Bb Cc*
A B c	*AA BB Cc*	*AA BB cc*	*AA Bb Cc*	*AA Bb cc*	*Aa BB Cc*	*Aa BB cc*	*Aa Bb Cc*	*Aa Bb cc*
A b C	*AA Bb CC*	*AA Bb Cc*	*AA bb CC*	*AA bb Cc*	*Aa Bb CC*	*Aa Bb Cc*	*Aa bb CC*	*Aa bb Cc*
A b c	*AA Bb Cc*	*AA Bb cc*	*AA bb Cc*	*AA bb cc*	*Aa Bb Cc*	*Aa Bb cc*	*Aa bb Cc*	*Aa bb cc*
a B C	*Aa BB CC*	*Aa BB Cc*	*Aa Bb CC*	*Aa Bb Cc*	*aa BB CC*	*aa BB Cc*	*aa Bb CC*	*aa Bb Cc*
a B c	*Aa BB Cc*	*Aa BB cc*	*Aa Bb Cc*	*Aa Bb cc*	*aa BB Cc*	*aa BB cc*	*aa Bb Cc*	*aa Bb cc*
a b C	*Aa Bb CC*	*Aa Bb Cc*	*Aa bb CC*	*Aa bb Cc*	*aa Bb CC*	*aa Bb Cc*	*aa bb CC*	*aa bb Cc*
a b c	*Aa Bb Cc*	*Aa Bb cc*	*Aa bb Cc*	*Aa bb cc*	*aa Bb Cc*	*aa Bb cc*	*aa bb Cc*	*aa bb cc*

Figure 2.19 Trihybrid cross.

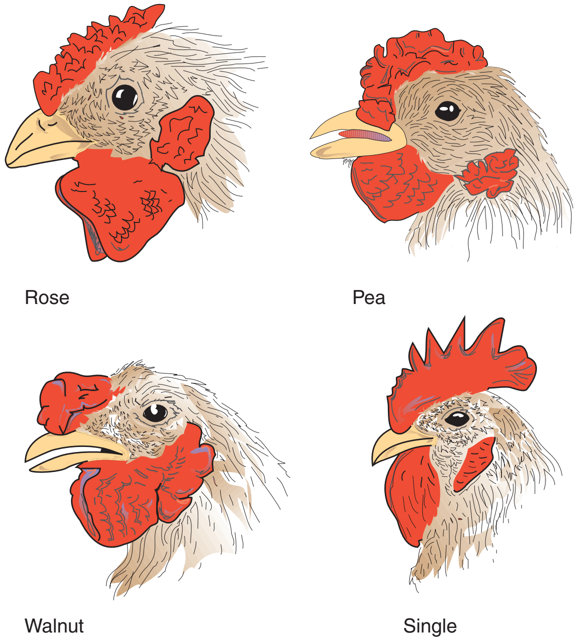
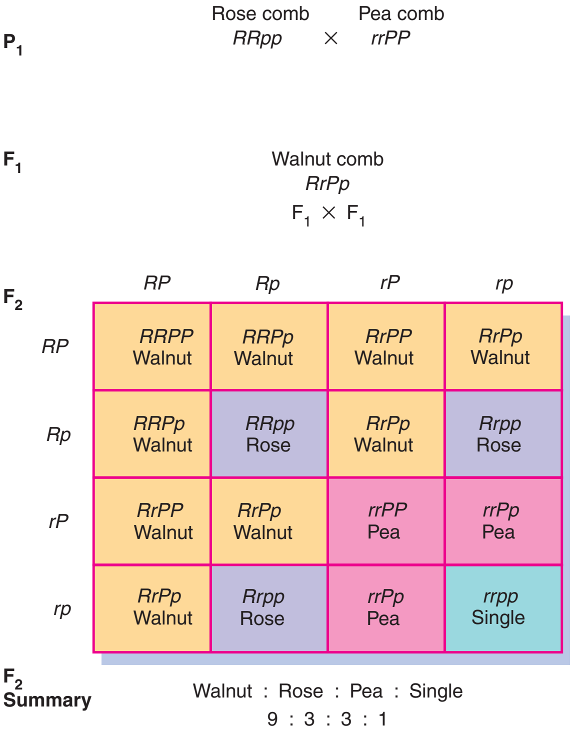


Figure 2.20 Four types of combs in fowl.



P_1 Rose comb *RRpp* × Pea comb *rrPP*

F_1 Walnut comb *RrPp*

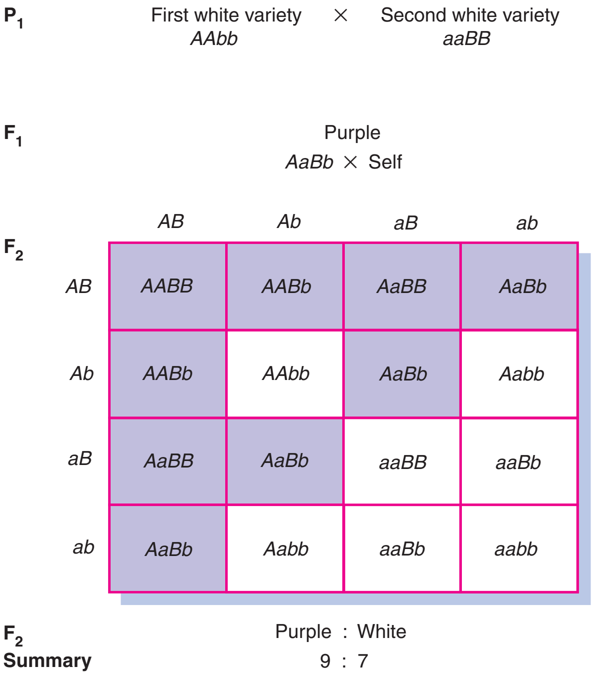
F_1 × F_1

F_2

	RP	*Rp*	*rP*	*rp*
RP	*RRPP* Walnut	*RRPp* Walnut	*RrPP* Walnut	*RrPp* Walnut
Rp	*RRPp* Walnut	*RRpp* Rose	*RrPp* Walnut	*Rrpp* Rose
rP	*RrPP* Walnut	*RrPp* Walnut	*rrPP* Pea	*rrPp* Pea
rp	*RrPp* Walnut	*Rrpp* Rose	*rrPp* Pea	*rrpp* Single

F_2 Summary Walnut : Rose : Pea : Single
9 : 3 : 3 : 1

Figure 2.21 Independent assortment in the determination of comb type in fowl.



