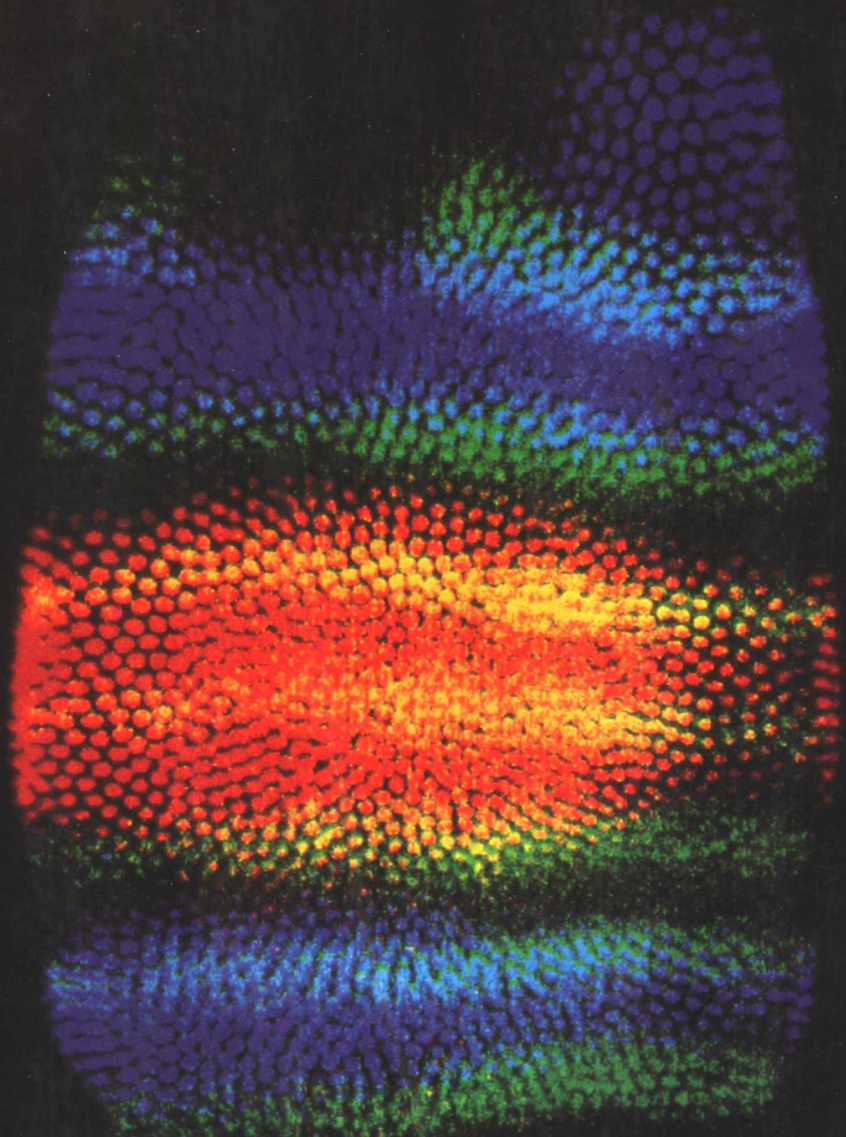
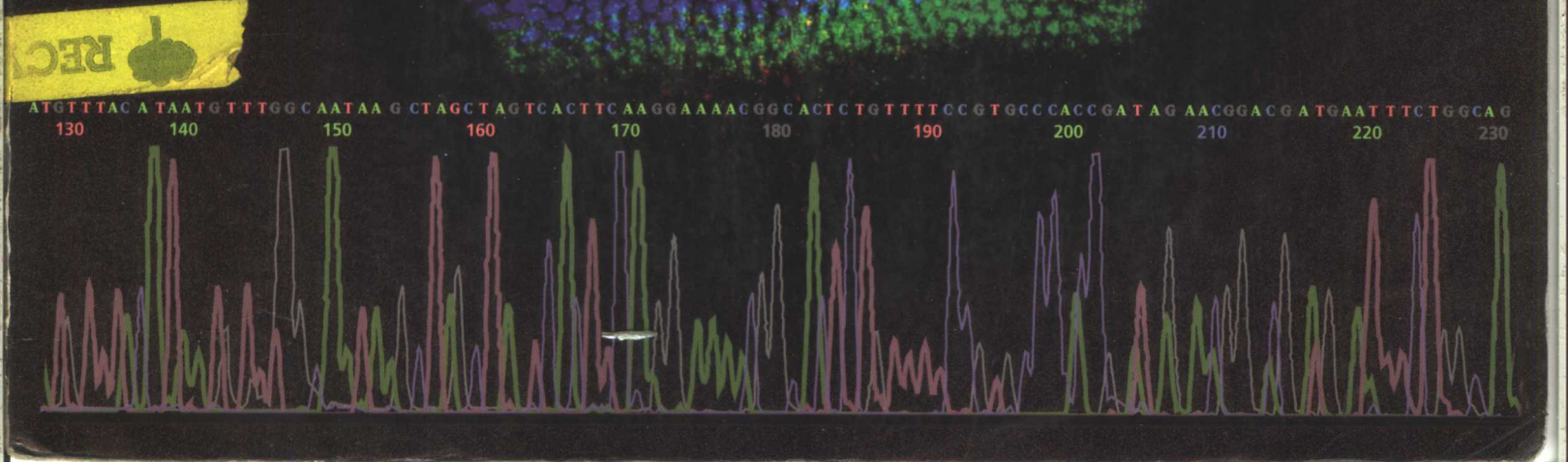
THIRD EDITION

