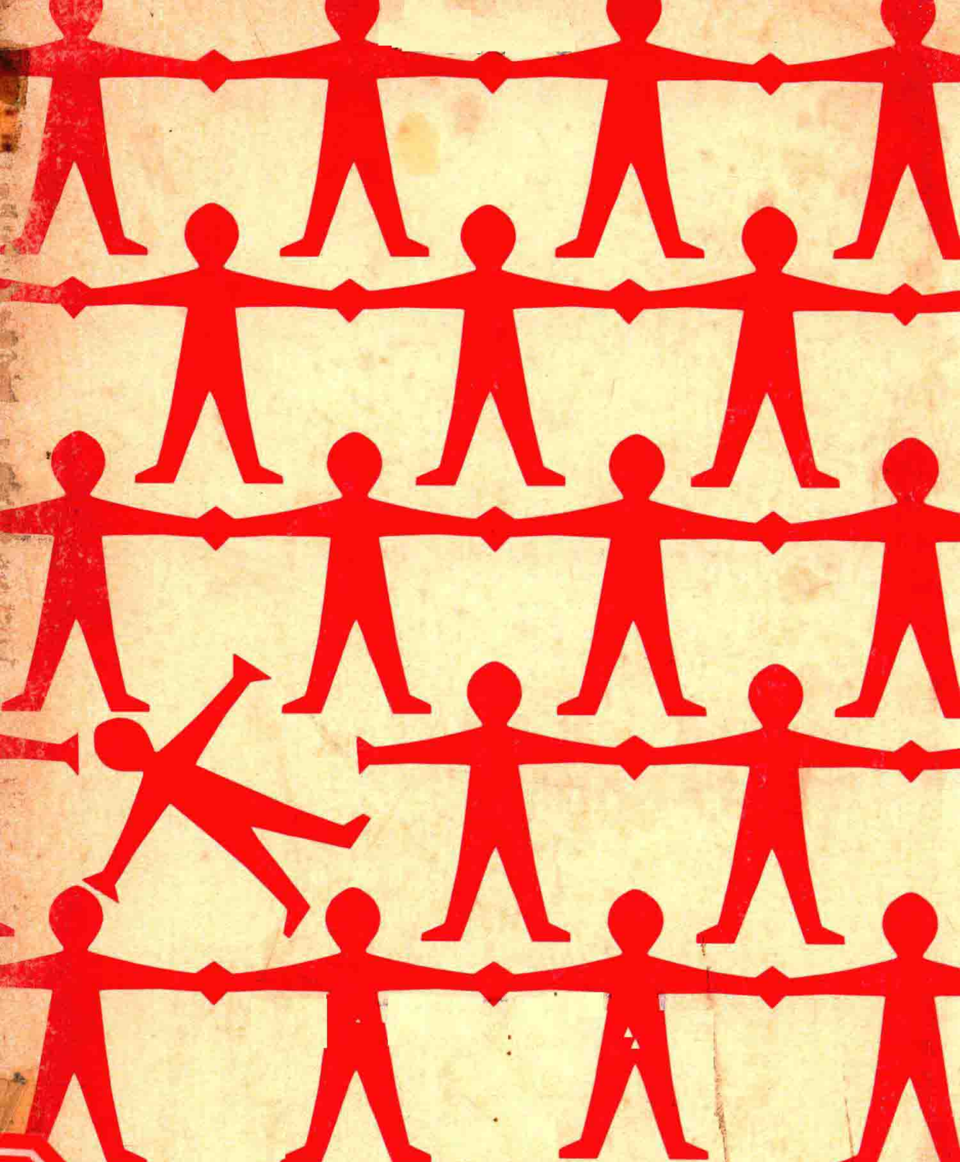

Introduction to Mendelian Genetics and Gene Action

Paul W. Sciulli

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Paul W. Sciulli
The Ohio State University

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CONTENTS

chapter one

THE ROOTS OF MODERN GENETICS

In 1866 Gregor Mendel presented a comprehensive report concerning his experiments in plant hybridization. Mendel began his work with the modest hope that the results would help to establish rules, if any existed, which governed the appearance of characteristics (such as height of plant or color of seeds) in various generations of pea plant hybrids. As we shall see, the results of Mendel's experiments not only established the basic rules governing the appearance of characteristics in plants, but these rules also became the foundation for the science of heredity, the laws of which are applicable to all organisms including humans.

