GENETICS
Second Edition

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PREFACE

In this second edition as in the first, I have tried to provide a balanced, comprehensive review of genetics in a book of reasonable length. The increasingly rapid pace of progress in genetics research makes the subject more exciting with each passing year, but it also presents a greater challenge to authors, instructors, and students to assimilate new information that unabatedly pours forth in journals, symposia, and monographs. The use of the historical perspective throughout *Genetics, second edition* acknowledges our debt to the pioneering geneticists and biochemists who paved the way in this field with their new experimental methods for probing gene structure, function, and regulation.

Many of the chapters in this edition were substantially rewritten to clarify and update information. Some topics were rearranged to comply with the suggestions of users of the earlier edition—for example, an introduction to probability and statistics is now offered in Chapter 2—and to enhance the logical flow of topics in accordance with newer areas of genetics research.

An expanded set of problems and questions (with answers provided in the back of the book) concludes each chapter and offers students ample opportunity to practice and test the concepts presented in that chapter. A list of pertinent readings and references follows each set of questions and problems. New to this edition is a glossary of almost six hundred terms, which provides definitions for virtually every boldfaced term in the text.

I wish to extend my appreciation to the reviewers of the first edition for their helpful suggestions and comments: Dave Axelrod, who helped me to sharpen my focus time and again as the project took shape; Sally Allen, University of Michigan at Ann Arbor; William Birky, Ohio State University; Philip Hedrick, University of Kansas; William Moore, Wayne State University; Simon Silver, Washington University; Herbert Wiesmeyer, Vanderbilt University.

I also very much appreciate the assistance of the reviewers of the second edition: Audrey Barnett, University of Maryland; William Birky, Ohio State University; Joseph Chimici, Virginia Commonwealth University; Robert Fowler, San Jose State University; Carl Heuther, University of Cincinnati; James Wild, Texas A & M University; and the many professors who kindly responded to a prerevision survey. In particular, I wish to thank Maurice Rosenstraus and David Fox for their patience and their meticulous attention to every part of the manuscript, by which it was substantially improved. I am grateful to the literary executor of the late Sir Ronald A. Fisher, F.R.S., to Dr. Frank Yates, F.R.S., and to Longman Group, Ltd., London, for their permission to reprint Table II from Statistical Tables for Biological Agricultural and Medical Research by Fisher and Yates.

Charlotte J. Avers

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CHAPTER 1

Mendelian Inheritance

The science of genetics is young, relative to physics or chemistry. In 1900 three European botanists independently discovered and cited the earlier studies of Gregor Mendel to help explain their own studies of inheritance. For more than eight years, Mendel, an Austrian monk at the monastery of St. Thomas in Brünn, Czechoslovakia, conducted hybridization experiments using the garden pea (Box 1.1). In 1865 Mendel reported his experimental results and conclusions to the Brünn Natural History Society, and the report was published in the journal of the Society in 1866. Until 1900 Mendel's publication was not fully appreciated because his proposed rules of inheritance could not be fit into the existing biological framework. In 1900 other discoveries facilitated a widespread understanding of Mendel's work and the confusing nature of the inheritance of biological characteristics began to reveal its mysteries to twentieth-century geneticists. Genetic studies have continued without interruption since 1900, and Mendelian rules of inheritance still provide the basis for interpreting heredity in sexually reproducing species.

Mendelian Rules of Inheritance

Before Mendel's time scientists had a general recognition and appreciation of inheritance based on hundreds of years of hybridization studies. These studies provided the basis for selective breeding programs for crops and ornamental plants and for domestic animals such as sheep and cattle. Indeed, the phenomenon of **inheritance,** that is, the transmission of characteristics from generation to generation in a family, has been recognized for thousands of years. For example, the Jewish Talmud has laws negating the requirement of circumcision for sons of women whose family members had disorders that lead to uncontrolled bleeding. In this and other cases, a practical approach to some particular problem or need often existed but little *generalization* was made to allow an understanding of inherited traits or to provide a means of predicting their occurrence and pattern of transmission. Each trait was studied and treated independently of other inherited characteristics, either in the same species or in different species of plants and animals. As a result of his experiments, Mendel was the first to formulate rules of inheritance that were generally applicable to any trait or species in question. His conclusions have been shown to apply to all organisms, including human beings.

