Human Genetics

An Introduction to the Principles of Heredity

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University of California, Santa Cruz

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Normal and sickled red blood cells from a person who has sickle-cell trait. Electron micrograph courtesy of Patricia N. Farnsworth.

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Preface

Most people are naturally interested in the subject of genetics, especially as it relates to the inheritance of physical and behavioral traits that run in human families. Nonetheless, genetics has the reputation of being a difficult subject, and many people deprive themselves of the fun of understanding how genetics works because they wrongly assume that the subject is too complicated for them. I have written this book in the hope of sharing with you what I think are the fundamentals, and some of the interesting highlights, of human genetics. Anyone with enough interest in the subject to pick up this book and browse through it will probably be able to understand what is written here, regardless of previous background in biological science.

The book has five chapters. The first two are concerned with how the inheritance of some characteristics that run in human family lines can be explained in cellular terms, and with how geneticists explain the fact that the human population is made up of nearly equal numbers of men and women. Chapter 3 explains how the hereditary material, DNA, brings about its effects, and how some human characteristics can be explained as

the results of chemical changes in DNA molecules. Chapter 4 is about the genetics of human populations. Here the emphasis is on the concept of "biological race" and on how heritable changes, or *mutations,* ultimately arise because of accidents that affect DNA molecules. Finally, chapter 5 explains how human characteristics, including those that pertain to behavior, oftentimes depend on the interactions of genetic and environmental factors, and then discusses some of the ways in which people can or could directly influence the genetic future of the human species.

For those who enjoy such things, the text is followed by some problems that pertain to the patterns of inheritance discussed in Chapters one and two. Answers and explanations are also provided. Anyone wanting to read more about human biology may be interested in a book entitled *The Biology of People* that I have written in collaboration with Henry R. Hilgard. (I have, in fact, taken the present volume from the larger work.)

I should sincerely like to thank the following professors who read over, commented on, or otherwise helped to improve my rough drafts: Henry R. Hilgard, Cedric I. Davern, Robert S. Edgar, and Ursula W. Goodenough. Thanks are also due to my friends at W. H. Freeman and Company, especially to Linda Chaput, Gunder Hefta, and John Painter. And finally, thanks to everyone who reads this book and thereby learns something, as I surely did while writing it.

Felton, California
January 1978

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The members of the Augustinian monastery in old Brno, Czechoslovakia in the early 1860s. Gregor Mendel is third from the right. (Photo courtesy of Dr. V. Orel of the Moravian Museum, Brno.)

Contents

CHAPTER 1

Traits and Chromosomes

In the mid-eighteenth century the city of Paris was the scene of a most unusual mating that aroused widespread public interest. The affair concerned a male rabbit who unexplainably showed great sexual interest in a certain barnyard hen. The hen, for her part in the matter, readily tolerated the rabbit's advances but would have nothing to do with roosters. These two unusual animals, both of whom belonged to a disconcerted clergyman, were observed to "mate" frequently, but the naturalists of the day doubted whether the union of the two was as complete as that of a rooster with a hen or a rabbit with another rabbit. So when the hen obligingly laid six normal-looking eggs, there was great excitement. What would hatch out?

Some people expected long-eared furry chickens to result; others, rabbits with beaks and feathers. But to the great disappointment of most neither rabbit nor chicken nor anything in between emerged. The well-watched eggs merely sat and decomposed.