Mendel's Experiments in Plant Hybridization

How did Mendel, an Augustinian monk working alone in his monastery garden, arrive at the results leading to the most profound and basic aspect of the biological sciences? The answer to this question is lost to history. However, we can examine Mendel's background and his work and gain some insights into his genius.

Gregor Mendel was born in 1822 in an area of eastern Europe now part of Czechoslovakia. After entering an Augustinian monastery he was ordained a priest in 1847. Shortly thereafter he was enrolled at the University of Vienna, where he acquired training in the natural sciences, especially physics and mathematics. (This training in the natural sciences provided Mendel with many skills, notably mathematical, which would be invaluable in the interpretation of his experimental data.) After graduating, Mendel returned to his monastery at Brünn and in 1854 began teaching and experimenting. In 1856 Mendel initiated the famous series of experiments which led to the definition of the laws of heredity.

Prior to the more famous experiments, however, Mendel studied the transmission of characters from parent to offspring and from generation to generation in a number of organisms. These early experiments no doubt guided Mendel both in his methodology and in his final choice for a suitable organism with which to study heredity. For example, Mendel had investigated character transmission in bees, mice, and various plants, and he knew of similar work being conducted by others. He was also aware that the unifying thread connecting all of these early studies in heredity was that little useful information was obtained.

Mendel noted from his own experiments and those of others various reasons for the lack of understanding heredity. First, the characteristics being studied were not consistently present in every generation. Part of this problem was that the expression or appearance of a physical characteristic would often change from one generation to another. Some of this variability was in the characteristics themselves; however, much of it was an artifact of the observer's "definition" of the characteristic. The size of various structures is an example of **trait**[1] variability (the terms *trait* and *characteristic* will be used interchangeably). How could one consistently distinguish, for example, between a small, medium-sized leaf and a medium, small-sized leaf when the trait (size) is continuous (that is, all sizes are possible)? To overcome ambiguity in trait identification, Mendel knew he needed an organism which exhibited traits that were discontinuous, meaning that there would be no overlap in the expression of characteristics–the appearance of a trait would be of the either/or type.

Mendel noted a second reason for not obtaining useful results in experiments concerning heredity. It was simply that individuals were very often placed in the wrong generation; parents, their offspring, and the progeny of the latter were frequently intermingled. To avoid assigning individuals to the wrong generation, Mendel knew he would have to keep an accurate record of the individuals and the generations to which they belong. An organism, such as a plant, whose offspring are associated with it (seeds) would make the keeping of records much easier.

A third source of confusion, as Mendel saw it, was that many experiments produced large numbers of individuals of various types and the rela-

[1] Boldface type indicates a term defined in the glossary.

tionship between the types was not always straightforward. For example, if in a given generation 5,793 plants had, say, red flowers and 2,170 had yellow flowers, a stated relationship of 5,793 plants with red flowers to 2,170 plants with yellow flowers is not as clear as saying there are about 3 plants with red flowers to every 1 plant with yellow flowers. Thus, Mendel, in order to keep the results clear and well organized, would ascertain the least complex statistical relationship between the various discontinuous traits in every generation. As we shall see, these three considerations greatly simplified the performance, analysis, and interpretation of Mendel's experiments. These methodological considerations, above all else, enabled Mendel to uncover regularities in the transmission of characters where others such as Charles Darwin, whose experiments produced results similar to Mendel's, failed. Darwin had the answer, but not the methodology to observe it.[2]