Mendel's methods and interpretations can be appreciated even more today in view of our current knowledge of the cell nucleus, DNA, and chromosomes that was unknown to Mendel and his contemporaries. His methods of analysis are as useful and applicable today as they were over 100 years ago. Mendel chose his experimental organism carefully and used a systematic approach to design and conduct his experiments. He was an innovator in these regards, and his approach was fundamental to the success of his experiments. In particular, Mendel

1. concentrated on one inherited characteristic at a time in an experiment;

2. selected single traits that showed clearly different, alternative forms;

3. kept accurate records for each experimental plant;

BOX 1.1 Gregor Johann Mendel

Johann Mendel was born in the Silesian town of Heinzendorf, which was part of Austria before 1918 and is now part of Czechoslovakia. He was the only son of a poor farmer and was interested in science from boyhood on. When he became a monk of the Augustinian order, he took the name of Gregor. Gregor Mendel, who taught high school classes for boys in his earlier years and later rose to the rank of prelate and abbot of his monastery in Brünn, conducted experiments in plant hybridization for many years in a small garden on the grounds of the monastery.

Mendel's reports on his experiments to the Brünn Society of Natural Science (which he helped to establish) in February and March of 1865 went entirely unappreciated. According to the recollections of some who attended those meetings, no discussion took place and no questions were asked after the presentations. Scientists celebrate 1900, the year Mendel was discovered, as the beginning of the science of genetics, rather than 1865, the year Mendel reported his discoveries on the mechanism of heredity. Mendel died long before his monumental contributions were recognized and appreciated by the scientific community.

His contemporaries in church and government considered Mendel a nonconformist because he was actively associated with liberal political and human causes. From all we know about him, he appeared to be dearly loved by his students, parishioners, and friends as a kind and generous man who was always willing to help others.

Gregor Johann Mendel, 1822–1884.

Like Charles Darwin, whose ideas and work he admired and accepted, Mendel proposed a scientific theory in place of mystical forces then believed to direct the natural world and its inhabitants. The mechanism proposed by Mendel to explain heredity and variation was later shown to fit beautifully into the concept of evolution by natural selection proposed by Darwin in 1869. Both Mendel and Darwin profoundly changed our ideas about, our natural place in, and our relationship to the world. In place of mysteries governed by magical forces, these two giants of nineteenth century science provided the theoretical foundations and explanations for natural mechanisms that govern change in living systems.

4. counted the different kinds of individuals produced in each experimental cross and could therefore quantitate information precisely; and

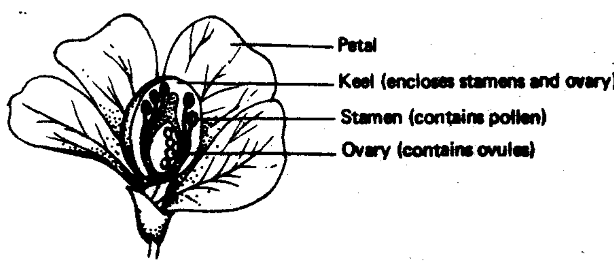
5. kept track of the pedigree, or history of transmission, of each trait in each set of plants over a number of generations.

Systematic attention to details and overall planning of sets of experiments enabled Mendel to formulate rules of inheritance. In view of the historical importance of Mendel's studies and their applicability to modern studies of inheritance, an examination of them in some detail will be instructive.