P_1 First white variety *AAbb* × Second white variety *aaBB*

F_1 Purple *AaBb* × Self

F_2

	AB	*Ab*	*aB*	*ab*
AB	*AABB*	*AABb*	*AaBB*	*AaBb*
Ab	*AABb*	*AAbb*	*AaBb*	*Aabb*
aB	*AaBB*	*AaBb*	*aaBB*	*aaBb*
ab	*AaBb*	*Aabb*	*aaBb*	*aabb*

F_2 Summary Purple : White
9 : 7

Figure 2.22 Color production in corn.

is dominant to *a* for black. The albino gene (c^a), when homozygous, is epistatic to the A gene; the A gene is hypostatic to the gene for albinism.

Mechanism of Epistasis

In this case, the physiological mechanism of epistasis is known. The pigment melanin is present in both the black and agouti phenotypes. The agouti is a modified black hair in which yellow stripes (the pigment phaeomelanin) have been added. Thus, with melanin present, agouti is dominant. Without melanin, we get an albino regardless of the genotype of the agouti gene because both agouti and black depend on melanin. Albinism is the result of one of several defects in the enzymatic pathway for the synthesis of melanin (fig. 2.24).

Knowing that epistatic modifications of the 9:3:3:1 ratio come about through gene interactions at the biochemical level, we can look for a biochemical explanation for the 9:7 ratio in corn kernel color (fig. 2.22). Two possible mechanisms for a 9:7 ratio are shown in figure 2.25. Either a two-step process takes a precursor molecule and turns it into purple pigment, or two precursors that must be converted to final products then combine to produce purple pigment. The dominant alleles from the two genes control the two steps in the process. Recessive alleles are ineffective. Thus, dominants are necessary for both steps to complete the pathways for a purple pig-

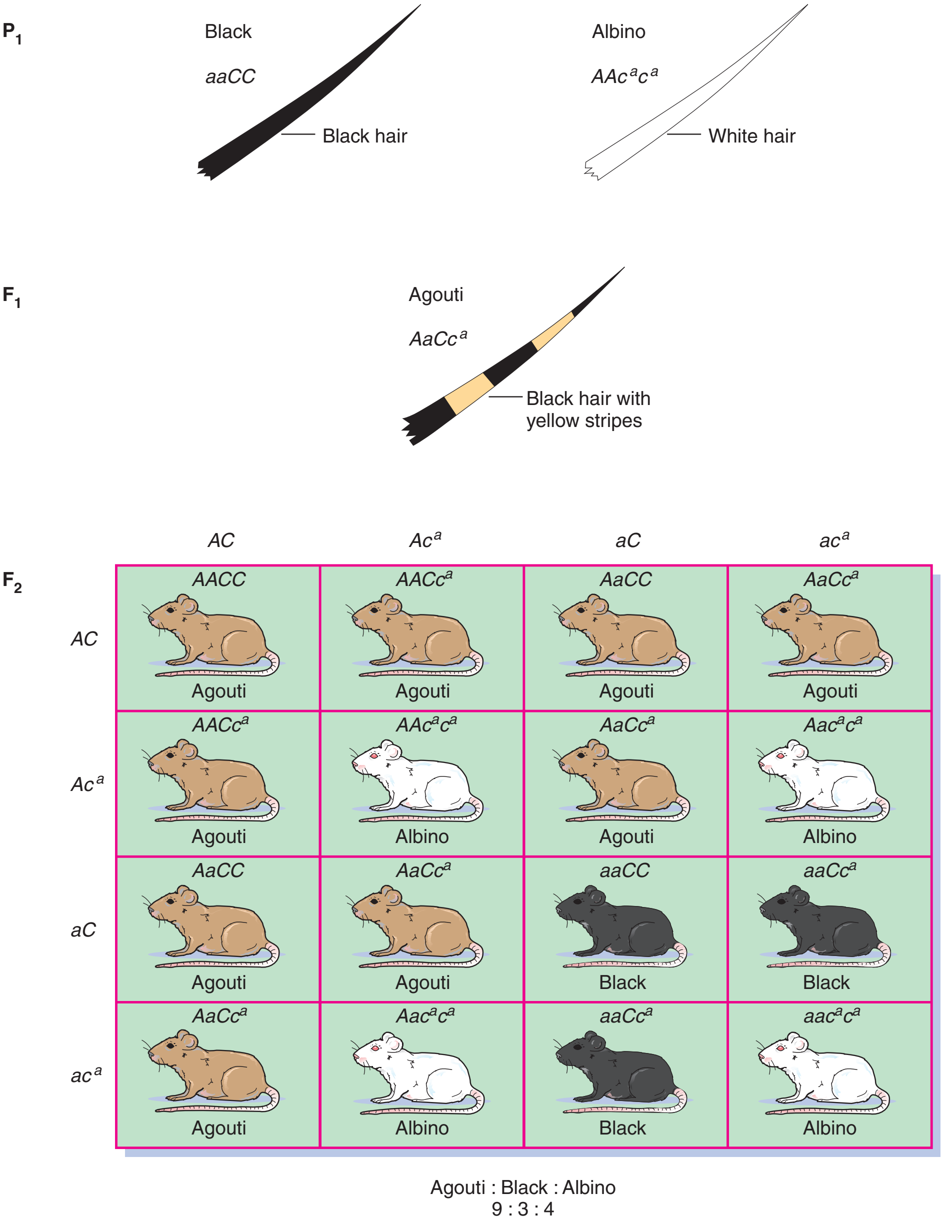


Figure 2.23 Epistasis in the coat color of mice.

ment. Stopping the process at any point prevents the production of purple color.