Mendel's plan of simplifying the approach to the study of heredity was time consuming. Eight years (1856-1863) were spent in experimentation. Initially, experiments were performed in order to find a suitable organism. From past experience Mendel knew that the common pea plant (genus *Pisum*) possessed several qualities making it a most favorable experimental subject with which to study heredity. For example, the floral structure of pea plants is peculiar in that its configuration enables easy self-fertilization while also affording protection against natural cross-fertilization. Thus Mendel could either artificially self-fertilize or cross-fertilize plants and be almost sure that the resulting offspring were indeed produced by the chosen parents. Secondly, because offspring (the seeds) were associated with the parents, it would not be difficult to place individuals in their correct generations. Finally, and importantly, pea plants will flourish with minimal care. Thus, one investigator with other duties could produce a large number of plants for study.

The initial two years of Mendel's experiments were spent searching for characteristics with constant, easily recognized expressions in each generation. Mendel found seven characteristics in the pea plant fitting this requirement (see chart, page 4). All seven traits were expressed as either of their two listed alternatives; none was intermediate in expression.

Mendel then produced, by self-fertilization, strains of plants that showed only one of the two expressions for a characteristic. For example, one strain may exhibit only tall plants in all generations while another produces only small plants. These "pure" or parental strains could now be crossed among themselves, with respect to the alternate forms of the traits, to produce hybrid plants. The form of the characteristics in the hybrid would then be noted.

[2]Charles Darwin's own experiments in breeding hybrid plants yielded results with essentially a whole-number ratio (3:1) of character expressions. The following pages will show the significance Darwin did not grasp.

	Characteristic	*Expression*	
		Either	*Or*
1.	Form of ripe seed	Smooth	Wrinkled
2.	Color of endosperm	Yellow	Green
3.	Color of seed coat	Grey	White
4.	Form of ripe seed pods	Smooth	Constricted
5.	Color of unripe seed pods	Green	Yellow
6.	Position of flowers	Along stem	Top of stem
7.	Length of stem	Tall, 6 to 7 feet	Short, 0.75 to 1.50 feet

Results of Mendel's Experiments

Mendel experimented with all seven of the characteristics independently by crossing two strains differing in the expression of one of the characters. For example, Mendel crossed plants having smooth seeds with plants having wrinkled seeds. The parental generation is usually symbolized as P and its offspring, the first filial generation, as F_1. Thus, the smooth with wrinkled cross can be designated in a shortened manner as:

P: smooth x wrinkled

The actual results of this experiment are quite simple:

P: smooth x wrinkled
F_1 : 100% smooth

All of the seeds in the F_1 generation of this experiment were smooth. Furthermore, each of the other six crosses produced an F_1 generation exhibiting only one of the alternate forms of the trait. In the list of characteristics and their expressions above, the forms under the column headed *Either* appeared at a 100% frequency in the F_1 generations.

The experiments were continued by self-fertilizing the F_1 generation. The resulting offspring are in the second filial generation, or the F_2. Again, we can look at the smooth x wrinkled cross, which exemplifies the results obtained from all F_2 generations.

P: smooth x wrinkled
F_1 : 100% smooth
F_2 : 5,474 seeds smooth
1,850 seeds wrinkled

The most obvious fact that emerges when the F_2 generation is observed is that the alternate form of the characteristic which was "lost" in the F_1 (in this case wrinkled) appears again in the F_2. However, the relationship between smooth and wrinkled in the F_2 is not really obvious. The F_2 results can be simplified somewhat by stating the percentage of smooth and wrinkled instead of the actual numbers. If this is done it can be seen that in the F_2 smooth seeds are present at a frequency of 5,474/7,324 = 0.747 or approximately 75% and wrinkled at a frequency of 1,850/7,324 = 0.253 or 25%. This can be stated in another way by saying that smooth seeds are 3 times more frequent than wrinkled seeds, or that the ratio of smooth to wrinkled seeds is 3:1. The F_2 generation of the other six experiments was also reported to have a 3:1 ratio between the characteristic present at 100% frequency in the F_1 and the characteristic lost in the F_1.[3]

Thus, for the first two hybrid generations (F_1 and F_2) Mendel noted three consistencies:

1. For all seven traits the F_1 generation possessed only one of the alternate forms. Both were never present.
2. The alternate form of the trait "lost" or hidden in the F_1 reappeared in the F_2 at a 25% frequency.
3. These results were always the same regardless of the sex of the parent exhibiting the alternate forms. A parent with wrinkled seeds providing pollen for a parent with smooth seeds gave the same results as a parent with round seeds providing pollen for a parent with wrinkled seeds.