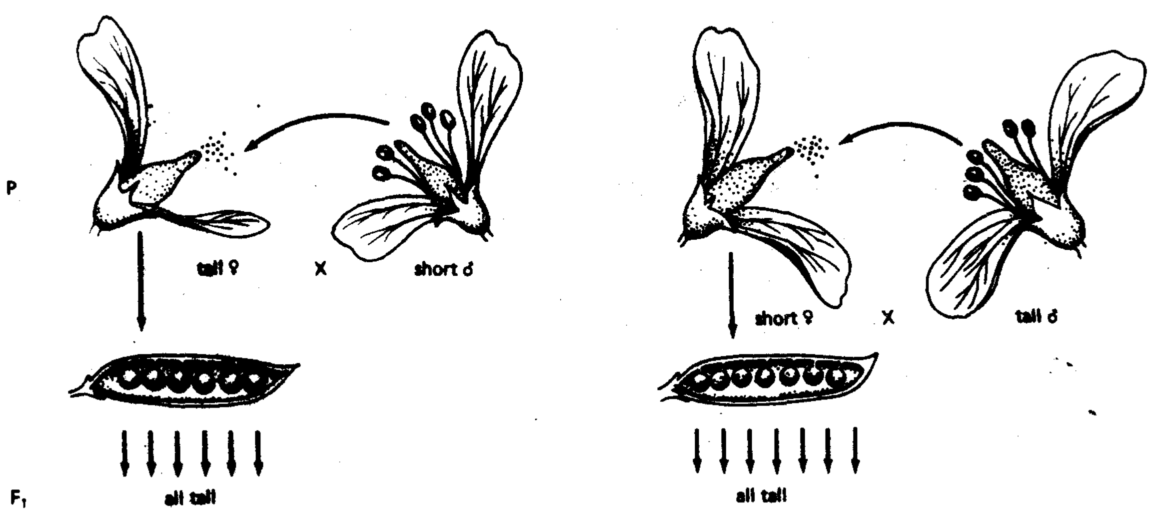
BOX 1.2 Garden Pea Flower Structure and Hybridization Method

The garden pea is normally self-fertilizing, that is, pollen and eggs from the same flower engage in fertilization that leads to a new generation of plants. The pollen-bearing **stamen** (male reproductive structure) and the ovule-bearing **ovary** (female reproductive structure) are enclosed within a floral part called the **keel.** Pollen from another flower cannot reach the receptive female structures because of the keel enclosure, but pollen from the same flower has complete access to the ovary of that flower. When left undisturbed, self-fertilization takes place in each flower of the plant.

In order to cross a plant of one type with that of another, the keel must be removed, the stamens must be cut off, but the ovary left untouched. Pollen from another flower can then be applied to the female component of the experimental flower. The procedure is performed reciprocally for reciprocal crosses, as the diagram indicates. After fertilization, the ovary enlarges as the ovules, which contain the fertilized eggs, enlarge and develop. The ovary develops into the fruit, or pod, and its ovules develop into seeds (peas, in this case). Each seed contains an embryo that, upon germination and growth, develops into the plant of the next generation. The plants of this next generation can then be analyzed to determine their phenotypic features.



Cutaway view of pea flower



In a typical experiment, plants of different strains or phenotypes are cross-fertilized, and the seeds are collected when ripe. The seeds grow into the F_1 generation of plants. In order to proceed to the F_2 generation, F_1 plants are allowed to self-fertilize by natural means, that is, the flowers are left intact. The seeds that are produced in pods of the F_1 plants are then planted and grow into the F_2 individuals, which, in turn, are analyzed.

1.1 Systematic Approach

Mendel collected 14 varieties of the garden pea (*Pisum sativum*) that differed in seven distinct traits, or physical characteristics. Each trait was represented by paired contrasting varieties, and each member of a pair showed one of the two possible contrasting forms of the selected characteristic. For example, a *tall* variety and a *short* variety represented contrasting forms of the characteristic of *height*. Hence each pair of varieties in the final collection was part of a carefully selected experimental group, with easily distinguished characteristics occurring in unambiguously contrasting forms. For example, there was no difficulty in distinguishing tall plants that were 6 to 7 feet high from short plants less than 2 feet in height, or green seeds from yellow seeds.