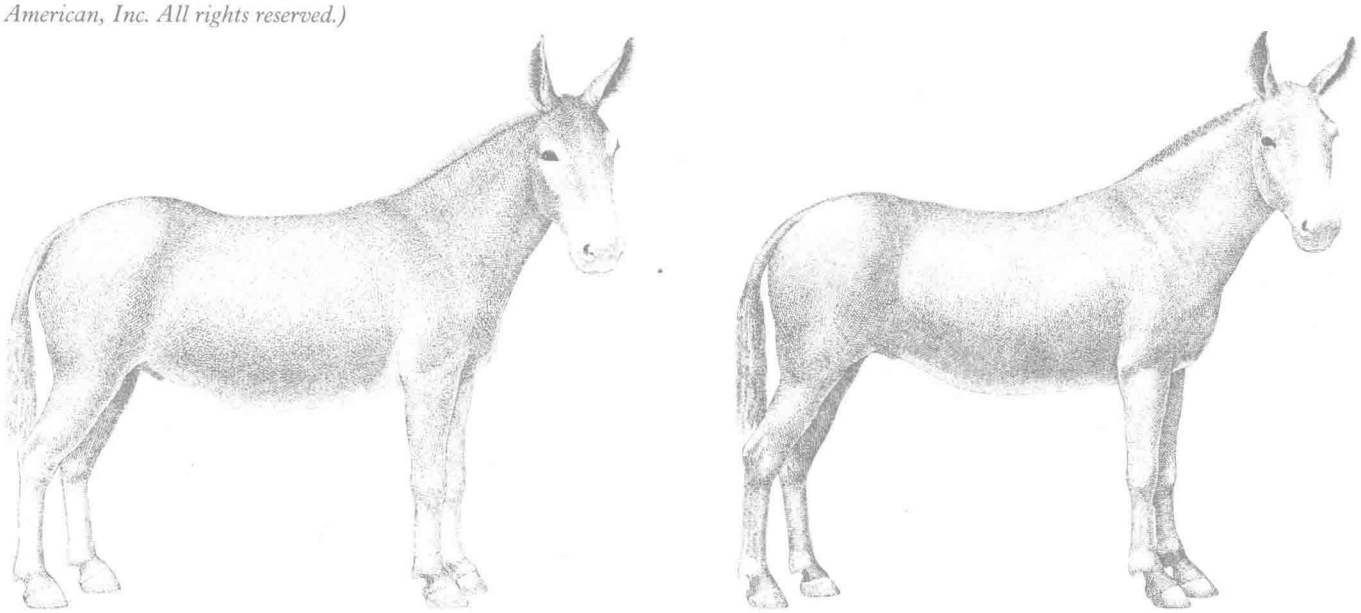
The eggs failed to develop because rabbits and chickens are different species of animals. As you may know, *species* may be defined as populations of organisms that retain their individuality in nature because they are reproductively isolated from other species around them. In general, reproductive isolation among animal species has two important and interrelated aspects: behavior and genetics.

The Parisian observers of the ill-fated "mating" of the rabbit and the hen were as familiar with the behavioral aspects of reproductive isolation as we are. They were well aware that animals of different species generally show no interest whatsoever in mating with one another. But what the Parisians did not realize was that even if the behavioral aspect of reproductive isolation occasionally goes awry, the individuality of a species is still protected because species are genetically distinct from one another. What exactly does this mean?

Animals produce sex cells of two different types—eggs from the female and sperm from the male. The genetic uniqueness of sexually-reproducing species (and this includes virtually all animals) may be thought of as having its basis in different blueprints, or programs, for the elaboration of different species from fertilized eggs. As we shall see, each egg and each sperm usually contain within their nuclei half of the information necessary to set into motion the complicated process of elaborating a particular kind of animal according to the program of the species to which the parents belong. But in order for proper development to occur, both sex cells that merge to form the fertilized egg, or *zygote,* must contain the same basic program.

When the Parisian rabbit and hen mated it is not likely that their union resulted in a fertilized egg. This is because reproductive isolation operates even in sex cells, and rabbit sperm would be unlikely to penetrate and fertilize chicken eggs. In fact, even if we forced a rabbit sperm to fertilize a chicken egg by accurate mechanical injection of the sperm, the mating still would not produc feathered rabbits or long-eared chickens. A chicken egg fertilized in this way ha received two conflicting programs, one for constructing a chicken and one fo constructing a rabbit. And the programs for each are different enough that the artificially fertilized egg burns up its supply of intracellular fuel and then dies in the confusion of attempting to initiate the development of a composite creature from conflicting plans.