Another example of epistasis occurs in the snapdragon (*Antirrhinum majus*). There, a gene called *nivea* has alleles that determine whether any pigment is produced; the *nn* genotype prevents pigment production, whereas the *NN* or *Nn* genotypes permit pigment color genes to express themselves. The *eosinea* gene controls the production of a red anthocyanin pigment. In the presence of the *N* allele of the *nivea* gene, the genotypes *EE* or *Ee* of the *eosinea* gene produce red flowers; the *ee* genotype produces pink flowers. When dihybrids are self-fertilized, red-, pink-, and white-flowered plants are produced in a ratio of 9:3:4 (fig. 2.26). The epistatic interaction is the *nn* genotype masking the expression of alleles at the *eosinea* gene. In other words, regardless of the genotypes of the *eosinea* gene (*EE, Ee,* or *ee*), the flowers will be white if the *nivea* gene has the *nn*

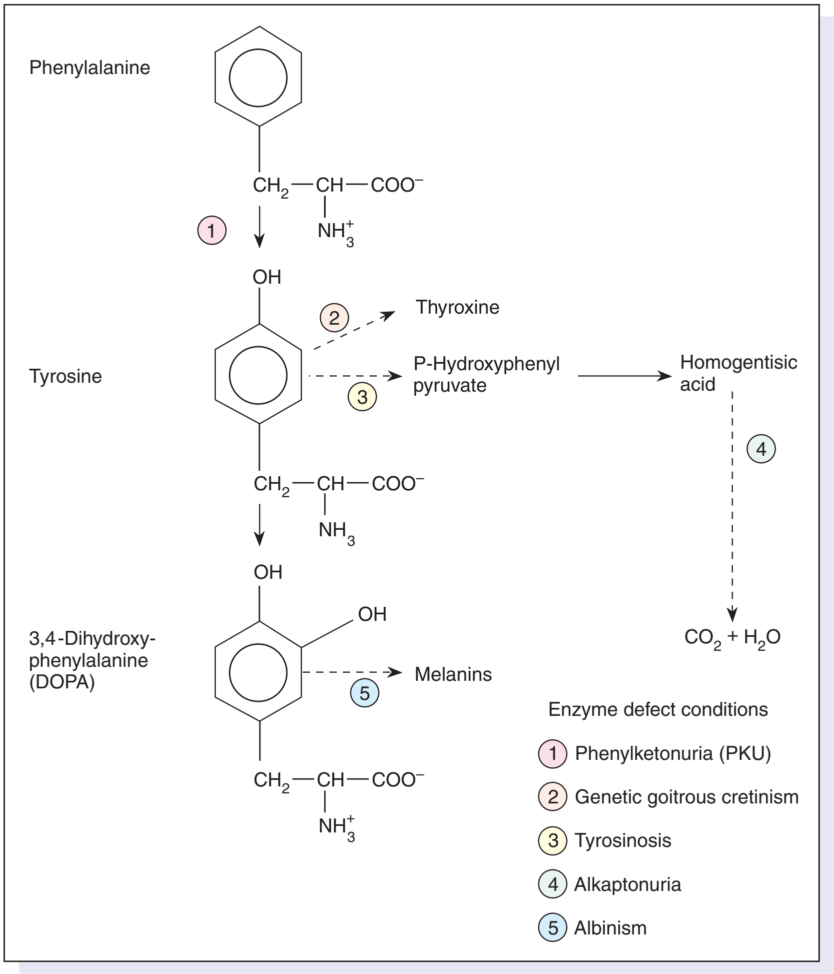


Figure 2.24 In humans, errors in melanin synthesis produce different physical conditions and diseases, depending on which part of the tyrosine (an amino acid) metabolic pathway is disrupted. The broken arrows indicate that there is more than one step in the pathways; the conditions listed occur only in homozygous recessives.

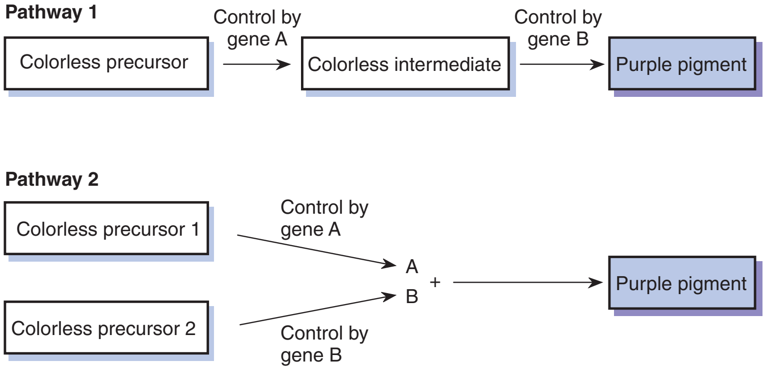


Figure 2.25 Possible metabolic pathways of color production that would yield 9:7 ratios in the F_2 generation of a self-fertilized dihybrid.

combination of alleles. Thus, *nivea* is epistatic to *eosinea,* and *eosinea* is hypostatic to *nivea.* (We should add that at least seven major colors occur in snapdragons, along with subtle shade differences, all genetically controlled by the interactions of at least seven genes.)

Other types of epistatic interactions occur in other organisms. Table 2.4 lists several. We do not know the exact physiological mechanisms in many cases, especially when developmental processes are involved (e.g., size and shape). However, from an analysis of crosses, we can know the number of genes involved and the general nature of their interactions.

BIOCHEMICAL GENETICS

Inborn Errors of Metabolism

The examples of mouse coat color, corn kernel color, and snapdragon flower petal color demonstrate that genes control the formation of enzymes, proteins that control the steps in biochemical pathways. For the most part, dominant alleles control functioning enzymes that catalyze biochemical steps. Recessive alleles often produce nonfunctioning enzymes that cannot catalyze specific steps. Often a heterozygote is normal because one allele produces a functional enzyme; usually only half the enzyme quantity of the dominant homozygote is enough. The study of the relationship between genes and enzymes is generally called **biochemical genetics** because it involves the genetic control of biochemical pathways. A. E. Garrod, a British physician, pointed out this general concept of human gene action in *Inborn Errors of Metabolism,* published in 1909. Only nine years after Mendel was rediscovered, Garrod described several human conditions, such as albinism and alkaptonuria, that occur in individuals who are homozygous for recessive alleles (see fig. 2.24).

