

GENETICS

SECOND EDITION

M.W. Farnsworth

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PREFACE

Genetics occupies a central position in biology and has become one of the most exciting fields of modern science. To appreciate fully the contributions to genetics made by the application of the new techniques of analyzing DNA, it is first necessary to understand the basic rules of inheritance and the conceptual framework that preceded and made possible the current molecular approaches to the nature of the gene. Also helpful is some experience with genetics as a way of thinking, a way of drawing inferences and logical deductions from observations and data. For these reasons, the organization of the first edition has been retained in the present text.

This book is intended for a one-semester course in genetics for students majoring in the biological sciences who have had some work in college-level biology and chemistry. Although the text employs a historical approach, starting with Mendelian genetics, instructors who prefer to begin with chromosomes and meiosis can do so by changing the order of subject matter and beginning their course with Chapter 4. Similarly, those who prefer to begin with DNA can do so with little difficulty by starting with Chapter 9.

NEW TO THIS EDITION

In this revision major emphasis has been placed on molecular topics. New material includes a thorough discussion of chromosome structure, DNA replication, gene structure and transcription, the control of transcription in viruses and in bacteria, and the transposable elements of prokaryotes and eukaryotes. Gene regulation in eukaryotes includes a discussion of the role of homeotic genes in establishing the body plan in animals, the origin and splicing together of immunoglobulin genes, and the possible role of enhancers and Z-DNA in the activation and repression of transcription. A new chapter reviewing the current methods and results of DNA analysis and gene cloning has also been added. A summary follows the text of each chapter, and a glossary of terms has been placed at the end of the book.

Since genetics is an experimental, problem-solving science, problems that permit the student to apply genetic principles have been included with each chapter. The answers to these problems, as well as the means of their solution, are given at the end of the book.

Although undergraduate students rarely pursue the references, they are of use to some as a means of gaining entrée into the literature, both classical and

current. The citations to the sources of illustrations appearing in the text also provide a means of pursuing some particular area of interest or the work of some particular author.

ACKNOWLEDGMENTS

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 permission to reprint Tables III and IV from their book *Statistical Tables for Biological, Agricultural and Medical Research* (6th edition, 1974).

I am deeply indebted to the many authors who have most graciously provided original illustrations. Many thanks are also due to those who have read and criticized all or part of the manuscript and have provided numerous kind suggestions for its improvement: Adela Baer, Oregon State University; James T. Giesel, University of Florida; Carl A. Huether, University of Cincinnati; Duane L. Johnson, Colorado State University; William W. Johnson, The University of New Mexico; and Richard Eugene Rayle, Miami University. In a project of this size, some inaccuracies are unavoidable, and for these I must assume sole responsibility. I would be grateful if any such were brought to my attention.

M. W. Farnsworth

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1

THE BEGINNING OF GENETICS: MENDEL'S FIRST PRINCIPLE

Compared to astronomy, mathematics, chemistry, or natural history, genetics is a young science, originating only in 1900, with the rediscovery and independent proof of Mendel's principles. Since then, it has developed almost explosively to such a level of refinement and sophisticated technology that serious expectations are being raised about the possible manipulation of human genes. The more recent studies at the molecular level that give rise to these apprehensions can best be understood and appreciated when viewed in perspective and within the context of the science as a whole. Indeed, they owe their development and much of their meaning to concepts that were firmly established before the term DNA became a household word.

In tracing the development of genetics from its inception to its current status, we will endeavor to interweave the converging contributions of many persons and many disciplines so as to illuminate a constantly evolving central theme: the nature and activities of genetic material.