GENETICS

DANIEL L. HARTL





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HARVARD UNIVERSITY

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Cover: An embryo of a *Drosophila* approximately 3 hours after fertilization showing the combined patterns of expression of the genes *Hairy, Krüppel,* and *giant.* Cells in which *hairy* is expressed fluoresce green, those in which *Krüppel* is expressed fluoresce red, and those in which *giant* is expressed fluoresce blue. The combined expression of *hairy* (green) and *Krüppel* (red) shows up as yellow. Even at this early stage in development, there is already considerable linear differentiation in the patterns of gene expression. Below the embryo is the trace of a fluorescence pattern obtained from an automated DNA-sequencing machine and the DNA sequence. (*Drosophila* embryo courtesy of James Langeland, Stephen Paddock, and Sean Carroll.)

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Introduction: For the Student

You are possibly wondering what you are going to learn by taking a course in genetics. Will the material be interesting? Is there any reason to study genetics other than to satisfy an academic requirement? At the end of the course, will you feel glad that you took it? Will there be any practical value to what you will learn? The purpose of this introduction is to reassure you that the answer to each question is yes. Furthermore, the study of genetics is relevant not only to biologists, but also to all members of our modern, complex, technological society. Understanding the principles of genetics will help you to make informed decisions about numerous matters of political, scientific, and personal concern.

At least 4000 years ago in Sumeria, Egypt, and other parts of the world, farmers recognized that they could improve their crops and their animals by selective breeding. Their knowledge was based on experience and very incomplete, but they did recognize that many features of plants and animals were passed from generation to generation. Furthermore, they discovered that desirable traits—such as size, speed, and weight of animals—could sometimes be combined by controlled mating and that, in plants, crop yield and resistance to arid conditions could be combined by cross-pollination. The ancient breeding programs were not based on much solid information because nothing was known about genes or any of the principles of heredity.