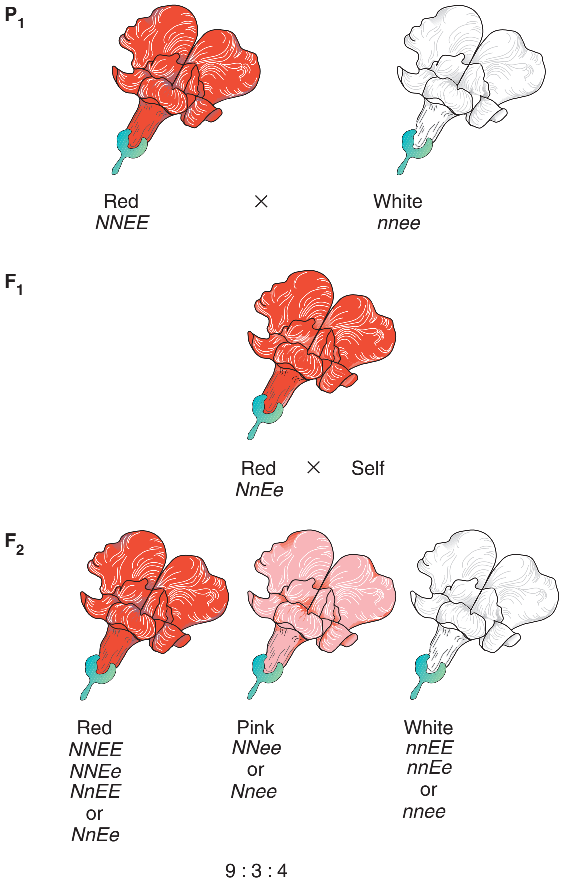


Figure 2.26 Flower color inheritance in snapdragons. This is an example of epistasis: an *nn* genotype masks the expression of alleles (*EE, Ee,* or *ee*) at the *eosinea* gene.

Table 2.4 **Some Examples of Epistatic Interactions Among Alleles of Two Genes**

Characteristic	Phenotype of F_1 Dihybrid (*AaBb*)	Phenotypic F_2 Ratio
Corn and sweet pea color	Purple	Purple:white 9:7
Mouse coat color	Agouti	Agouti:black:albino 9:3:4
Shepherd's purse seed capsule shape	Triangular	Triangular:oval 15:1
Summer squash shape	Disk	Disk:sphere:elongate 9:6:1
Fowl color	White	White:colored 13:3

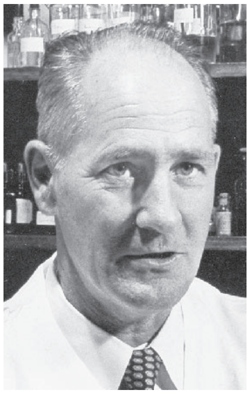
For example, people normally degrade homogentisic acid (alkapton) into maleylacetoacetic acid. Persons with the disease alkaptonuria are homozygous for a nonfunctional form of the enzyme essential to the process: homogentisic acid oxidase, found in the liver. Absence of this enzyme blocks the degradation reaction so that homogentisic acid builds up. This acid darkens upon oxidation. Thus, affected persons can be identified by the black color of their urine after its exposure to air. Eventually, alkaptonuria causes problems in the joints and a darkening of cartilage that is visible in the ears and the eye sclera.

One-Gene-One-Enzyme Hypothesis

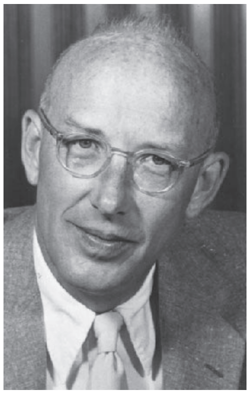
Pioneering work in the concept that genes control the production of enzymes, which in turn control the steps in biochemical pathways, was done by George Beadle and Edward Tatum, who eventually shared the Nobel Prize for their work. They not only put forth the **one-gene-one-enzyme hypothesis,** but also used mutants to work out the details of biochemical pathways. In 1941, Beadle and Tatum were the first scientists to isolate mutants with nutritional requirements that defined steps in a biochemical pathway. In the early 1940s, they united the fields of biochemistry and genetics by using strains of a bread mold with specific nutritional requirements to discover the steps in biochemical pathways in that organism.

Through this century, the study of mutations has been the driving force in genetics. The process of mutation produces alleles that differ from the wild-type and shows us that a particular aspect of the phenotype is under genetic control. Beadle and Tatum used mutants to work out the steps in the biosynthesis of niacin (vitamin B_3) in pink bread mold, *Neurospora crassa.*

Normally, *Neurospora* synthesizes niacin via the pathway shown in figure 2.27. Beadle and Tatum isolated mutants that could not grow unless niacin was provided in the culture medium; these mutants had enzyme deficiencies in the synthesizing pathway that ends with niacin. Thus, although wild-type *Neurospora* could grow on a medium without additives, the mutants could not. Beadle and Tatum had a general idea, based on the structure of niacin, as to what substances would be in the niacin biosynthesis pathway. They could thus make educated guesses as to what substances they might add to the culture medium to enable the mutants to grow. Mutant B (table 2.5), for example, could grow if given niacin or, alternatively, 3-hydroxyanthranilic acid. It could not grow if given only kynurenine. Thus, Beadle and Tatum knew that the B mutation affected the pathway between kynurenine and 3-hydroxyanthranilic acid. Similarly, mutant A could grow if given 3-hydroxyanthranilic acid or kynurenine instead of niacin. Therefore, these two prod-



George W. Beadle (1903–89). Courtesy of the Archives, California Institute of Technology.



Edward L. Tatum (1909–75). Courtesy of the Proceedings for the National Academy of Sciences.

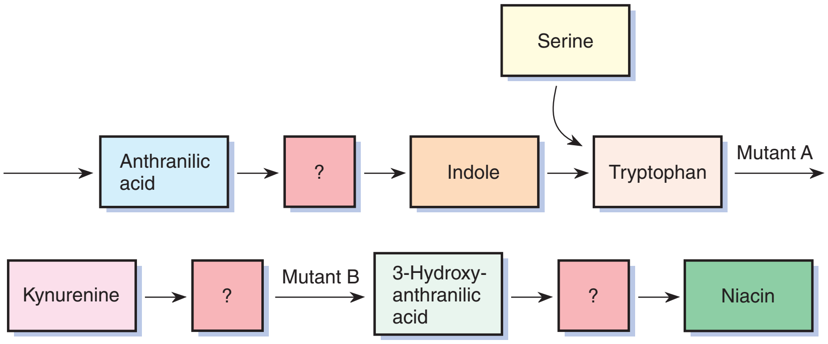


Figure 2.27 Pathway of niacin synthesis in *Neurospora.* Each *arrow* represents an enzyme-mediated step. Each *question mark* represents a presumed but (at the time Beadle and Tatum were working) unknown compound.