GENETICS IN THE TIME OF MENDEL

The observations of Gregor Mendel on heredity in the edible garden pea represent the first disciplined, analytical inquiry into the mechanism of inheritance. Mendel was a clergyman and a teacher, in later life becoming prelate of the Augustinian monastery of St. Thomas in the town of Brunn, in what is now Czechoslovakia. His interest in botany began early in life, for farming and the development of new varieties of apples were his family's chief occupation. This early interest was further stimulated by his formal education which centered around mathematics, physics, and the botanical and zoological sciences. Mendel entered the monastery in 1845 and was ordained in 1848, becoming a parish priest and, subsequently, a teacher in a nearby high school. The monastery of St. Thomas provided a stimulating environment. It was a center of cultural, intellectual, and religious life, and its members and visitors included many notable scholars and scientists of the period. In 1851, at the encouragement of the prelate, Mendel entered the University of Vienna, and upon completion of his course of studies in 1854, he returned to his teaching responsibilities at Brunn. His exper- 1

iments in plant hybridization were carried out in the monastery garden over several years, beginning in 1856.

By this period of the nineteenth century, botany had become a flourishing discipline. Sexuality in plants had been described by Rudolf Camerarius in 1694 and by Nehemiah Grew in 1782. It was known that pollen functioned as the male element and that the ovules of flowers contained the female element (eggs), both being necessary for fertilization and the formation of a new individual. Artificial pollination had long been practiced, and the first experiments in plant hybridization had been successfully carried out by Joseph Kölreuter in 1760. A number of botanists contemporary with Mendel were industriously crossing pure-breeding varieties of plants in an effort to produce improved strains of economic importance. Detailed descriptions of the hybrids resulting from these experiments had been published, and it was known that these plants did not breed true, but instead produced offspring that varied with respect to the original parental characters. Actually, the phenomena we now identify as dominance and segregation were clearly evident in several of these investigations, but the significance of the observations was not recognized, and in none of these studies was systematic, quantitative analysis employed.

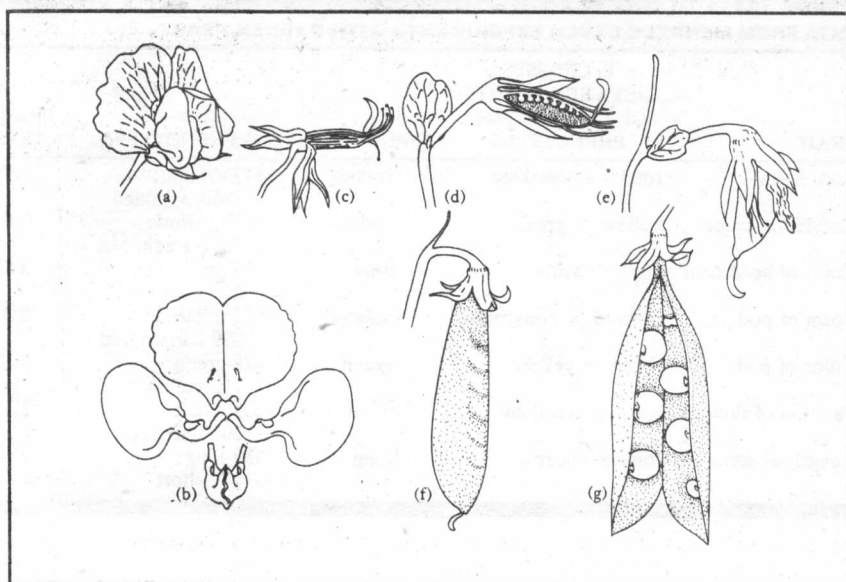
Although Mendel was undoubtedly influenced by the work of his predecessors and contemporaries, he approached his experiments in an innovative way. First, he deliberately restricted his attention to the single character whose inheritance was under consideration in any one experiment. Second, he kept accurate pedigree records for each plant. And, finally, he counted the different kinds of individuals that resulted from his experimental crosses. This last procedure was crucial, for more than anything else, it was the numerical data that permitted Mendel to formulate his rules of inheritance. Since his methods of analysis are as applicable and useful today as they were over 100 years ago, it is worthwhile to examine his work in some detail.