The scientific study of heredity is called **genetics.** The modern approach to genetics can be traced to the middle of the nineteenth century, when Gregor Mendel undertook his careful analyses of inheritance in peas. Mendel's experiments were simple and direct and brought forth significant principles that determine how traits are passed from one generation to the next. In Chapter 1, you will learn the rules followed by genes and chromosomes as they pass from generation to generation, and you will be able to calculate in many instances the probabilities that organisms with particular traits will be produced. The calculations require only simple arithmetic, and so there is no reason to be intimidated—even if higher mathematics is not a comfortable part of your repertory.

Mendel's kind of experiments, which occupied most of genetic research until the middle of the twentieth century, is called **transmission genetics.** Some people have called it formal genetics because the subject can be understood and the rules clearly seen without reference to the biochemical nature of genes or gene products. Geneticists of that period concerned themselves with a variety of organisms. One was the fruit fly, *Drosophila melanogaster*; others were corn (maize), chickens, mice, and, later, various fungi. The main reasons for the study of these model organisms were the following:

1. Genetic analysis needs traits that are easily detected and a large collection of variants (called mutants). *Drosophila* is extraordinary in this respect because natural populations include variants with different eye color, wing shape, bristle type, and so forth, and new mutations are readily detected in the laboratory. Corn is a good choice, too, because variants of kernel type and color are easily seen.
2. Genetic analysis requires sizable numbers of individuals. In genetic experiments, a sufficient number of organisms must be examined to determine the frequencies with which traits appear in each generation and to compare theoretical probabilities with observations. Again, *Drosophila* is excellent because hundreds of culture bottles can be maintained in a laboratory. Corn is good because a large number of plants can be grown in a fairly small plot of land. Although colonies of mice are maintained in smaller number, mice compensate for this limitation by possessing traits present in higher organisms and of direct relevance to human disease—for example, different mouse strains with hereditary diabetes, hypertension, cancer, and various immunological disorders have been developed.
3. Ideally, generation times should be short so that the transmission of traits from one generation to the next can be followed in a reasonable period of time. From this point of view, Mendel's original choice of peas was good, but not the best, because he could grow

only one or two crops per year. In *Drosophila*, the time interval between fertilization of an egg and production of a fertile adult is less than two weeks. Corn has its disadvantages in this respect (only one or two generations per year), but one compensation is its importance as an agricultural crop.

4. The organisms should be easy to maintain in the laboratory or field. Clearly, a population of fruit flies is more manageable than a pride of lions, and mice are more convenient than elephants.

Beginning about 1900, geneticists began to wonder about the biochemical nature of the gene. How could information be maintained in molecules, and how could this information be transmitted from one generation to the next? In what way is the information different in a mutant? At that time, there was no logical starting point for such an investigation, no experimental "handle." However, beginning in the 1920s and later in the 1940s, a few critical observations were made (they are documented in Chapter 4), that implicated a molecule discovered in 1869—deoxyribonucleic acid (DNA). With the discovery of the structure of DNA in 1953 by James Watson and Francis Crick, genetics entered the DNA age. Within a decade, there came an understanding of the chemical nature of genes and how genetic information is stored, released to a cell, and transmitted from one generation to the next. During the first three decades after the discovery of DNA structure, the body of genetic knowledge grew with a two-year doubling time. These were exciting times, indeed, and you will be presented with a distillation of these findings in the chapters of this book that deal with **molecular genetics.** Just to give a sample, we know with clarity how a gene is copied, how a mutation arises, how genes are turned on and off when their activity is needed or not needed, how patterns of embryonic development are initially established; we also know, by direct isolation of macromolecules, the chemical products of thousands of genes and, by elegant chemical procedures, the precise sequence of the DNA bases for many genes.