Table 2.5 **Growth Performance of *Neurospora* Mutants (plus sign indicates growth; minus sign indicates no growth)**

	Additive			
	Tryptophan	**Kynurenine**	**3-Hydroxyanthranilic Acid**	**Niacin**
Wild-type	+	+	+	+
Mutant A	−	+	+	+
Mutant B	−	−	+	+

ucts must be in the pathway *after* the step interrupted in mutant A. Conversely, since neither of these mutant organisms could grow when given only tryptophan, Beadle and Tatum knew that tryptophan occurred in the pathway before the steps with the deficient enzymes. By this type of analysis, they discovered the steps in several biochemical pathways of *Neurospora.* Many biochemical pathways are similar in a huge range of organisms, and thus Beadle and Tatum's work was of general importance. (We will spend more time studying *Neurospora* in chapter 6.)

Beadle and Tatum could further verify their work by observing which substances accumulated in the mutant organisms. If a biochemical pathway is blocked at a certain point, then the substrate at that point cannot convert into the next product, and it builds up in the cell. For example, in the niacin pathway (fig. 2.27), if a block occurs just after 3-hydroxyanthranilic acid, that substance will build up in the cell because it cannot convert into the next substance on the way to niacin.

This analysis could be misleading, however, if the built-up substance is being "siphoned off" into other biochemical pathways in the cell. Also, the cell might attempt to break down or sequester toxic substances. This would mean there might not be an obvious buildup of the substance just before the blocked step.

Beadle and Tatum concluded from their studies that one gene controls the production of one enzyme. The one-gene-one-enzyme hypothesis is an oversimplification that we will clarify later in the book. As a rule of thumb, however, the hypothesis is valid, and it has served to direct attention to the functional relationship between genes and enzymes in biochemical pathways.

Although a change in a single enzyme usually disrupts a single biochemical pathway, it frequently has more than one effect on phenotype. Multiple effects are referred to as **pleiotropy.** A well-known example is sickle-cell anemia, caused by a mutation in the gene for the β chain of the hemoglobin molecule. In a homozygote, this mutation causes a sickling of red blood cells (fig. 2.28). The sickling of these cells has two major ramifications.

First, the liver destroys the sickled cells, causing anemia. The phenotypic effects of this anemia include physical weakness, slow development, and hypertrophy of the bone marrow, resulting in the "tower skull" seen in some of those afflicted with the disease. The second major effect of sickle-cell anemia is that the sickled cells interfere with capillary blood flow, clumping together and resulting in damage to every major organ. The individual can suffer pain, heart failure, rheumatism, and other ill effects. Hence, a single mutation shows itself in many aspects of the phenotype.

Figure 2.28 Sickle-shaped red blood cells from a person with sickle-cell anemia. Red blood cells are about 7 to 8 μm in diameter. (Courtesy of Dr. Patricia N. Farnsworth.)

SUMMARY

STUDY OBJECTIVE 1: To understand that genes are discrete units that control the appearance of an organism 17–18

Genes control phenotypic traits such as size and color. They are inherited as discrete units.

STUDY OBJECTIVE 2: To understand Mendel's rules of inheritance: segregation and independent assortment 18–22

Higher organisms contain two alleles of each gene, but only one allele enters each gamete. Zygote formation restores the double number of alleles in the cell. This is Mendel's rule of segregation.

Alleles of different genes segregate independently of each other. Mendel was the first to recognize the 3:1 phenotypic ratio as a pattern of inheritance; the 9:3:3:1 ratio demonstrates independent assortment in hybrids. Mendel was successful in his endeavor because he performed careful experiments using discrete characteristics, large numbers of offspring, and an organism (the pea plant) amenable to controlled fertilizations.

STUDY OBJECTIVE 3: To understand that dominance is a function of the interaction of alleles; similarly, epistasis is a function of the interaction of nonallelic genes 22–37

There can be many alleles for one gene, although each individual organism has only two alleles for each gene. A phenotype is dominant if it is expressed when one or two copies of its allele are present (heterozygote or homozygote). Dominance depends, however, on the level of the phenotype one looks at.

Genes usually control the production of enzymes, which control steps in metabolic pathways. Many human metabolic diseases are due to homozygosity of an allele that produces a nonfunctioning enzyme.

Nonallelic genes can interact in producing a phenotype so that alleles of one gene mask the expression of alleles of another gene. This process, termed *epistasis,* alters the expected phenotypic ratios.

STUDY OBJECTIVE 4: To define how genes generally control the production of enzymes and thus the fate of biochemical pathways 37–39

Beadle and Tatum used mutants with mutations in the niacin biosynthesis pathway to work out the steps in the pathway. A single mutation can have many phenotypic effects (pleiotropy).

SOLVED PROBLEMS

PROBLEM 1: In corn, rough sheath (*rs*) is recessive to smooth sheath (*Rs*), midrib absent (*mrl*) is recessive to midrib present (*Mrl*), and crinkled leaf (*cr*) is recessive to smooth leaf (*Cr*). (Alleles are named for the mutants, which are all recessive.) What are the results of testcrossing a trihybrid?