From these results Mendel noted that traits could be hidden (in the F_1) but not lost. As a result of this he termed the traits that could be hidden "recessive traits" and their alternate forms "dominant traits." Since the recessive traits were not expressed in the F_1, whatever factors that determine recessive traits must have been hidden because the trait is not lost. Therefore, traits hidden in the F_1 are determined by recessive *factors*. It follows then that dominant *factors* (which show **dominance** over recessive factors) determine the traits not hidden in the F_1. Extending this reasoning to the parental generation (pure lines) we can see that parents with dominant traits must possess only dominant factors and parents with recessive traits have only recessive factors because they were bred to show only one of the traits and they did so consistently. The F_1 generation plants, however, must contain both the dominant and the recessive factors because they produce offspring having either dominant or recessive traits.

The results and interpretation of the experiments discussed thus far would have been a significant contribution to the study of, among other fields, evolution. During the 19th century a popular theory used to explain the mechanism of heredity was that of a blending of fluids (for example, in

[3]Mendel's results seem to be "too good," that is, too close to what is expected. R. A. Fisher and Sewall Wright each discuss the possible reasons underlying the excessive goodness of fit (see *Suggestions for Further Reading*).

animals such terms as *blood, bloodlines,* and *good blood* are often used) so that offspring were considered intermediate between, or an average of, the parents. Initially, Charles Darwin employed this theory of blending as the hereditary mechanism underlying species variations and, of course, it was upon the variations that natural selection acted. It was this aspect of Darwin's theory of natural selection that was most controversial and most criticized.[4] The lack of a convincing mechanism to explain the hereditary basis of variation made many biologists cautious about accepting the total theory of natural selection. In fact, Darwin never could adequately explain the mechanism of heredity which was the crux of this theory of natural selection. Much controversy could have been avoided if Mendel's work had been appreciated by his contemporaries.

Mendel's results indicated that blending was not the sole mechanism of heredity, at least in pea plants, if it was a mechanism at all. The results indicated, rather, that the factors controlling the traits were particulate in nature (that is, they behaved as indivisible particles, not as a fluid). But Mendel also wondered how many factors determined a trait. The first two generations of pea plants do not yield enough information to answer this question. However, the next generation produced by Mendel, the F_3, gives the needed information.

The F_3 generation was produced by self-fertilization of the F_2 plants. Mendel noted that the F_2 plants possessing recessive traits produced offspring having *only* recessive traits. These F_2 plants behaved like the "recessive parents" (pure lines) when self-fertilized. F_2 plants with dominant traits, however, did not always produce only plants having dominant traits in the F_3. In the experiment we have been discussing (the one concerned with seed form), the F_2 dominant parents could be divided into two types based on their F_3 offspring: those that produced offspring with only round seeds (dominant) and those that produced both round and wrinkled plants in a 3:1 ratio. The actual results showed that of the 565 F_2 plants with smooth seeds, 193 produced F_3 offspring with only smooth seeds and the remaining 372 plants each produced smooth and wrinkled plants. Thus 372/565 or about 2/3 acted like F_1 plants exhibiting dominant traits. Diagrammatically this breeding experiment produced the results shown on page 7. Further generations, the F_4, F_5, etc., derived from the F_3 showed similar results. The offspring of plants with wrinkled seeds, as always, produced plants with only wrinkled seeds. The F_3 plants derived from F_2 plants producing only smooth seeds always had smooth seeds themselves and always produced F_4 offspring with

[4]In 1867, F. Jenkins criticized this theory on the basis that variation would be reduced by one-half in each generation of blending, so variation upon which natural selection could act would soon no longer remain in the population.