Actually, rare instances of successful interspecies mating do occur, not only among animals in experimental circumstances, but in nature too. (Also, interspecies crosses are much more common among plants than among animals.) Generally, such crosses occur only between species that are closely related by evolutionary descent, and that therefore presumably have similar genetic



1–1
The mule, left, is a familiar hybrid that is produced by the mating of a female horse with a male donkey. The hinny, right, is more horselike in appearance and results from the mating of a female donkey with a male horse. (From "The Mule," by Theodore H. Savory. Copyright © 1970 by Scientific American, Inc. All rights reserved.)

programs. Perhaps the most familiar animal issuing from an interspecies cross is the mule, the offspring of the mating of a female horse with a male donkey, but viable crosses also occur among closely related species of fish, birds, and porpoises, among others (Figure 1-1). But the animals resulting from these interspecific crosses are often incapable of reproduction themselves and they are clearly exceptions to the rule of reproductive isolation.

Differences in genetic programs between species are in large part responsible for the fact that animal species are usually morphologically distinct: that is, one can usually tell different species apart merely by looking at them. But then it is possible in many instances to distinguish animals from one another *within* a species, too (intraspecific variation). This is especially true of land-dwelling vertebrates, and is nowhere more obvious than in the human species, which is by far the most variable species known. Human beings have various skin colors ranging from almost pure white to jet black, have head and body hair ranging from perfectly straight to tightly kinked, and have unique fingerprints and faces—except for identical twins, who, as we shall see, have identical genetic programs. Yet within the human species, as is true of all others, the characteristics of individuals are not randomly distributed throughout the entire population. There are clear-cut geographic and racial differences as well as differences between related family lines.

The science of genetics is concerned with the study of heritable differences, both how they originate and how they relate to an individual's genetic program. Genetics also concerns itself with the biological basis of the transmission of traits in lineages and with the distribution of heritable characteristics within the populations that make up a given species. In chapters to come we will investigate the biochemical basis of heritable traits in individual people and see how at least some of these traits may have come to have the distributions we observe within the human population today. But in this chapter our main concern is with identifying and explaining the simple patterns of inheritance shown by some rather clear-cut human characteristics that obviously run in families. For the most part, human patterns of inheritance can best be described by some basically simple—yet decidedly unobvious—principles first worked out in the 1860s by an Augustinian monk named Gregor Mendel (frontispiece).

What Mendel Did

Mendel discovered the basic patterns of inheritance by performing carefully planned experiments on the common garden pea, and his success was partly due to his wise choice of experimental subject. Pea plants are good subjects for simple genetic experiments for several reasons. First of all, individual pea plants have clear-cut differences in some easily recognizable alternate characteristics. For example, the ripe seeds may be either smooth or wrinkled, and either yellow or an intense green. Mendel chose to experiment with seven clearly alternate traits in his search for patterns in the way such traits are passed on from parents to offspring (Figure 1-2).

1–2

Mendel's early experiments were conducted upon seven pairs of alternate characteristics of garden pea plants.

Another reason pea plants make good experimental subjects is that they are self-fertilizing. That is, pea blossoms are so constructed that the male sex cells, which are contained in pollen grains, and the female sex cells, or eggs, are located in the same blossoms. (In other species, male and female sex cells may be produced separately, either by separate male and female flowers on the same plant or by flowers on separate male and female plants.) Self-fertilizing plants tend to breed "true," which means that their offspring usually resemble the parents exactly, at least in the alternate traits Mendel observed and recorded. True-breeding plants are thus good subjects for crosses of individual plants that differ in one or more alternate traits.

Mendel crossed plants that bred true for alternate traits and carefully recorded the distribution of these traits in their offspring. What he found is best illustrated by a recounting of some of his experiments.