Answer: The trihybrid has the genotype *Rsrs Mrlmrl Crcr.* This parent is capable of producing eight different gamete types in equal frequencies, all combinations of one allele from each gene (*Rs Mrl Cr, Rs Mrl cr, Rs mrl Cr, Rs mrl cr, rs Mrl Cr, rs Mrl cr, rs mrl Cr,* and *rs mrl cr*). In a testcross, the other parent is a recessive homozygote with the genotype *rsrs mrlmrl crcr,* capable of producing only one type of gamete, with the alleles *rs mrl cr.* Thus, this cross can produce zygotes of eight different genotypes (and phenotypes), one for each of the gamete types of the trihybrid parent: *Rsrs Mrlmrl Crcr* (smooth sheath, midrib present, smooth leaf); *Rsrs Mrlmrl crcr* (smooth sheath, midrib present, crinkled leaf); *Rsrs mrlmrl Crcr* (smooth sheath, midrib absent, smooth leaf); *Rsrs mrlmrl crcr* (smooth sheath, midrib absent, crinkled leaf); *rsrs Mrlmrl Crcr* (rough sheath, midrib present, smooth leaf); *rsrs Mrlmrl crcr* (rough sheath, midrib present, crinkled leaf); *rsrs mrlmrl Crcr* (rough sheath, midrib absent, smooth leaf); and *rsrs mrlmrl crcr* (rough sheath, midrib absent, crinkled leaf). Each should make up one-eighth of the total number of offspring.

PROBLEM 2: Summer squash come in three shapes: disk, spherical, and elongate. In one experiment, researchers crossed two squash plants with disk-shaped fruits. The first 160 seeds planted from this cross produced plants with fruit shapes as follows: 89 disk, 61 sphere, and 10 elongate. What is the mode of inheritance of fruit shape in summer squash?

Answer: The numbers are very close to a ratio of 90:60:10, or 9:6:1, an epistatic variant of the 9:3:3:1, with the two 3/16ths categories combined. If this is the case, then the parent plants with disk-shaped fruits were dihybrids (*AaBb*). Among the offspring, 9/16ths had disk-shaped fruit, indicating that it takes at least one dominant allele of each gene to produce disk-shaped fruits (*A-B-*: *AABB, AaBB, AABb,* or *AaBb*). The 1/16th category of plants with elongate fruits indicates that this fruit shape occurs in homozygous recessive plants (*aabb*). The plants with spherical fruit are thus plants with a dominant allele of one gene but a homozygous recessive combination at the other gene (*AAbb, Aabb, aaBB,* or *aaBb*). In summary, then, two genes combine to control fruit shape in summer squash. The epistatic interactions between the two genes produce a 9:6:1 ratio of offspring phenotypes when dihybrids are crossed.

PROBLEM 3: A geneticist studying the pathway of synthesis of phenylalanine in *Neurospora* isolated several mutants that require phenylalanine to grow. She tested whether each mutant would grow when provided additives that she believed were in the pathway of phenylalanine synthesis (see table); a plus indicates growth and minus indicates the lack of growth in the three mutants tested.

	Additive			
	Phenylpyruvate	Prephenate	Chorismate	Phenylalanine
Wild-type	+	+	+	+
Mutant 1	−	−	−	+
Mutant 2	+	+	−	+
Mutant 3	+	−	−	+

Where in the pathway to phenylalanine synthesis does each of the additives belong, if at all?

Answer: The wild-type grows in the presence of all additives. This is not surprising since the wild-type can grow, by definition, in the absence of all the additives because it can synthesize phenylalanine *de novo.* Mutant 1 cannot grow in the presence of any additive except phenylalanine, indicating that its mutation affects the step just before the end of the pathway at phenylalanine. In other words, each of the other additives occurs in the phenylalanine pathway before the point of the mutation in mutant 1. Mutant 2 can grow if given any additive but chorismate, indicating that chorismate is at the beginning of the pathway, and the mutation affects the pathway just after that step. Finally, mutant 3 can grow if given phenylpyruvate or phenylalanine, indicating that its mutation affects the step before phenylpyruvate and phenylalanine, but after the earlier part of the pathway. Putting all of this information together indicates that the pathway to phenylalanine, with mutants indicated, is:

$$\text{chorismate} \xrightarrow{2} \text{prephenate} \xrightarrow{3} \text{phenylpyruvate} \xrightarrow{1} \text{phenylalanine}$$

EXERCISES AND PROBLEMS[*]

SEGREGATION

1. Mendel crossed tall pea plants with dwarf ones. The F_1 plants were all tall. When these F_1 plants were selfed to produce the F_2 generation, he got a 3:1 tall-to-dwarf ratio in the offspring. Predict the genotypes and phenotypes and relative proportions of the F_3 generation produced when the F_2 generation was selfed.
2. What properties of fruit flies and corn made them the organisms of choice for geneticists during most of the first half of the twentieth century? (Molecular geneticists have made great strides working with bacteria and viruses. You could begin thinking at this point about the properties that have made these organisms so valuable to geneticists.)
3. State precisely the rules of segregation and independent assortment. (See also the Exercises and Problems section on Independent Assortment.)
4. In *Drosophila,* a cross between a dark-bodied fly and a tan-bodied fly yields seventy-six tan and eighty dark flies. Diagram the cross.
5. If two black mice are crossed, ten black and three white mice result.
   - **a.** Which allele is dominant?
   - **b.** Which allele is recessive?
   - **c.** What are the genotypes of the parents?
6. In *Drosophila,* two red-eyed flies mate and yield 110 red-eyed and 35 brown-eyed offspring. Diagram the cross and determine which allele is dominant.

DOMINANCE IS NOT UNIVERSAL

7. Explain how Tay-Sachs disease can be both a recessive and an incomplete dominant trait. What are the differences between incomplete dominance and codominance?
8. How does the biochemical pathway in figure 2.13 explain how alleles I^A and I^B are codominant, yet both dominant to allele *i*?

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[*] Answers to selected exercises and problems are on page A-1.

9. Two short-eared pigs are mated. In the progeny, three have no ears, seven have short ears, and four have long ears. Explain these results by diagramming the cross.

10. A plant with red flowers is crossed with a plant with white flowers. All the progeny are pink. When the plants with pink flowers are crossed, the progeny are eleven red, twenty-three pink, and twelve white. What is the mode of inheritance of flower color?

NOMENCLATURE

11. In fruit flies, a new dominant trait, washed eye, was discovered. Describe different ways of naming the alleles of the washed-eye gene.

12. The following is a list of ten genes in fruit flies, each with one of its alleles given. Are the alleles shown dominant or recessive? Are they mutant or wild-type? What is the alternative allele for each? Is the alternative allele dominant or recessive in each case?