P: smooth x wrinkled

F_1: smooth (self-fertilized to produce F_2)

F_2: smooth smooth smooth wrinkled (self-fertilized)

3 smooth: 1 wrinkled

F_3: smooth wrinkled

3 smooth: 1 wrinkled

smooth seeds. Whenever a plant produced offspring in a ratio of 3 smooth: 1 wrinkled, 1/3 of the smooth offspring produced only smooth offspring and 2/3 of the smooth offspring produced both smooth and wrinkled offspring. These results also held true for the remaining six crosses. The F_1 always consisted of 100% dominant plants (plants exhibiting the dominant traits), the F_2 produced 3 dominant to 1 recessive, and the F_3 always conformed to the pattern seen in the seed form experiment.

These results clearly show that plants producing offspring with both dominant and recessive types contain both the dominant and the recessive factor. Although the recessive factor may be hidden, it cannot be lost. We can now return to the question posed earlier. How many factors does each plant contain? We have just seen that some plants must contain at least two factors, a dominant (D) and a recessive (R). These are plants that give rise to offspring in a 3:1 ratio. If we symbolize these plants as DR, then plants producing offspring with only dominant traits must be DD while RR plants then are those producing only offspring with recessive traits. Since plants contain only two factors under this hypothesis,[5] when mating occurs only one factor must be contributed by each parent (in self-fertilization one factor is contributed by the male part of the plant and one by the female). We can assume for the sake of argument that each factor is present in equal numbers and the chance of either being contributed to the offspring is also equal. Thus when a fertilization occurs each parent contributes one randomly chosen factor.

Let's work through the mating presented above and see if the observed results fit the hypothesis. Since in the above mating smooth is the dominant trait and wrinkled the recessive, we can symbolize the factor for smooth as *S* (large S) and the factor for wrinkled as *s* (small s). The parental generation is thus *SS* x *ss*. According to the present hypothesis, when these plants are crossed each parent should contribute one randomly chosen factor. Since smooth plants only have *S* factors and wrinkled plants only *s*, the offspring or the F_1 must be *Ss*. When this *Ss* F_1 type is self-fertilized the mating can

[5]It's always easiest to start with the simplest hypothesis and make assumptions that will further simplify analysis. If we find this does not work we can move on to more complicated ideas.

be considered of the type *Ss* x *Ss*. Again each parent or each sexual part of the plant will contribute only one randomly chosen factor. *Since each factor is equally frequent and chosen randomly we have to find all the combinations from each parent.* The male (pollen) parent can produce and contribute equally either an *S* or *s* factor. This is also true of a female egg. Thus, the possible combinations are:

		Female (egg) *S*	Female (egg) *s*
Male (pollen)	*S*	*SS*	*Ss*
	s	*Ss*	*ss*

These are the exact types, and in the same ratio, as observed in the F_2. Three-fourths of the plants have the dominant characteristic (*SS, Ss, Ss*) and 1/4 have the recessive characteristic (*ss*)—a 3:1 ratio. Further, of the plants with the dominant characteristic (*SS, Ss, Ss*), 1/3 are of the same type as the pure-line parent (*SS*) and 2/3 are of the F_1 type (*Ss, Ss*). Again, this is what was observed. Thus Mendel showed that *hybrids* (F_1 type) *between two pure parental lines contain both parental factors and when the hybrids mate these factors separate, or segregate, from each other and are randomly passed on to their offspring.* This phenomenon of **segregation** has come to be known as *Mendel's First Law* or the *Law of Segregation.* These results have been demonstrated time and again for many hybrid generations in many species.