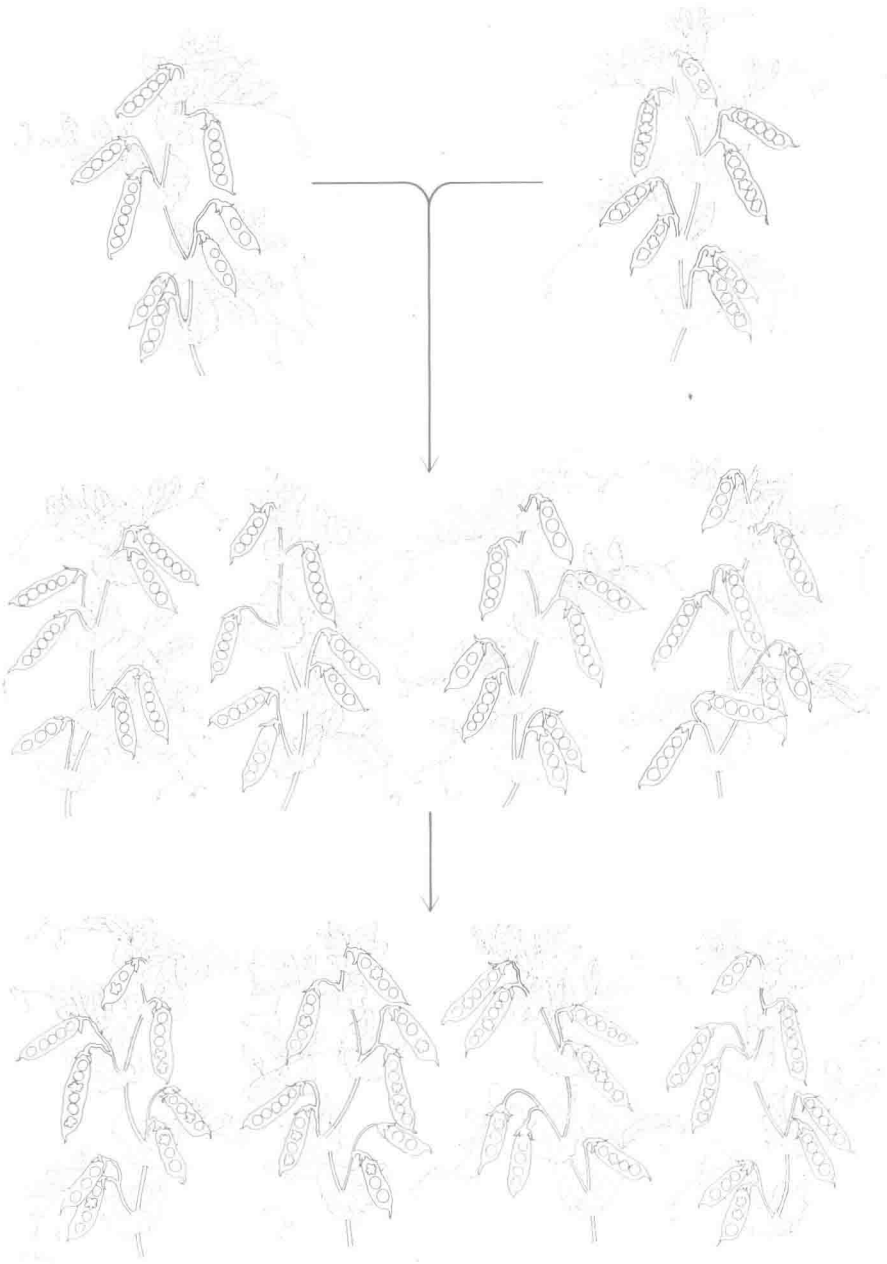
Mendel began with two varieties of true-breeding pea plants, whose self-fertilized (self-pollinated) offspring had ripe seeds that were either round or wrinkled. He pinched off the pollen-producing parts (anthers) of each blossom on plants that produced only wrinkled seeds, and then fertilized the blossoms with pollen from plants that bred true for round seeds. (He also fertilized some "round blossoms" with "wrinkled pollen" and produced essentially the same results discussed in the following sentences.) Mendel then tied little paper bags over the blossoms to prevent any wind-borne or insect-borne pollen from contacting the artificially fertilized plants. When he opened the pods of his experimental plants he found that all of the seeds were round. The alternate trait, "wrinkled," seemed to have disappeared in the first generation of progeny produced from the cross, the F_1 generation. Mendel then planted the round seeds produced in the cross and allowed the resulting plants to fertilize themselves, as they usually do. When he examined the seeds produced by the second generation (the F_2 generation), he sometimes found round and wrinkled seeds lying together in the same pod (Figure 1-3). To be more exact, he found that about 25 percent of the total number of seeds were wrinkled. The trait "wrinkled," which had disappeared in the F_1 generation, had once again turned up in the F_2 generation about 25 percent of the time.