Name of Gene	Allele
yellow	y^+
Hairy wing	*Hw*
Abruptex	Ax^+
Confluens	*Co*
raven	rv^+
downy	*dow*
Minute(2)e	$M(2)e^+$
Jammed	*J*
tufted	tuf^+
burgundy	*bur*

MULTIPLE ALLELES

13. In the ABO blood system in human beings, alleles I^A and I^B are codominant, and both are dominant to the *i* allele. In a paternity dispute, a type AB woman claimed that one of four men, each with different blood types, was the father of her type A child. Which of the following could be the blood type of the father of the child on the basis of the evidence given?

a. Type A
b. Type B
c. Type O
d. Type AB

14. Under what circumstances can the phenotypes of the ABO system be used to refute paternity?

15. In blood transfusions, one blood type is called the "universal donor" and one the "universal recipient" because of their ABO compatibilities. Which is which?

16. Among the genes having the greatest number of alleles are those involved in self-incompatibility in plants. In some cases, hundreds of alleles exist for a single gene. What types of constraints might exist to set a limit on the number of alleles a gene can have?

17. In the human ABO blood system, the alleles I^A and I^B are dominant to *i.* What possible phenotypic ratios do you expect from a mating between a type A individual and a type B individual?

18. In screech owls, crosses between red and silver individuals sometimes yield all red; sometimes 1/2 red:1/2 silver; and sometimes 1/2 red:1/4 white:1/4 silver offspring. Crosses between two red owls yield either all red, 3/4 red:1/4 silver, or 3/4 red:1/4 white offspring. What is the mode of inheritance?

19. A premed student, Steve, plans to marry the daughter of the dean of nursing. The dean's husband was sterile, and the daughter was conceived by artificial insemination. Steve's father puts pressure on Steve to marry someone else. Having served as an anonymous sperm donor, he is concerned that Steve and his fiancé may be half brother and sister. Given the following information, deduce whether Steve and his fiancé could be related. (The MN and Ss systems are two independent, codominant blood-type systems.)

	Blood Type
Dean	A, MN, Ss
Her daughter	O, M, S
Steve's father	A, MN, Ss
Steve	O, N, s
Steve's mother	B, N, s

INDEPENDENT ASSORTMENT

20. Mendel self-fertilized dihybrid plants (*RrYy*) with round and yellow seeds and got a 9:3:3:1 ratio in the F_2 generation. As a test of Mendel's hypothesis of independent assortment, predict the kinds and numbers of progeny produced in testcrosses of these F_2 offspring.

21. Four o'clock plants have a gene for color and a gene for height with the following phenotypes:

RR: red flower
Rr: pink flower
rr: white flower

TT: tall plant
Tt: medium height plant
tt: dwarf plant

Give the proportions of genotypes and phenotypes produced if a dihybrid plant is self-fertilized.

22. A particular variety of corn has a gene for kernel color and a gene for height with the following phenotypes:

CC, Cc: purple kernels
cc: white kernels

TT: tall stem
Tt: medium height stem
tt: dwarf stem

Give the proportions of genotypes and phenotypes produced if a dihybrid plant is selfed.

23. To determine the genotypes of the offspring of a cross in which a corn trihybrid (*Aa Bb Cc*) was selfed, a geneticist has three choices. He or she can take a sample of the progeny and (a) self-fertilize the individual plants, (b) testcross the plants, or (c) cross the individuals with a trihybrid (backcross). Which method is preferable?

24. In figure 2.17, the F_2 phenotypic ratio is 3:1:3:1:6:2. What are the phenotypic segregation ratios for each blood system (AB, Rh) separately? Are they segregating properly? What phenotypic ratio in the F_2 generation would indicate interference with independent assortment?

25. Assume that Mendel looked simultaneously at four traits of his pea plants (and each trait exhibited dominance). If he crossed a homozygous dominant plant with a homozygous recessive plant, all the F_1 offspring would be of the dominant phenotype. If he then selfed the F_1 plants, how many different types of gametes would these F_1 plants produce? How many different phenotypes would appear in the F_2 generation? How many different genotypes would appear? What proportion of the F_2 offspring would be of the fourfold recessive phenotype?

26. A geneticist crossed two corn plants, creating an F_1 decahybrid (ten segregating loci). He then self-fertilized this decahybrid. How many different kinds of gametes did the F_1 plant produce? What proportion of the F_2 offspring were recessive homozygotes? How many different kinds of genotypes and phenotypes were generated in the F_2 offspring? What would your answer be if the geneticist test-crossed the decahybrid instead?

27. Consider the following crosses in pea plants and determine the genotypes of the parents in each cross. Yellow and green refer to seed color; tall and short refer to plant height.

	Progeny			
Cross	**Yellow, Tall**	**Yellow, Short**	**Green, Tall**	**Green, Short**
a. Yellow, tall × yellow, tall	89	31	33	10
b. Yellow, short × yellow, short	0	42	0	15
c. Green, tall × yellow, short	21	20	24	22

28. A brown-eyed, long-winged fly is mated with a red-eyed, long-winged fly. The progeny are

51 long, red　18 short, red
53 long, brown　16 short, brown

What are the genotypes of the parents?

29. True-breeding flies with long wings and dark bodies are mated with true-breeding flies with short wings and tan bodies. All the F_1 progeny have long wings and tan bodies. The F_1 progeny are allowed to mate and produce:

44 tan, long　14 tan, short
16 dark, long　6 dark, short

What is the mode of inheritance?

30. In peas, tall (*T*) is dominant to short (*t*), yellow (*Y*) is dominant to green (*y*), and round (*R*) is dominant to wrinkled (*r*). From a cross of two triple heterozygotes, what is the chance of getting a plant that is

a. tall, yellow, round?
b. short, green, wrinkled?
c. short, green, round?

31. In corn, the genotype *A- C- R-* is colored. Individuals homozygous for at least one recessive allele are colorless. Consider the following crosses involving colored plants, all with the same genotype. Based on the results, deduce the genotypes of the colored plants.

colored × *aa cc RR* → 1/2 colored; 1/2 colorless
colored × *aa CC rr* → 1/4 colored; 3/4 colorless
colored × *AA cc rr* → 1/2 colored; 1/2 colorless

32. Consider the following crosses in *Drosophila.* Based on the results, deduce which alleles are dominant and the genotypes of the parents. Orange and red are eye colors; crossveins occur on the wings.