It was by studying the alternate forms of single traits that Mendel arrived at the Law of Segregation. After making this discovery he turned his attention to the behavior of alternate forms of *two* characteristics simultaneously. With this end in mind Mendel produced by self-fertilization two pure lines, one with smooth *and* yellow seeds and one with green *and* wrinkled seeds. From the earlier experiments Mendel knew that smooth and yellow were controlled by dominant factors and green and wrinkled by recessive factors. The mating of these two lines produced, as expected because of dominance, F_1 plants with only smooth and yellow seeds. Thus,

P: smooth yellow x green wrinkled
F_1: 100% smooth yellow

The F_1 when self-fertilized, however, produced seeds in a ratio not seen before. The results were:

F_1: smooth yellow (self-fertilized)
F_2 seeds: 315 smooth yellow: 108 smooth green: 101 wrinkled yellow: 32 wrinkled green
F_2 ratio: 9:3:3:1

How can these results be explained and be consistent with the earlier findings? This problem can be approached in two ways. First we can diagram the crosses, taking into account various simplifying assumptions, and second we can look at the expected results in terms of probability. When diagramming the crosses we know two facts from the prior experiments: (1) smooth and yellow are dominant and wrinkled and green are recessive, and (2) the dominant factors are independent of the recessive factors for each trait. But what is the relationship between the traits? First let us represent the cross as:

P: *SSYY* (smooth yellow) x *ssyy* (wrinkled green)

Since the dominant and recessive factors are independent for each trait, let us assume they are independent between the traits.[6] If they are independent between the traits, the pollen and egg must contain all of the combinations of factors for both traits. Thus, the parent's egg or pollen contains the following combinations:

	Y	*Y*
S	*SY*	*SY*
S	*SY*	*SY*

and

	y	*y*
s	*sy*	*sy*
s	*sy*	*sy*

In all cases the smooth yellow parent produces only one type of *gamete* (a general term referring to reproductive cells, that is, eggs, pollen, sperm), *SY*, and the wrinkled green parent also produces only one type of gamete, *sy*. Thus,

P: *SSYY* x *ssyy*

P gametes: *SY* *sy*

F_1: *SsYy*

Because of dominance the F_1 seeds should all appear smooth and yellow. That is what was actually seen by Mendel. Independence between the traits can explain the results so far. Let's approach the production of the F_2 in the same way. We saw that, according to the hypothesis of independence between traits, the F_1 consisted of the following factors: *SsYy*. Again, if the traits seed form and seed shape are independent, the gametes of either sex should contain all the possible combinations of the factors. We can find the possible combinations in the gametes by:

[6]On page 7 we assumed that the chance of either factor being contributed to an offspring was equal and stated this was a simplifying assumption. Here we will assume that the factors for different traits are independent, that is, have no effect on one another, again to simplify our approach.

		Gametes from *Yy*	
		Y	*y*
Gametes from *Ss*	*S*	*SY*	*Sy*
	s	*sY*	*sy*

These four types of gametes will be produced by both sexes of F_1 individuals. To find the kinds of F_2 individuals produced we can make a chart like that used above to find the types of gametes, but the margins will now be occupied by the types of gametes produced because we want to know what factors the F_2 individuals will contain. Thus:

		Eggs (female gametes)			
		SY	*Sy*	*sY*	*sy*
Pollen (males gametes)	*SY*	*SSYY*	*SSYy*	*SsYY*	*SsYy*
	Sy	*SSYy*	*SSyy*	*SsYy*	*Ssyy*
	sY	*SsYY*	*SsYy*	*ssYY*	*ssYy*
	sy	*SsYy*	*Ssyy*	*ssYy*	*ssyy*

If both of the factors are independent in each trait and the factors for the different traits are independent, then the F_2 should consist of these 16 types of individuals. Do Mendel's observations conform to expectation? Remember that Mendel found a 9:3:3:1 ratio in the F_2. When the above table is analyzed as to the number of different types it can be seen that 9 individuals are of the type *S_Y_*, that is, 9 contain at least one dominant factor of each trait and thus appear as smooth and yellow. The types *ssY_* and *S_yy* each appear 3 times and, because of dominance, appear wrinkled and yellow or smooth and green, respectively. The final individual is *ssyy* and appears wrinkled and green. Thus, the hypothesis of independence *between* the traits yields expected results identical to the results observed by Mendel–9 smooth yellow: 3 smooth green: 3 wrinkled yellow: 1 wrinkled green.