As shown in Table 1-1, Mendel found the same pattern for all seven of the traits he studied. For example, when true-breeding plants that had yellow seeds were crossed with those whose seeds were green, only yellow-seeded offspring were produced. Accordingly, Mendel called the member of the alternate pair of characteristics that showed up in all of the offspring of the F_1 generation, and in about 75 percent of the offspring in the F_2 generation, a *dominant trait.* And he

TABLE 1–1

Mendel's results from crosses involving some alternate characteristics of the common garden pea.

PARENT CHARACTERISTICS	F_1	F_2	F_2 RATIO
1. Round × wrinkled seeds	All round	5,474 round : 1,850 wrinkled	2.96 : 1
2. Yellow × green seeds	All yellow	6,022 yellow : 2,001 green	3.01 : 1
3. Gray × white seedcoats	All gray	705 gray : 224 white	3.15 : 1
4. Inflated × pinched pods	All inflated	882 inflated : 299 pinched	2.95 : 1
5. Green × yellow pods	All green	428 green : 152 yellow	2.82 : 1
6. Axial × terminal flowers	All axial	651 axial : 207 terminal	3.14 : 1
7. Long × short stems	All long	787 long : 277 short	2.84 : 1



1–3
Mendel found that the wrinkled trait disappeared in the F_1 generation but turned up again in the F_2. (From "The Gene", by Norman H. Horowitz. Copyright © 1956 by Scientific American, Inc. All rights reserved.)

named the trait that disappeared in the F_1, only to reappear in about 25 percent of the F_2, a *recessive trait.*

In order to explain the patterns he observed, Mendel proposed that inherited traits are transmitted from parents to offspring by means of independently inherited "factors" that are now known as *genes.* Furthermore, he found that he could predict the results of his experiments if he assumed that true-breeding lines of plants contributed either a dominant or recessive factor to their offspring in the F_1 generation, and that members of the F_1 were therefore *hybrids.* That is, Mendel postulated that each member of the F_1 contained both dominant and recessive factors. This enterprising monk then invented a shorthand notation by which he could follow his hypothetical dominant and recessive factors through various lineages.

Mendel labeled the factor responsible for the dominant trait (round seeds) *A*, and he designated the factor responsible for the recessive trait (wrinkled seeds) *a*. (Geneticists still use capital letters to represent the genes responsible for dominant traits and lower-case letters to represent those responsible for recessive ones. Which letter is chosen to represent a given pair of alternate traits is arbitrary.) When both parents contribute an *A* to their offspring, the offspring are *AA*, and they produce only round seeds. In *aa* plants, which received an *a* from each parent, only wrinkled seeds are produced. Thus, true-breeding lines of plants are either *AA* (round), or *aa* (wrinkled). What happens if two such lines are crossed, as they were by Mendel to produce the F_1 generation? Clearly, all the offspring receive an *A* from one parent and an *a* from the other, so that all members of the F_1 must be *Aa* with respect to the alternate traits "round" or "wrinkled." What do *Aa* plants look like? Because *A* is dominant to *a*, all individuals in the F_1 will have round seeds. The trait "wrinkled" will seemingly have disappeared from the F_1, just as Mendel observed. But, in fact, the factor responsible for the recessive trait has not disappeared; its effects are simply masked by the presence of the factor *A* and, in later crosses, the effect of *a* can become obvious once again.

Consider what happens when the hybrid plants of the F_1 are allowed to self-fertilize and to produce offspring. All of the parents are *Aa*, and can contribute either *A* or *a* to their offspring, and in fact do so in equal proportions. About half the offspring get *A* and half get *a* from *each* parent. This means that three different kinds of offspring can result: *AA* or *aa* plants if both parents happen to contribute the same factor, and *Aa* plants if each parent happens to contribute a different factor.