Using peas as the experimental organism had several advantages. Pea plants, which are easily raised in cultivation, are normally *self-fertilizing* (or inbred); that is, before the flower opens each set of female (♀) sex cells, or eggs, is fertilized by the male (♂) sex cells, or pollen, from the same flower. Many other species are normally *cross-fertilizing;* that is, the eggs in one flower are fertilized by pollen from the flowers of another plant.

Before initiating the main set of experiments, Mendel spent two years testing the purity of each of the 14 varieties to verify that the desired characteristic appeared in each of the plants and in each generation of breeding and was therefore an inherited trait. Determining whether each variety was pure-breeding simply required planting seeds and examining the features of the seeds and plants of the subsequent generation in each of the two years.

Mendel initiated the hybridization experiments by performing artificial cross-fertilization, removing the pollen-bearing anthers of the flower and dusting the female floral structures with pollen taken from a different plant (Box 1.2). He then covered each experimental flower or group of flowers to prevent accidental contamination by foreign pollen. This practice is still common in modern hybridization procedures for many plants.

Since Mendel was studying seven pairs of contrasting inherited characteristics, he performed seven separate experiments in the first year. In each experiment he made *reciprocal crosses* between the contrasting strains of the paired varieties. For example, he used pollen from the short variety to fertilize the eggs of the tall variety (symbolized as tall ♀ × short ♂) and pollen from tall plants to fertilize the eggs of the short plants (short ♀ × tall ♂). Since the original parents of the experiment are involved, these crosses can be designated as the parental or P crosses, or as the **P generation** (Table 1.1, see next page).

The progeny resulting from P crosses comprise the first filial generation, or **F_1 generation.** In peas we may examine the seeds of P plants and score their characteristics, or we may plant these seeds and inspect the resulting adult plants and their flowers for the characteristic under study. Both the seeds and the plants grown from these seeds are members of the F_1 generation. Since Mendel obtained similar results for all seven sets of reciprocal crosses, the results of crosses between tall and short plants

Table 1.1 Seven traits studied in the garden pea by Mendel and results of reciprocal crosses between strains with contrasting expressions for each trait.

trait	crosses between plants of alternative characteristics	appearance of F_1 progeny plants
height	tall × short	tall
seed shape	round × wrinkled	round
cotyledon color	yellow × green	yellow
seed coat color	gray × white	gray
pod shape	inflated × constricted	inflated
pod color	green × yellow	green
position of flowers	axial × terminal	axial

will serve to illustrate this general observation. All F_1 plants were tall regardless of whether the cross was tall ♀ × short ♂ or short ♀ × tall ♂. There were no short plants among the numerous F_1 progeny; the characteristic had seemingly disappeared.

In order to analyze the nature of the tall F_1 plants, Mendel permitted them to self-fertilize and produce the second filial or **F_2 generation.** He then collected seeds of each self-fertilized F_1 plant and planted them to obtain adult plants of the F_2 generation. When these were inspected, Mendel counted 787 tall and 277 short, a ratio of approximately 3 tall : 1 short in the total group of 1064 individual plants. Each self-fertilized F_1 plant had produced F_2 plants that exhibited a ratio of 3 tall plants for every short plant, regardless of the absolute number of individuals counted. The tall and short F_2 plants were indistinguishable from their tall and short grandparents (P generation), F_2 talls being about 6 to 7 feet high and shorts about 2 feet high. The short alternative of the characteristic of plant height had reappeared unchanged from the original parental generation.

1.2 Analysis of Monohybrid Crosses

Each of Mendel's seven sets of experiments focused on a single inherited characteristic. Each was therefore a **monohybrid cross** involving transmission of a pair of contrasting expressions of one characteristic. The progeny (F_1) of each parental cross resembled only one of the two parental forms. When the F_1 plants were allowed to self-fertilize, both parental varietal forms were represented among their progeny (F_2). The parental variety that appeared in the F_1 was represented in ¾ of the F_2 plants. The other variety was represented in ¼ of the F_2 plants. The two parental varieties were expressed in the F_2 generation in a ratio of 3:1 (Table 1.2).