If the chance for a seed to be smooth or wrinkled is independent of its chance to be yellow or green, that is, if form has no effect on color, then each trait can be analyzed separately and combined by multiplying the chance of each characteristic occurring independently. Thus, the F_1 of a smooth x wrinkled cross would consist entirely of smooth seeds. The F_2 would consist of 3 smooth: 1 wrinkled. Similarly for yellow and green, the F_1 are all yellow and F_2 are 3 yellow: 1 green. If these two traits are *independent*, their frequencies when they are considered together in the F_2 should equal the *products* of the two independent crosses. Thus:

3 yellow: 1 green
x 3 smooth: 1 wrinkled

9 smooth yellow: 3 smooth green: 3 wrinkled yellow: 1 wrinkled green

Mendel crossed the various F_2 plants in order to test the kinds of factors present. The offspring in all cases conformed in type and frequency to those expected if the factors for the different traits were independent. In all these cases, independence between traits could theoretically produce results consistent with Mendel's observations. *Hybrids containing alternate factors for two traits show the separation, or segregation, of one pair of factors independently of the segregation of the other pair.* This finding has become known as *Mendel's Second Law* or the *Law of Independent Assortment.*

From experiments thus far Mendel has shown independence between factors determining a single trait (segregation) and independence between factors determining different traits (independent assortment). One of the final experiments performed by Mendel considered three trait differences. One pure line, or variety, had smooth and yellow seeds and violet flowers (all dominant, *SSYYVV*) and the second variety had wrinkled, green seeds and white flowers (all recessives, *ssyyvv*). The results of this cross could also be explained by independent assortment of the three sets of factors. The F_1 consisted of all smooth yellow seeds and violet flowers (*SsYyVv*) as expected. The number and types of gametes produced by F_1 individuals can be found as before. To check the results as to the number of gametes, let n equal the number of factor pairs that differ in the F_1. The quantity 2^n will give the number of different gametes produced by F_1 individuals. In this case $n = 3$ and $2^3 = 8$. Thus, the male and female in F_1 will each produce eight types of gametes and, if all the combinations are independent, 64 types of F_2 individuals are expected. If this $F_1 \times F_1$ (or F_1 self-fertilization) is diagrammed, it will be seen that, because of dominance, the 64 types of individuals can be reduced to a ratio of 27:9:9:9:3:3:3:1. Results closely approximating this ratio were observed by Mendel.[7]

Response to Mendel's Work

The results of Gregor Mendel's eight years of experimentation led him to the discovery of two basic laws of heredity: independence between factors con-

[7] A total of 639 plants were classified as 269 *S_Y_V_*: 98 *S_Y_vv*: 86 *S_yyV_*: 88 *ssY_V_*: 27 *S_yyvv*: 34 *ssYYvv*: 30 *ssyyV_* : 7 *ssyyvv*. The expected numbers, based on the expected ratio, are, respectively, 269.6:89.8:89.8:89.8:30.0:30.0:30.0:10.0. See footnote 3 in this chapter.

trolling a trait and independence between sets of factors controlling separate traits. Mendel presented his work to the Brünn Society of Natural Science in 1865 and in the following year his results were published in the Society's Proceedings. Although this journal was widely distributed throughout Europe and even reached America, a response to Mendel's work was lacking. Why? One of the probable reasons was that no one else understood Mendel's "numerology" as it applied to problems in biology. In addition, since most of the knowledge of the cell and reproduction was yet to be established in Mendel's day, his findings must have seemed very abstract, almost arbitrary. Mendel's results also indicated that variability among the hybrid generations could be traced back to the parents—that is, variability was not the product of new factors but rather the new arrangement of factors. Many biologists of Mendel's time were searching for a source of variation in evolution and Mendel's results also indicated that variability among the hybrid generations determined traits. This concept of constancy must have been unacceptable to a 19th-century evolutionist. Many forces were operating at this time which helped obscure Mendel's work.