An easy way to predict what will happen in a given cross is to construct a table that allows us to keep track of all possible combinations of factors. Across the top of the table are listed the factors that one parent can contribute; those from the other parent are listed down the left-hand side. In our example, both parents are hybrids, so they both can contribute either *A* or *a*, and we represent this as follows:

	A	*a*
A		
a		

Then by simply drawing in the boxes and combining the factors we generate the following table. (Capital letters are always written first.)

	A	*a*
A	*AA*	*Aa*
a	*Aa*	*aa*

Thus, the combinations we should expect in the offspring are *AA*, *Aa*, and *aa*. Notice that *Aa* appears in the table twice. This means that about two out of every four offspring will be *Aa*. Or, more generally, about 50 percent of the offspring will be *Aa*. Similarly, about 25 percent of the offspring will be *AA* and the remaining 25 percent, *aa*. Looking at it another way, 75 percent of the offspring

are either *Aa* or *AA* and therefore have round seeds, and 25 percent are *aa* and have wrinkled seeds. These ratios are exactly those observed by Mendel in the F_2 generation.

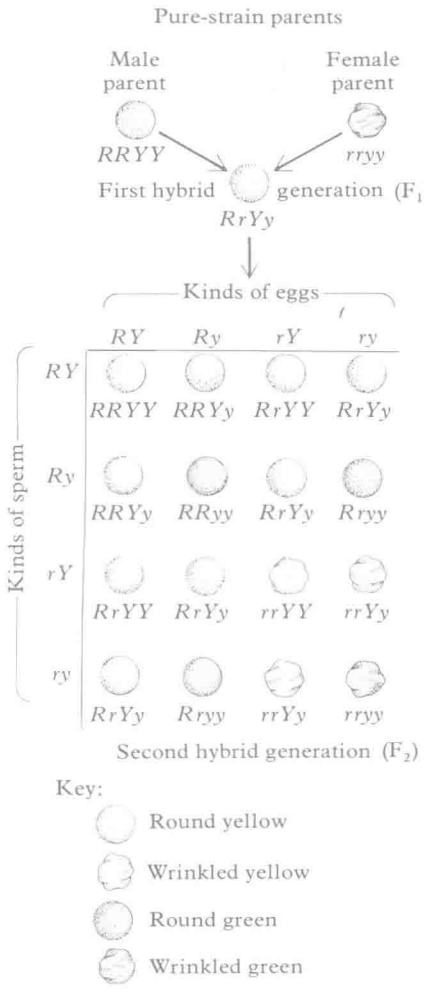
Using the same kind of reasoning Mendel predicted what would happen if he crossed plants differing in *two* alternate characters. He crossed plants that had round yellow peas (both dominant) with plants bearing wrinkled green peas (both recessive) and, as predicted, all members of the F_1 were round and yellow. He then allowed the F_1 hybrids to self-fertilize. If the factors he postulated did indeed exist and behave as independent units, then he expected to find four kinds of peas in the F_2: round yellow, wrinkled yellow, round green, and wrinkled green. Moreover, he predicted he would find them in the ratio 9:3:3:1. He performed the crosses and found the actual ratios to be exactly as he predicted, allowing for small deviations introduced by chance (Figure 1-4).

Mendel had discovered the most fundamental patterns of inheritance, and they have stood the test of time to the present day. We shall soon see how they apply to human lineages. He published his results in 1866, but for the most part his manuscript was ignored. By and large this was because Mendel's "factors" could not be seen; they were rather mysterious units for which no physical basis was known. But all that had changed when Mendel's work was rediscovered in 1900, when it was fully appreciated for the first time. What made the difference was that in the interim biologists had discovered what they presumed to be the physical basis of Mendel's mysterious factors. They had discovered chromosomes.