EXPERIMENTS WITH MONOHYBRIDS AND DERIVATION OF THE PRINCIPLE OF SEGREGATION

For his studies Mendel obtained a number of pure-breeding varieties of the garden pea (*Pisum sativum*) (Figure 1-1), a plant previously used for a similar purpose by Alexander Seton in 1822. This plant species offers the advantages of being easy to grow and fertilizing itself before the flower opens. The male (δ) sex cells, or sperm, contained in the pollen grains of a flower fertilize the female (φ) sex cells, or eggs, of that same flower. Self-fertilization, or selfing, is a type of natural inbreeding found in many plants. Cross fertilization is easily accomplished by removing the pollen-producing anthers of the flower and introducing pollen taken from a different plant. A cross between two varieties can be performed by this method, a procedure generally known to botanists as hybridization.

Mendel's Experiments

Mendel worked with 14 pure-breeding varieties that could be arranged as seven pairs, the members of each such pair exhibiting alternative inherited states of some single aspect of plant structure or color. For example, one such aspect of structure was the height of the plant, and the alternative states of that



Flower, fruit, and seeds of the garden pea, *Pisum sativum*: (a) flower; (b) the five petals; (c) flower with petals removed so that the stamen tube which surrounds the pistil may be seen; (d) arrangement of ovules as seen in a longitudinal section of the pistil; (e, f, g) stages in the development of the fruit from the pistil and of the seeds from ovules. [Figure 153 (p. 355) from *Textbook of Botany*, revised edition, by E. N. Transeau, H. C. Sampson, and L. H. Tiffany. Copyright 1940, 1953 by Harper & Row, Publishers, Inc.]

aspect were represented by two varieties, one tall, the other short. We can refer to tallness and shortness as contrasting *phenotypes*, the term phenotype referring to appearance or condition with respect to any aspect, or character, under consideration, in this case, height.

Before attempting hybridization, Mendel cultivated his varieties for two generations. This preliminary step was undertaken to verify the purity of each line, that is, to make sure that the phenotype characteristic of each was indeed inherited by all offspring. The purity being established, he then performed crosses between individuals of contrasting phenotypes. Since he had seven pairs of inherited, contrasting characters, he carried out seven separate experiments (Table 1-1), only one of which need be used as a representative example. The best example, because the data are more extensive, is the experiment involving crosses between plants with yellow and green cotyledons. Cotyledons are embryonic leaves containing stored food; they comprise the bulk of the seed, and their color can be seen through the seed coat.

Mendel initially carried out *reciprocal crosses* using pollen from the yellow variety to fertilize the eggs of the green variety and vice versa: yellow ♂ × green ♀ and green ♂ × yellow ♀. Since these crosses involved the original parents of the experiment, they can be designated as the *parental* or P_1 crosses.

TABLE 1-1
DATA FROM MENDEL'S SEVEN EXPERIMENTS WITH GARDEN PEAS

P ₁ CROSSES BETWEEN PLANTS OF ALTERNATIVE PHENOTYPES					F ₂ PHENOTYPIC RATIO
TRAIT		F ₁ PHENOTYPE	F ₂ PHENOTYPES		
Seed form	round × wrinkled	round	5474 round: 1850 wrinkled	2.96:1	
Cotyledon color	yellow × green	yellow	6022 yellow: 2001 green	3.01:1	
Color of seed coat	gray × white	gray	705 gray: 224 white	3.15:1	
Form of pod	inflated × constricted	inflated	882 inflated: 299 constricted	2.95:1	
Color of pod	green × yellow	green	428 green: 152 yellow	2.85:1	
Position of flower	axial × terminal	axial	651 axial: 207 terminal	3.14:1	
Length of stem	long × short	long	787 long: 277 short	2.84:1	