Since the early 1970s, genetics has undergone yet another revolution: the development of recombinant DNA technology. This technology is a collection of methods that enable genes to be transferred, at the will of the molecular geneticist, from one organism to another. This branch of genetics is known as **genetic engineering.** Genetic engineering has had an enormous effect on genetic research, particularly in our ability to understand gene expression and its regulation in plants and animals. Topics formerly unapproachable suddenly became amenable to experimental investigation. Currently, genetic engineering is giving us new tools of economic importance and of value in medical practice: projects of great interest include the genetic modification of plants and domesticated animals and the production of clinically active substances. New recombinant DNA strategies have made it possible to study whole **genomes** (the totality of genetic information in an organism) rather than single genes. The complete set of DNA instructions has been determined by direct DNA sequencing in a number of viruses (and in cellular organelles such as mitochondria), and programs are well underway to determine the complete DNA sequence of bacteria, yeast, nematodes, *Drosophila*, and even the complete DNA sequence in the human genome.

For the past fifty years or so, by far the greatest practical influence of genetics has been in the fields of agriculture and medicine. Studies of the genetic composition of economically important plants have enabled plant breeders to institute rational programs for developing new varieties. Among the more-important plants that have been developed are high-yield strains of corn and dwarf wheat, disease-resistant rice, corn with an altered and more-nutritious amino acid composition (high-lysine corn), and wheat that grows faster, allowing crops to be grown in short-season regions such as Canada and Sweden. The techniques for developing some of these strains are presented in this book. Often, new plant varieties have shortcomings, such as a requirement for increased amounts of fertilizer or decreased resistance to certain pests. How to overcome these shortcomings is a problem for the modern geneticist, who has the job of manipulating the inherited traits. Genetic engineering is also providing new procedures for such manipulations, and quite recently there have been dramatic successes.

Genetics has also made important contributions to medicine and modern clinical practice, and, once again, progress is accelerating because of the increased emphasis on genomic analysis. Genetic studies of the immune system have yielded information about immunological diseases and are enabling physicians to develop programs for organ transplantation. Recent genetic experiments have revealed thousands of new genetic markers in the human genome and have given us new methods for the detection of mutant genes—not only in affected persons, but also in their relatives and in members of the population at large. These methods have given genetic counseling new meaning. Human beings are heir to several thousand different inherited diseases. Married couples can be informed of the possibility of their producing an affected offspring and can now make choices between childbearing and adoption. Consider the relief afforded a woman and a man who learn that neither carries a particular defective gene and that they can produce a child without worry. Furthermore, even with the knowledge that an offspring might be affected with a genetic disorder, techniques are available to determine *in utero* if a fetus is, in fact, affected.

As a pedagogical aid, important terms are printed in **boldface** in the text. These terms are collected at the end

of each chapter in a section titled "Key Terms." You should know their meanings because they form the basic vocabulary of genetics. Each chapter also includes a summary at the end of the text. Sample problems are worked in the section titled "Examples of Worked Problems." Each chapter ends with a fairly large collection of problems. The first few problems test your knowledge of the vocabulary in the text and the more-elementary facts. The problems then increase in difficulty. It is essential that you work as many of the problems as you can because experience has shown that practice with problems is a good way to learn genetics and to identify particular points or concepts that have been misunderstood. Sometimes, it is not even necessary to solve a problem completely but only to read the problem and decide whether you could solve it if asked to do so. The answers to all of the problems, and full explanations, are given at the back of the book. A problem will be more useful to you if you take a fair shot at it before turning to the answer.

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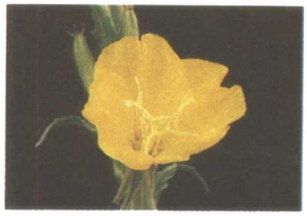

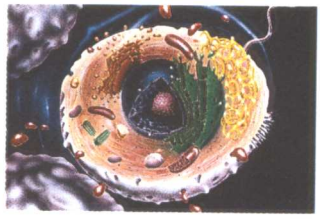

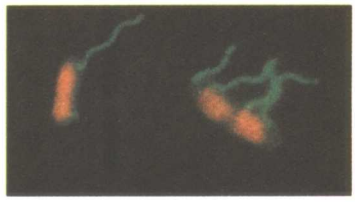

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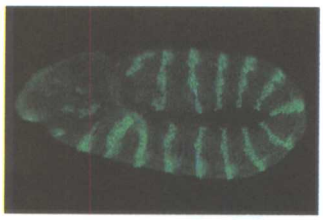