Based on observations of monohybrid ratios, Mendel hypothesized that the F_1 plants contained hereditary factors from both parents, even though the plants resembled only one of the original parents. In the case of tall and short alternatives for height, the tall F_1 plants must have possessed a hereditary factor for tall since ¾ of the F_2 offspring were tall. In addition, each F_1 plant must also have carried a hereditary factor for short because ¼ of their F_2 offspring were short. The characteristic that was expressed in the F_1 generation Mendel called **dominant,** and the characteristic that was hidden, or masked, in the F_1 he called **recessive.** We say tall is dominant over short. We call an individual a dominant or a recessive.

It was also apparent to Mendel that all the tall plants were not genetically alike. In two years of preliminary tests, self-fertilized tall P plants had produced only tall progeny, thereby showing that the tall variety was pure-breeding. Self-fertilized tall hybrid F_1 plants, on the other hand, produced both tall and short F_2 progeny. We must, therefore, make a distinction between the appearance of an individual, or its **phenotype,** and its underlying genetic constitution, or **genotype.**

Mendel tested his interpretations by conducting further experiments in which F_2 plants were allowed to self-fertilize, thereby producing an F_3 generation. Repeating such

Table 1.2 Data from some of Mendel's monohybrid crosses showing numbers and ratios of F_2 progeny types after self-fertilizations of F_1 plants.

appearance of F_1 plants	**number of F_2 plants observed**	**F_2 ratios calculated**
round seeds	5474 round:1850 wrinkled	2.96:1
yellow cotyledons	6022 yellow:2001 green	3.01:1
gray seed coats	705 gray:224 white	3.15:1
inflated pods	882 inflated:299 constricted	2.95:1
green pods	428 green:152 yellow	2.85:1
axial flowers	651 axial:207 terminal	3.14:1
tall plants	787 tall:277 short	2.84:1

self-fertilizations through six generations of progeny, he found tall and short plants in each generation of progeny; both tall and short plants were typically parental in phenotype.

When Mendel observed the breeding behavior of *each* individual plant, however, it was clear that F_2, F_3, F_4, and F_5 progeny differed from the F_1 in the transmission pattern of the inherited characteristic (Fig. 1.1, p. 8). All the hybrid F_1 plants were tall, and each self-fertilized F_1 plant produced both tall and short F_2 descendants in a ratio of 3:1. The F_2 generation, therefore, included both parental phenotypes, tall and short, and not just the dominant tall phenotype expressed in the F_1 generation. The recessive short F_2 plants produced only short F_3 progeny by self-fertilization and were, therefore, true-breeding like the original short P plants. In contrast, self-fertilized tall F_2 plants either were true-breeding or produced both short and tall plants. From the actual counts of the two kinds of self-fertilized tall F_2 plants, Mendel found that ⅓ were true-breeding for the dominant phenotype and ⅔ *segregated* 3 tall:1 short F_3 descendants. He found the same pattern in each of the subsequent self-fertilized generations, namely, all the recessives bred true, ⅓ of the dominant type bred true, and ⅔ of the dominant phenotype segregated 3 dominant:1 recessive in the next generation. The F_2 genotypic ratio, therefore, was ¼ pure-breeding dominant:½ segregating dominant:¼ pure-breeding recessive.

These experimental results verified the dominance and recessiveness of the hereditary factors. Since ⅔ of the tall plants continued to segregate both tall and short progeny, they must have carried the masked recessive factor as well as the expressed dominant factor. The plants true-breeding for the dominant or recessive phenotype must have carried only the dominant or only the recessive factor and, therefore, produced progeny that were identical to each other and to the true-breeding parental plants. Only by examining the breeding behavior of an individual, can we determine whether the individual carries one kind or both kinds of alternative hereditary factors of a pair.