During the latter half of the 19th century a number of advances were made in the study of cell division. Chromosomes had been discovered and the particular nature of their behavior during cell division was noted. Mathematical approaches to problems in biology were also now more frequent thanks to the impetus of men such as Francis Galton, the 19th-century scholar responsible for introducing the mathematical tool known as regression analysis. Considering these developments, it is not too surprising that in the year 1900 the laws of heredity were rediscovered. It is surprising, however, that the laws were independently rediscovered by three different investigators. Thus, even though Mendel did discover the basic laws of heredity, the development of the science of genetics would have been the same had he never lived. The three rediscoverers of both the laws of heredity and Mendel's work were Hugo De Vries, Carl Correns, and Erick von Tschermak, who published their reports, respectively, in March, April, and June of 1900.[8]

By 1900 much information had been collected concerning cell division and especially the behavior of the dark-staining bodies in the nucleus called **chromosomes.** In 1903 a correspondence between the behavior of chromosomes during cell division and the theoretical behavior of Mendelian factors was pointed out by Walter Sutton and Theodor Boveri. For example, chromosomes were known to be present in pairs, one of maternal origin and one of paternal origin. According to Mendel, factors also occurred in pairs, one of

[8]Von Tschermak's paper was actually not a rediscovery of Mendel's laws since, unlike those of Correns and De Vries, it presented results without the fundamental analysis.

maternal and one of paternal origin. In addition, during the cell division that produced gametes **(meiosis)** the chromosomes of each pair separated, one going to each gamete. This is consistent with Mendel's Law of Segregation. Also during meiosis, chromosome pairs are arranged independently of each other, that is, one pair's arrangement in no way influenced the arrangement of any other pair. This accords with Mendel's Law of Independent Assortment. Finally, gametes contain only *one* chromosome of every pair but each chromosome is united with its partner at fertilization. Mendel's factors are also present singly in gametes and pairs are produced at fertilization. This correspondence is very striking and the hypothesis of Sutton and Boveri that the chromosomes were the vehicles carrying the Mendelian factors was favorably received. Experiments during the following ten years provided a great deal of evidence that the Sutton-Boveri hypothesis was, in fact, true.

The early 1900s also saw a flurry of research aimed at testing Mendel's laws in organisms other than the garden pea. Experiments conducted during this time provided evidence that Mendel's laws were generally applicable to all organisms. However, some results indicated that Mendelian factors were *not always* transmitted independently of each other nor were the expressions of the factors always independent. Later, mainly through the work of Thomas Morgan, the former exception to Mendel's laws was explained. Organisms possess more traits than chromosomes. Since chromosomes are the vehicles carrying the factors controlling traits, more than one factor must be carried by each chromsome. If so, two or more characters will be transmitted together, that is, they will appear **linked** in their transmission from parent to offspring. The second apparent exception to Mendel's laws, the fact that the expression of factors was not always independent, was ultimately explained through investigations into the mode of action of Mendel's factors, initiated by Sewall Wright in 1915. Investigations of this type employed biochemical, physiological, and histological data to determine how Mendelian factors influenced the growth and development of traits. In time it was seen that observable traits are the result of a number of biochemical reactions, each mutually interdependent and each governed by a Mendelian factor. Thus, although two or more Mendelian factors may be transmitted independently, their expressions may be dependent on one another because they govern biochemical reactions in a pathway leading to the same trait. This topic will be explored more fully in Chapter 3.

Included among the various organisms investigated in the early 1900s were humans. The study of our own species presented a number of difficulties, as we shall see in Chapter 2. Nevertheless, in 1909 Sir Archibald Garrod, in his monograph *Inborn Errors of Metabolism,* presented evidence showing that four traits (diseases) in humans were transmitted in Mendelian fashion.