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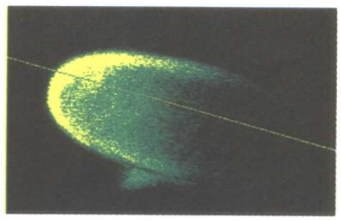
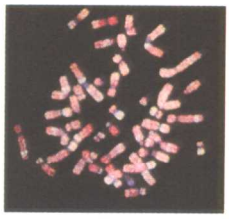




CHAPTER OUTLINE

Genetics is the study of inheritance. The fundamental concept of the science is that:

> Inherited traits are determined by chemical entities that are transmitted from parents to offspring in reproduction.

The unit of inheritance is called a **gene.** The elements of heredity and the rules governing their transmission from generation to generation were discovered by Gregor Mendel in 1866 in experiments with garden peas. Although the molecular biology of genes and gene action was not understood until after the 1950s, Mendel's principles of inheritance formed the foundation for the development of genetics and much of modern biology. Mendel's breakthrough experiments and concepts are the subject of this chapter.

Left: Gregor Mendel carried out his genetic experiments in this small garden in the monastery of St. Thomas in Brno, Czech Republic. The flowers are maintained as a memorial. There is also a Mendel Museum, which is located in the wing of the building at the right. (Photographed by the author in 1990.)

1–1
Mendel and His Experiments

During the period in which Mendel developed his theory of heredity, he was a monk and a teacher of science in a public high school in what is now Brno, Czechoslovakia. He lived in a monastery, and it was there that he carried out his experiments on heredity. The principal difference between Mendel's approach and that of other scientists who were interested in similar problems is that Mendel thought in quantitative terms about traits that could be classified into a small number of categories. He proceeded by posing simple questions to be answered by experiments and then looking for statistical regularities that might identify general rules.

Mendel selected peas for his experiments for two reasons: (1) he had access to varieties that differed in observable alternative characteristics, and (2) his earlier studies of flower structure (Figure 1–1) indicated that peas usually reproduce by self-pollination, in which pollen produced in a flower is transferred to the stigma of the same flower. To produce hybrids by cross-pollination, he needed only to open the keel petal (enclosing the reproductive structures), remove the immature anthers before they had shed pollen, and dust the stigma with pollen taken from a flower on another plant.

Mendel recognized the need to study inherited characteristics that were uniform within any given line of peas but different between lines. Therefore, at the beginning of his experiments, he established **true-breeding** lines in which the plants produced only progeny like themselves when allowed to self-pollinate normally. These different lines (which bred true for flower color, pod shape, or any of the other well-defined characters that Mendel had selected for investigation—Figure 1–2) provided the parents for subsequent hybridization. A **hybrid** is the offspring of a cross between inherently unlike parents.

From an examination of a few of Mendel's original experiments, we will learn what his methods were and how he interpreted his results. One pair of characters that he studied was round versus wrinkled seeds. When pollen from a line of plants with wrinkled seeds was used to cross-pollinate plants from a line with round seeds, all of the hybrid seeds produced were round. He also performed the **reciprocal cross,** in which plants from the line with round seeds were used as the pollen parents and those from the line with wrinkled seeds as female parents. As before, all of the hybrid seeds were round.