Chromosomes and Mendel's Patterns

When Mendel published his results in 1866 it was well known that cells are the basic building blocks of all living things. But at that time these fundamental units were poorly known and largely undescribed, because the manufacturing of microscopes and the preparation of specimens for microscopic study had not yet become highly developed arts. Nonetheless, it was known that most plant and animal cells have a distinct nucleus inside them, and that within the dividing nucleus are rodlike structures called chromosomes. In general, chromosomes are clearly visible only in cells that are in the process of dividing. As we discuss later in this chapter, in resting, nondividing cells, the chromosomes are still inside the nucleus, but they are much thinner and are highly entangled with one another so that individual chromosomes cannot be distinguished. (We should mention here that the relatively simple *prokaryotic* cells of bacteria and blue-green algae lack a distinct nucleus and have a single, unpaired chromosome that is never visible through the light microscope and that is much less complex than the chromosomes of eukaryotic cells that we are discussing here. We will have more to say about the structure of prokaryotic and eukaryotic chromosomes in Chapter 3.)

By the time Mendel's work was rediscovered in 1900 enough was known about the remarkable behavior of chromosomes in dividing cells to suggest that the observed patterns of inheritance could be explained in cellular terms by assuming that Mendel's independent factors were located on chromosomes. The gist of the evidence, as first described about the turn of the century, is this: within the nucleus chromosomes exist in pairs, except in a single, revealing instance. The exception is the sex cells, whose nuclei contain only one member of each



1–4
The results of a cross of pea plants that differ in two *pairs of alternate characteristics (round and yellow versus wrinkled and green).*

pair, or half the number of chromosomes in other body cells. How does this tie in with the inheritance of alternate traits described by Mendel?

Assume that the dominant and recessive forms of a particular factor are located one each on the two chromosomes of a particular pair. Thus, an *Aa* individual has an *A* on one chromosome of a given pair and an *a* on the other. When the individual produces sex cells, pairs of chromosomes separate so that each egg or sperm contains either an *A* chromosome or an *a* chromosome. Then, when self-fertilization occurs, pairs of chromosomes are reunited once again, and the resulting offspring are either *AA, Aa,* or *aa,* depending on which factors happened to be located on the particular chromosome pairs that were reunited.

You will recall that Mendel followed the patterns of inheritance of seven pairs of alternate traits of the common garden pea. It turns out that pea plants have seven pairs of chromosomes, which correlates with Mendel's observation that all seven of the traits he studied behaved independently. That is, Mendel's factors showed *independent assortment* because virtually all of the traits he studied are determined by factors located on different pairs of chromosomes. (Mendel was thus not only careful, but lucky, too.)

It is now known that the number of chromosome pairs normally present in the nucleus can vary widely from species to species. (Remember that only one member of each pair is present in an animal's sex cells.) It is also known that each chromosome pair usually carries factors responsible for many different traits.

How does all of this relate to people? Our discussion of Mendel's work provides a background for discussing human chromosomes and for relating them to the patterns of inheritance shown by some alternate traits in human families. But before we go any further we should first introduce some terms that describe the genetic make-up of an individual, human or otherwise. Familiarize yourself with these words now, for they will be used repeatedly in the discussion that follows.

Some Definitions

Mendel's inherited factors, the units of heredity, are now called *genes.* We will discuss the biochemical basis of genes in following chapters. The two (or more) forms of genes responsible for alternate traits (*A* and *a* in our example) are called *alleles.*

Individuals in whom the two alleles of a given pair are the same (*AA* or *aa*) are called *homozygotes,* whereas *heterozygotes* are individuals in whom the two alleles of a given pair are different (*Aa*).

Recall that you cannot distinguish *Aa* heterozygotes from *AA* homozygotes merely by looking at them. (Both have round seeds.) But the two can be told apart if they are crossed with known heterozygotes (*Aa*). Thus, if wrinkled seeds (*aa*) turn up in the offspring, we can conclude that both parents must have been *Aa.* If only round seeds are produced, then the offspring are either *Aa* or *AA,* and the parent crossed with the known heterozygote must have been *AA.* To distinguish individuals that look alike but nonetheless have different genetic constitutions geneticists use the terms *phenotype* and *genotype.* Phenotype is a description of what an individual looks like, and genotype describes the individual's genetic constitution. In our example, individuals of phenotype "round" may be either of two genotypes, *Aa* and *AA.*

With these terms in mind, let us discuss the chromosomes of the human