It is easy to see that the segregating tall individuals must have carried two hereditary factors for height—one for tall and one for short—but how can we argue for the presence of two factors in an individual true-breeding for the dominant or recessive phenotype? The answer lies in comparing the contributions of hereditary factors that were made by parents to gametes in a reciprocal cross of the P generation. No matter which parent contributed each factor, all F_1 hybrids received one of each factor so there could not have been more factors contributed by one parent than by the other. Since

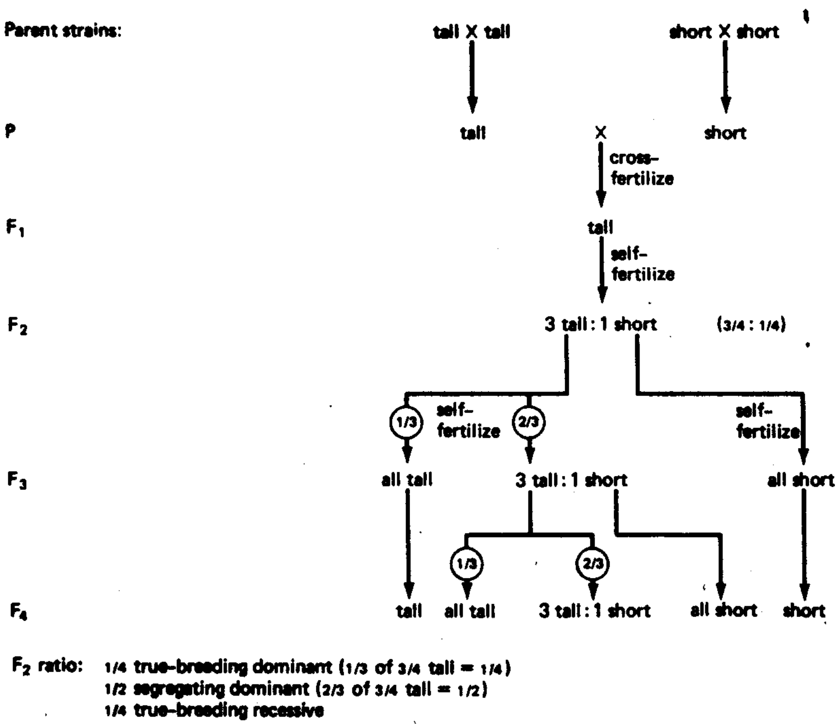


Figure 1.1 Breeding analysis of tall and short plants reveals dominance and recessiveness of the pair of alternative traits and distinguishes true-breeding from segregating individuals. By allowing self-fertilization of each plant, Mendel found that each F_1 tall plant segregated 3 tall : 1 short in the F_2 progeny. In contrast, self-fertilized tall plants of the F_2 and later generations were either true-breeding (⅓ of the individuals) or segregating (⅔ of the individuals). All the short plants, however, were true-breeding. Segregating tall plants must therefore carry both the masked recessive hereditary factor and the expressed dominant hereditary factor for height. True-breeding talls or shorts carried only the dominant or recessive hereditary factor, respectively.

each F_1 hybrid contained two hereditary factors for height, one derived from each parent, it is likely that any individual arising from the union of two gametes must possess two hereditary factors for a particular characteristic. It follows that since the tall parent produced only tall offspring by self-fertilization, it must have had two factors for tall. Similarly, the short parent, which produced only short offspring by selfing, must have possessed two hereditary units for shortness. If each true-breeding tall or short parent carried two factors for the same alternative expression of height, then it follows that any true-breeding tall or short plant will also have a pair of identical hereditary factors for height. This is true for any true-breeding trait and for any filial generation.

At this stage we should introduce some more specific terms for genetic analysis. Mendel's hereditary factors, or units of inheritance, are **genes; alleles** are the alternative forms of a gene. The terms *dominant* and *recessive* can refer to these allelic forms or to the phenotypes that these alleles produce. The alternative forms of the gene for height are the dominant allele for tall and the recessive allele for short stature. In our example, tall is the dominant phenotype for height, and short is its recessive alternative.

Individuals having two identical alleles of a gene are **homozygous** for the allele under