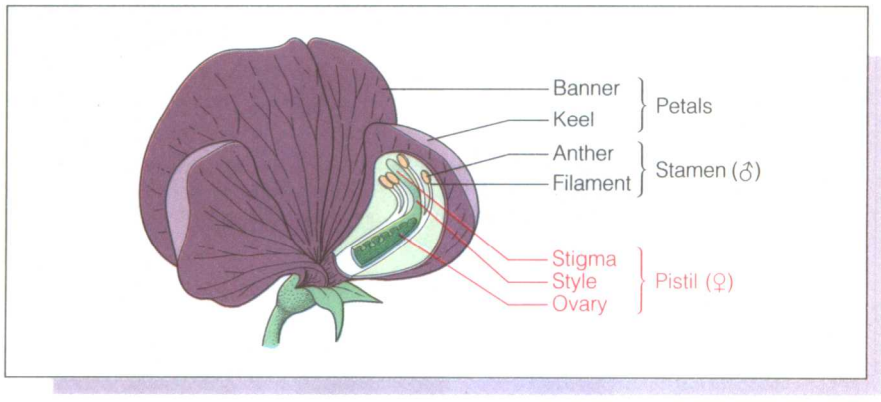


Figure 1–1
A pea flower with section removed to show the reproductive structures. Each flower has a single ovary that develops into the seed pod, and each ovary contains as many as ten ovules, which give the seeds. The pistil is shown in green.

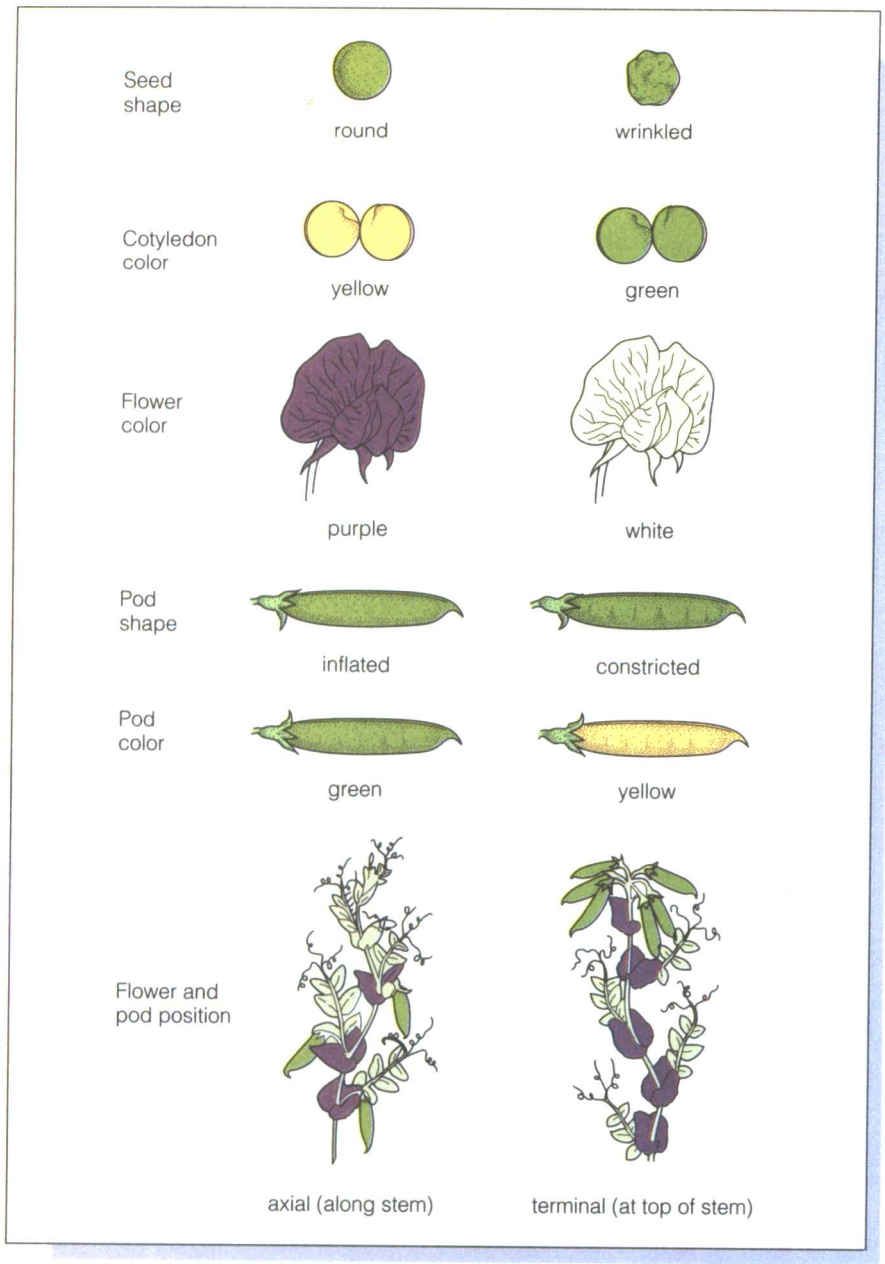
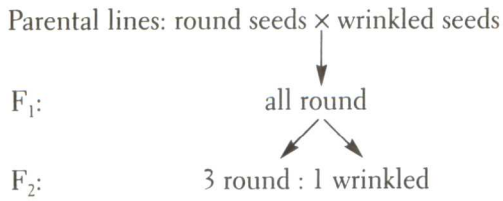