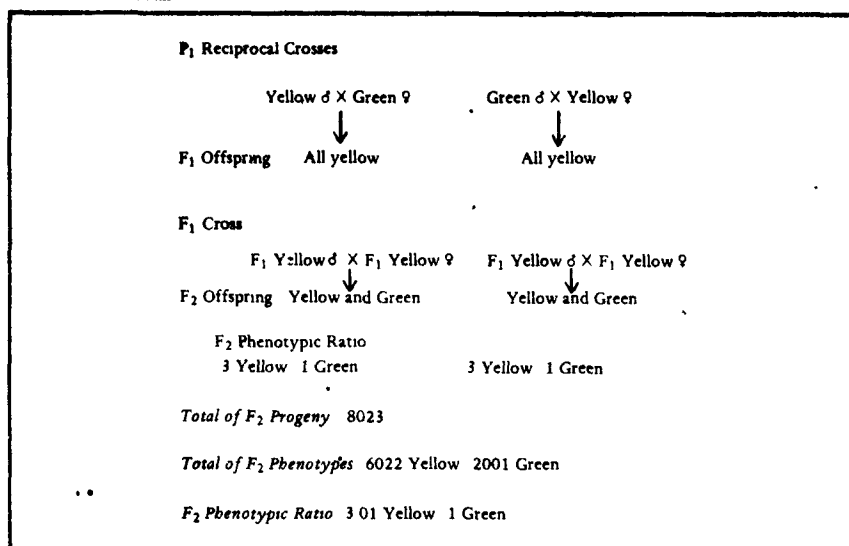
The mature seeds that formed from each experimental pollination comprised the *first filial* or F_1 generation. These seeds were collected and classified as to color, and it was found that all were yellow and that reciprocal crosses yielded identical results. The green characteristic was not apparent in the seeds of any plant and seemed to have disappeared entirely (Figure 1-2). The seeds were saved and planted the following spring, and the resulting F_1 plants, grown to maturity, were allowed to self-fertilize. They produced a *second filial* or F_2 generation totaling 8023 individuals, of which 6022 were yellow and 2001 were green, a phenotypic ratio of approximately 3 yellow:1 green. Pedigree records indicated that this same 3:1 phenotypic ratio occurred in the descendants of both reciprocal P_1 crosses. In addition, the green phenotype had not only reappeared, but also seemed to be unaltered, for the F_2 green seeds were indistinguishable in color from those of the original P_1 green strain.

Mendel's experiments included one further (and crucial) step, but let us pause for a moment to analyze the results obtained thus far.

We have seen that all members of the F_1 generation were themselves yellow; yet they transmitted the green characteristic to their offspring. From this we can infer that the F_1 plants must have possessed a hereditary factor for green, as well as one for yellow, even though the factor for green was not expressed in the F_1 phenotype. We must therefore conclude that the F_1 individuals were hybrid in their genetic makeup.

Comparison of the yellow F_1 's with the yellow P_1 parental type shows that, despite identity in appearance, the genetic constitution of the F_1 clearly differed from that of the yellow parent. The P_1 parental variety, when self-fertilized, yielded only yellow offspring, but the F_1 individuals, when self-fertilized, produced both yellow and green progeny. It is apparent that we must make a distinction between the appearance, or phenotype, of an organism and its

FIGURE 1-2



A summary of the data from Mendel's experiments with green and yellow peas.

underlying genetic constitution, or *genotype*, for although the phenotype may be predicted from the genotype, the reverse does not necessarily hold.

Mendel ascribed the fact that the hybrid nature of the F₁ individuals was not apparent in their phenotype to a phenomenon he called *dominance*. It was clear that the hereditary factor for green had to be present in the F₁ hybrids in order to appear in their offspring. Yet, when in company with the factor for yellow, only yellow was expressed in the F₁. Although Mendel could not explain the reasons for this phenomenon, he recognized it and took it into account. The character that was not expressed in a hybrid was called the *recessive*; the character that was expressed in the hybrid was called the *dominant*. It should be emphasized that Mendel also clearly recognized that heredity is particulate, in contrast to earlier ideas that inheritance was a fluid blending process, such as the mixing of blood.

Additional inferences with respect to the genotype can also be drawn from Mendel's data. We know that a new individual is formed by the union of male and female sex cells (*gametes*, sperm and eggs), and we can infer from the data that we cannot assign a greater hereditary contribution to the pollen than to the egg, or vice versa. Both contribute equally to the inheritance of cotyledon color, for no matter which way the original reciprocal crosses were made, the results were the same in that identical F₁ hybrids were formed. Furthermore, if the F₁ individuals can be shown to possess two hereditary factors for cotyledon color, one being received from each parent via fertilization, then it is likely that all individuals arising from the union of male and female sex cells will also possess

two hereditary factors for any character under consideration. If so, it follows that the P_1 yellow parent, since it yields only yellow offspring by selfing, must contain two identical factors for yellow. Similarly, the P_1 green parent, which when inbred yields only green offspring, must contain two factors for green. From this it follows that green color can be expressed in the phenotype only when its genetic determinant is doubly present in the genotype.