	Progeny			
Parents	**Orange, crossveins**	**Orange, crossveinless**	**Red, crossveins**	**Red crossveinless**
a. Orange, crossveins × orange, crossveins	83	26	0	0
b. Red, crossveins × red, crossveinless	20	18	65	63
c. Red, crossveinless × red, crossveins	0	0	74	81
d. Red, crossveins × red, crossveins	28	11	93	34

33. In *Drosophila melanogaster,* a recessive autosomal gene, *ebony,* produces a dark body color when homozygous, and an independently assorting autosomal gene, *black,* has a similar effect. If homozygous *ebony* flies are crossed with homozygous *black* flies,

a. what will be the phenotype of the F_1 flies?

b. what phenotypes and what proportions would occur in the F_2 generation?

c. what phenotypic ratios would you expect to find in the progeny of the backcrosses of $F_1 \times$ *ebony*? $F_1 \times$ *black*?

34. *A, B,* and *C* are independently assorting Mendelian factors (genes) controlling the production of black pigment in a rodent species. Alleles of these genes are indicated as *a, b,* and *c,* respectively. Assume that *A, B,* and *C* act in this pathway:

$$\begin{tikzcd}
\text{colorless} \arrow[r, "\text{control by } A"] & \text{red} \arrow[d] & \\
 & + \arrow[r, "\text{control by } C"] & \text{black} \\
\text{colorless} \arrow[r, "\text{control by } B"] & \text{red} \arrow[u] &
\end{tikzcd}$$

A black *AA BB CC* individual is crossed with a colorless *aa bb cc* to give black F_1 individuals. The F_1 individuals are selfed to give F_2 progeny.

a. What proportion of the F_2 generation is colorless?

b. What proportion of the F_2 generation is red?

35. In a particular *Drosophila* species, there are four strains differing in eye color: wild-type, orange-1, orange-2, and pink. The following matings of true-breeding individuals were performed.

Cross	**F_1**
wild-type × orange-1	all wild-type
wild-type × orange-2	all wild-type
orange-1 × orange-2	all wild-type
orange-2 × pink	all orange-2
F_1 (orange-1 × orange-2) × pink	1/4 orange-2: 1/4 pink:1/4 orange-1: 1/4 wild-type

What F_2 ratio would you expect if the F_1 progeny from orange-1 × orange-2 were selfed?

GENOTYPIC INTERACTIONS

36. In a variety of onions, three bulb colors segregate: red, yellow, and white. A plant with a red bulb is crossed to a plant with a white bulb, and all the offspring have red bulbs. When these are selfed, the following plants are obtained:

Red-bulbed	119
Yellow-bulbed	32
White-bulbed	9

What is the mode of inheritance of bulb color, and how do you account for the ratio?

37. When studying an inherited phenomenon, a geneticist discovers a phenotypic ratio of 9:6:1 among offspring of a given mating. Give a simple, genetic explanation for this result. How would you test this hypothesis?

38. You notice a rooster with a pea comb and a hen with a rose comb in your chicken coop. Outline how you would determine the nature of the genetic control of comb type. How would you proceed if both your rooster and hen had rose combs?

39. Suggest possible mechanisms for the epistatic ratios given in table 2.4. Can you add any further ratios?

40. What are the differences among dominance, epistasis, and pleiotropy? How can you determine that pleiotropic effects, such as those seen in sickle-cell anemia, are not due to different genes?

41. You are working with the exotic organism *Phobia laboris* and are interested in obtaining mutants that work hard. Normal phobes are lazy. Perseverance finally pays off, and you successfully isolate a true-breeding line of hard workers. You begin a detailed genetic analysis of this trait. To date you have obtained the following results:

hard worker × nonworker
↓
F_1: all nonworkers of both sexes
F_1 female × worker male
↓
3/4 hard workers:1/4 nonworkers of both sexes

From these results, predict the expected phenotypic ratio from crossing two F_1 nonworkers.

BIOCHEMICAL GENETICS

42. The following is a pathway from substance Q to substance U, with each step numbered:

$$Q \xrightarrow{1} R \xrightarrow{2} S \xrightarrow{3} T \xrightarrow{4} U$$

Which product should build up in the cell and which products should never appear if the pathway is blocked at point 1? At 2? At 3? At 4?

43. The following chart shows the growth (+) or lack of growth (−) of four mutant strains of *Neurospora* with various additives. The additives are in the pathway of niacin biosynthesis. Diagram the pathway and show which steps the various mutants block. Which compound would each mutant accumulate? When you complete this problem, compare your results with figure 2.27. What effect on growth would you observe following a mutation in the pathway of serine biosynthesis?

	Mutants			
Additives	**1**	**2**	**3**	**4**
Nothing	−	−	−	−
Niacin	+	+	+	+
Tryptophan	+	+	−	−
Kynurenine	+	+	−	−
3-Hydroxyanthranilic acid	+	+	+	−
Indole	−	+	−	−

44. The following shows the growth (+) or lack of growth (−) of various mutants in another biosynthesis pathway. Determine this pathway, the point of blockage for each mutant, and the substrate each mutant accumulates.

	Mutants				
Additives	**1**	**2**	**3**	**4**	**5**
Nothing	−	−	−	−	−
A	−	+	+	+	+
B	−	+	−	+	−
C	−	+	−	+	+
D	−	−	−	+	−
E	+	+	+	+	+

45. Maple sugar urine disease is a rare inborn error of human metabolism in which the urine of affected individuals smells like maple sugar.

a. If two unaffected individuals have an affected child, what is the probable mode of inheritance of the disease?

b. What is the chance that the second child will be unaffected?

CRITICAL THINKING QUESTIONS

1. In the shepherd's purse plant, the seed capsule comes in two forms, triangular and rounded. If two dihybrids are crossed, the resulting ratio of capsules is 15:1 in favor of triangular seed capsules. What type of biochemical pathway might generate that ratio?

2. Assume Mendel made the cross of two true-breeding plants that differed in all seven traits under study, one with all dominant traits, the other with all recessive traits. What would the ratio of phenotypes be in the F_2 generation?

Suggested Readings for chapter 2 are on page B-1.