Figure 1–2

Six of the seven character differences in peas studied by Mendel (the seventh difference was long versus short stems). In each case, the characteristic shown at the left is seen in the hybrid.

When the hybrid seeds from the round × wrinkled cross were allowed to undergo self-fertilization, the progeny were of two types—round and wrinkled—in definite numerical proportions. Mendel counted 5474 seeds that were round and 1850 that were wrinkled and noted that this ratio was approximately 3 : 1.

The hybrid progeny produced by crossing the lines with round and wrinkled seeds constitute the **F_1 generation,** and all of the F_1 seeds were round. The progeny produced by self-fertilization of the F_1 generation constitute the **F_2 generation,** and the F_2 progeny appeared in the proportions 3 round : 1 wrinkled. (The letter *F* in the F_1, F_2 terminology stands for *filial*, referring to sons or daughters.) These results can be summarized in the following way:



Similar results were obtained when Mendel made crosses between plants differing in six other pairs of alternative characteristics. The results of some of these experiments are summarized in Table 1–1. The principal observations were:

1. The F_1 hybrids possessed only one of the parental traits.
2. In the F_2 generation, both parental traits were present.
3. The trait that appeared in the F_1 generation was always present in the F_2 about three times as frequently as the alternative trait.

In the remainder of this section, we will see how Mendel followed up these basic observations and performed experiments that led to his concept of discrete genetic units and to the principles governing their inheritance.

Particulate Hereditary Determinants

The prevailing concept of heredity in Mendel's time was that the traits of the parents became blended in the hybrid, as though the hereditary material consisted of fluids that became permanently mixed when combined. However, Mendel's observation that one of the parental characteristics was absent in F_1 hybrids and reappeared in unchanged form in the F_2 generation was inconsistent with the idea of blending. From this result, Mendel concluded that the traits from the parental lines were transmitted as two different elements *of a particulate nature* that retained their purity in the hybrids. The element associated with the trait seen in the F_1 hybrids (round seeds, in the example just used) he called **dominant,** and the other element, associated with the trait not seen in the hybrids but reappearing in their progeny (wrinkled seeds), he called **recessive.**

Table 1–1 **Results of several of Mendel's experiments**

Parental characteristics	F_1	Number of F_2 progeny	F_2 ratio
round × wrinkled (seeds)	round	5474 round, 1850 wrinkled	2.96 : 1
yellow × green (cotyledons)	yellow	6022 yellow, 2001 green	3.01 : 1
purple × white (flowers)	purple	705 purple, 224 white	3.15 : 1
inflated × constricted (pods)	inflated	882 inflated, 299 constricted	2.95 : 1
long × short (stems)	long	787 long, 277 short	2.84 : 1