Although we have yet to explain the 3:1 phenotypic ratio obtained in the F_2 generation, it can be seen from the above analysis that a remarkable amount of information can be derived from Mendel's simple experiments. Our next step must be the formulation of a hypothesis that not only will account for all of the data, but whose validity can be tested experimentally. Before doing so, however, it is useful to introduce some convenient terms.

Some Necessary Terms

Today, in the functional sense, we call Mendel's hereditary factors *genes*, and we refer to the alternative states of a gene that control contrasting phenotypes as *allelic states* or *alleles*. As commonly used, the terms dominant and recessive are applied to allelic states themselves, as well as to the phenotypes that they produce. Thus, we can characterize a gene as a dominant or a recessive allele, and we can also describe the character that it produces as a dominant or recessive trait.

In Mendel's experiment, the color of the embryonic leaves was determined by a gene present in two allelic states, one allele being dominant and determining yellow color and the other allele being recessive and determining green color. Although we can name this gene cotyledon color or anything else that we wish, it is more helpful if we choose symbols to represent the two allelic states. We can follow Mendel's example and use the capital letter *A* to represent the dominant allele for yellow and the lower case *a* to represent the recessive allele for green.

An individual whose genotype contains two identical alleles of a gene is called a *homozygote* or is said to be *homozygous* for the allele in question. As examples, we have inferred that Mendel's original P_1 green variety contained two genes for green color. If so, this variety was homozygous for the recessive allele, and we can symbolize its genotype as *aa*. Similarly, the P_1 yellow variety was presumably homozygous for the dominant allele, and its genotype can be given as *AA*.

When two different alleles of a gene are present in the genotype, the individual is called a *heterozygote* or hybrid or is said to be *heterozygous* for the alleles in question. In Mendel's experiments, the F_1 individuals were heterozygous, and their genotypes can be designated as *Aa*. We can also call these F_1 individuals *monohybrids*, because, as far as we know, they were heterozygous for only one pair of alleles. We must remember, however, that because of dominance, the two genotypes, *AA* and *Aa*, will both give rise to the same phenotype. As a result, the only means of distinguishing the homozygote (*AA*) from the heterozygote (*Aa*) is through additional crosses, whereby their genetic nature will be revealed by the types of offspring they produce.

As an aid to the correct use of terms, it should be emphasized that phenotypes are described in words, while symbols are used for designations of genotype.

Mendel's Hypothesis

Returning to our analysis of Mendel's data, let us apply the following hypothesis in an attempt to explain the origin of the 3:1 phenotypic ratio obtained in the F_2 generation.

If the P_1 plants contained two alleles for cotyledon color and yet each of the gametes that they produced contained only one, then some mechanism must exist whereby these genes are distributed to different sex cells, each such cell receiving one or the other, but not both, members of the allelic pair. Subsequent union of two such sex cells in the process of fertilization would restore the proposed double allelic condition. Applying this hypothesis to the F_1 hybrids, we would expect that the two alleles, A and a , present in the genotype would be segregated or separated from each other to pass into different reproductive cells. As a part of our hypothesis, let us also assume that these two classes of reproductive cells are produced in equal numbers in both sexes. Thus, within any one flower, the male sex cells would consist of two classes, one class carrying the allele A , the other containing the allele a , and equal numbers of the two classes would be formed. Similarly, in the pistillate, or female, structures of the flower, two types of eggs, A and a , would also be formed in equal numbers. If we assume that fertilization between these gametes is random, then we can expect that all possible combinations between eggs and pollen will occur, as illustrated in Figure 1-3. According to this hypothesis, the resulting F_2 generation should consist of the following classes and proportions:

- $\frac{1}{4}$ should be homozygous AA , and yellow in phenotype
- $\frac{1}{2}$ should be heterozygous Aa or aA , and yellow in phenotype
- $\frac{1}{4}$ should be homozygous aa , and green in phenotype

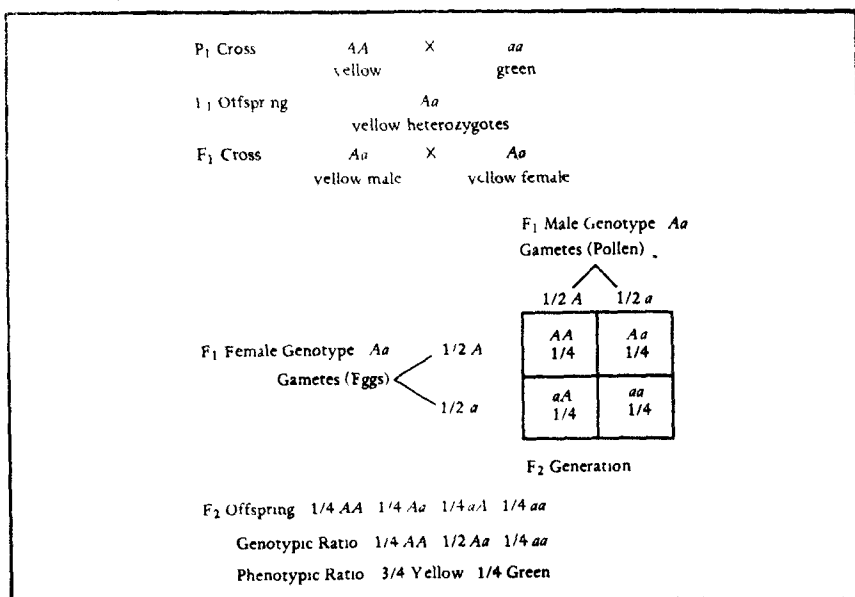
Due to dominance of the A allele for yellow over the a allele for green, the overall phenotypic ratio should be 3 yellow:1 green. However, if the hypothesis is wrong, that is, if the two types of eggs or pollen are not produced in equal numbers or fertilization between them is not random, then a phenotypic ratio other than 3 yellow:1 green should be obtained.

Comparing the expectations based on our hypothesis with Mendel's actual data, we can see that the hypothesis successfully accounts for the results. In addition, the likelihood that the hypothesis is correct is greatly strengthened by the fact that Mendel obtained similar data in experiments that involved six other pairs of contrasting characters (Table 1-1).

Proof of Mendel's Hypothesis

No matter how attractive or satisfying, an explanation cannot be unreservedly accepted without additional experimental proof. The hypothesis predicts that the 3:1 phenotypic ratio is the result of dominance imposed on an underlying genotypic ratio of $\frac{1}{4} AA : \frac{1}{2} Aa : \frac{1}{4} aa$ (1:2:1). Proof of the hypothesis requires a demonstration that the F_2 green individuals are indeed homozygous for the a allele and that the F_2 yellow individuals consist of two genotypic classes: those homozygous for the yellow allele and thus AA in genotype and those heterozygous or Aa . It must also be shown that there are twice as many yellow heterozygotes as yellow homozygotes. A test of the hypothesis thus requires that the genotypes of the F_2 individuals be determined. Since these genotypes are revealed only through the types of offspring produced, further crosses become necessary.

FIGURE 1-3

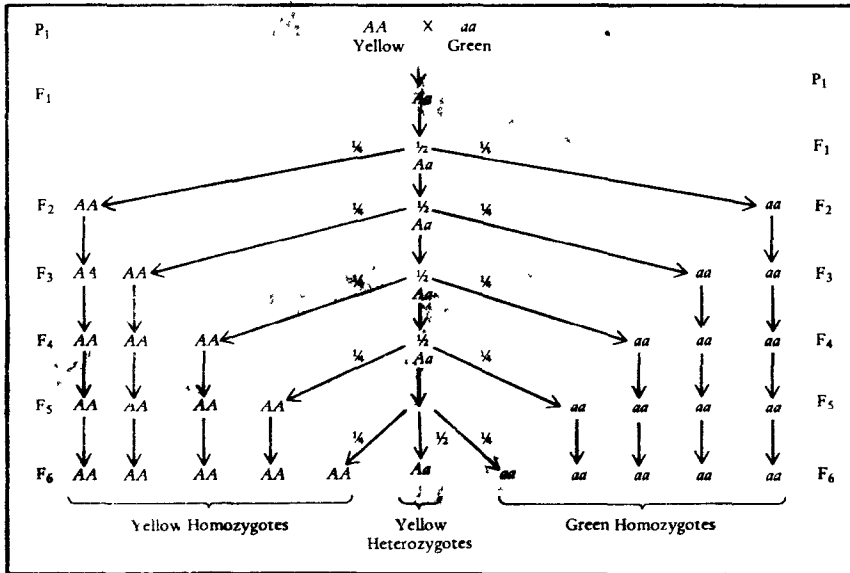


The results of Mendel's crosses according to the hypothesis of segregation of alleles to separate gametes, equal in number, followed by random fertilization between these gametes. Both phenotypes and genotypes are illustrated.

Mendel, perceiving this need, allowed the F_2 individuals to self-fertilize and produce a *third filial* or F_3 generation. This generation serves to indicate the genotypes present in the preceding F_2 progeny in the following way. Homozygous, self-fertilizing F_2 green plants should produce only green offspring. Similarly, F_2 yellow homozygotes should give rise to only yellow offspring. However, F_2 heterozygotes should be identical in genotype to the first generation F_1 hybrids, and through self-fertilization should yield both yellow and green progeny in a phenotypic ratio of 3:1.

Mendel's F_3 generation fully demonstrated the validity of the hypothesis by providing proof of the underlying 1:2:1 genotypic ratio present in the F_2 generation. F_2 green plants produced only green progeny and therefore must have been aa in genotype. Of the F_2 yellow plants, one-third yielded only yellow offspring, indicating that their genotype must have been homozygous AA . The other two-thirds produced offspring in the expected phenotypic ratio of 3 yellow: 1 green and therefore must have been heterozygous Aa in genotype. Mendel carried his proof further by allowing self-fertilization to continue through an F_6 generation. As anticipated, he found that homozygotes continued to produce only homozygotes, while heterozygotes gave rise to progeny in the proportion of 3 yellow:1 green (Figure 1-4). On the basis of all of these substantiating results, we can accept the hypothesis.

FIGURE 1-4



Distribution of genotypes in the progeny of Mendel's crosses through the sixth inbred generation. In each generation homozygotes give rise only to homozygotes, while heterozygotes produce offspring in the genotypic ratio of $\frac{1}{4}$ AA : $\frac{1}{2}$ Aa : $\frac{1}{4}$ aa.

More formally expressed, our hypothesis states that during the process of sex cell (gamete) formation in any individual, the members of a pair of allelic genes are segregated from one another into separate gametes, such gametes being produced in equal numbers, and that subsequent fertilization between these gametes is random. This principle of the separation of allelic genes at sex cell formation is sometimes called Mendel's First Principle or the Principle of Segregation, and it is the basis for inheritance in all organisms that reproduce by means of the union of sexual cells.

Since Mendel's time, his principles and ratios have been verified many times. For example, that allele segregation produces two types of gametes, equal in number, can be demonstrated by the examination of pollen phenotypes in corn. Plants heterozygous for the presence or absence of starch produce two types of pollen, and if the pollen is stained with an iodine solution, the pollen grains containing starch are colored dark blue, while those without starch remain unstained (Figure 1-5). Counts of the two types of pollen indicate that they are produced in a 1:1 ratio.

Single-celled organisms with gametic and zygotic life forms have also demonstrated gametic and zygotic ratios. These ratios are illustrated in the unicellular alga *Chlamydomonas*. During one stage in its life cycle (see Chapter 4), *Chlamydomonas* produces cells that are the equivalent of the gametes of higher organisms. If a parent cell (zygote) is heterozygous for some biochemical trait,