CHAPTER I

THE FUNDAMENTAL PRINCIPLES OF GENETICS

THE modern theory of heredity is derived from numerical data obtained by crossing two individuals that differ in one or more characters. The theory is primarily concerned with the distribution of units between successive generations of individuals. In the same sense in which the chemist postulates invisible atoms and the physicist electrons, the student of heredity appeals to invisible elements called genes. The essential point in this comparison is that both the chemist and the student of heredity—the geneticist—have reached their conclusion from numerical and quantitative data. The theories justify themselves in so far as they permit numerical and quantitative prediction of a specific kind. In this essential respect the theory of the gene differs from earlier biological theories that have also postulated invisible units to which were arbitrarily assigned any desired properties. The theory of the gene reverses this order and derives the properties of the genes, so far as it assigns properties to them, from the numerical data alone.

Mendel's Two Laws.

We owe to Gregor Mendel the discovery of two of the fundamental laws of heredity on which the modern theory of heredity is based. Later work, done by others during the present century, has carried us further in the same direction and made possible the elaboration of the theory on a much broader basis. Mendel's discovery may be illustrated by a few familiar examples.

He crossed a tall variety of edible pea to a short variety. The offspring, or hybrids, F_1, were all tall (Fig. 1). These were allowed to self-fertilize. Their offspring were

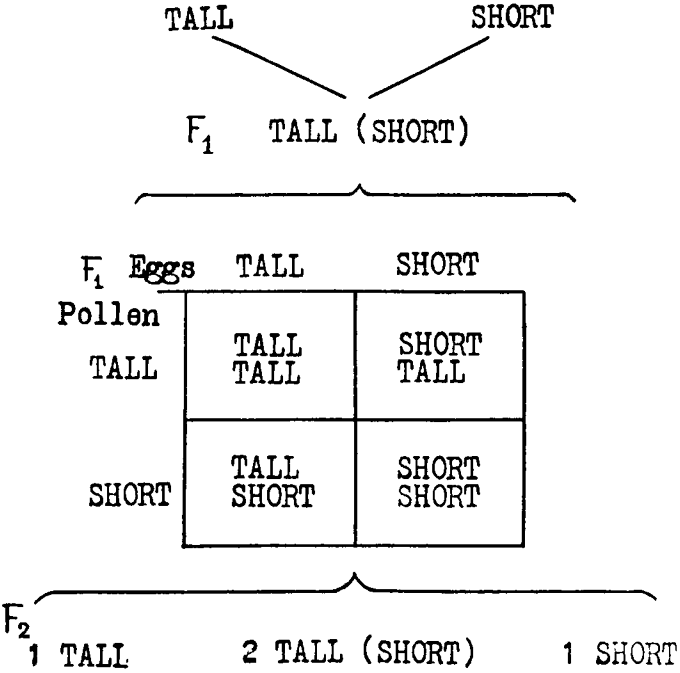

FIG. 1.

Tall peas crossed to short peas giving in the first generation (F_1), tall peas that are "hybrid," *viz.*, tall (short). The recombination of the gametes (eggs and pollen grains) are shown in the square. Three tall to one short peas result in the next or second (F_2) generation.

tall and short in the ratio of three talls to one short. If the tall variety contains in its germ-cells something that makes the plants tall, and if the short variety carries something in its germ-cells that makes the plants short, the hybrid contains both; and since the hybrid is tall it is evident that when both are brought together the tall *dominates* the short, or, conversely, *short is recessive to* tall.

Mendel pointed out that the 3 to 1 ratio that appears in the second generation can be explained by means of a very simple hypothesis. If the element for tall and the one for short (that are both present in the hybrid) separate in the hybrid when the eggs and pollen grains come to maturity, half the eggs will contain the tall and half the short element (Fig. 1). Similarly for the pollen grains. Chance fertilization of any egg by any pollen grain will give on the average three talls to one short; for, when tall meets tall a tall plant is produced; when tall meets short a tall plant results; when short meets tall, a tall plant is produced; and when short meets short, a short plant arises.

Eggs	short	short
F_1 Pollen		
tall	short tall	short tall
short	short short	short short

FIG. 2.

A "back-cross" of F_1 hybrid, tall (short) peas to the recessive type (short), giving equal numbers of tall and short offspring.

Mendel put this hypothesis to a simple test. The hybrid was back-crossed to the recessive type. If the germ-cells of the hybrid are of two kinds, tall and short, there should be two kinds of offspring, tall and short in equal numbers (Fig. 2). The results confirm the expectation.

The same relation shown by the tall and the short peas can be illustrated by the inheritance of eye color in man. Blue eyes mated to blue, give only blues; brown eyes

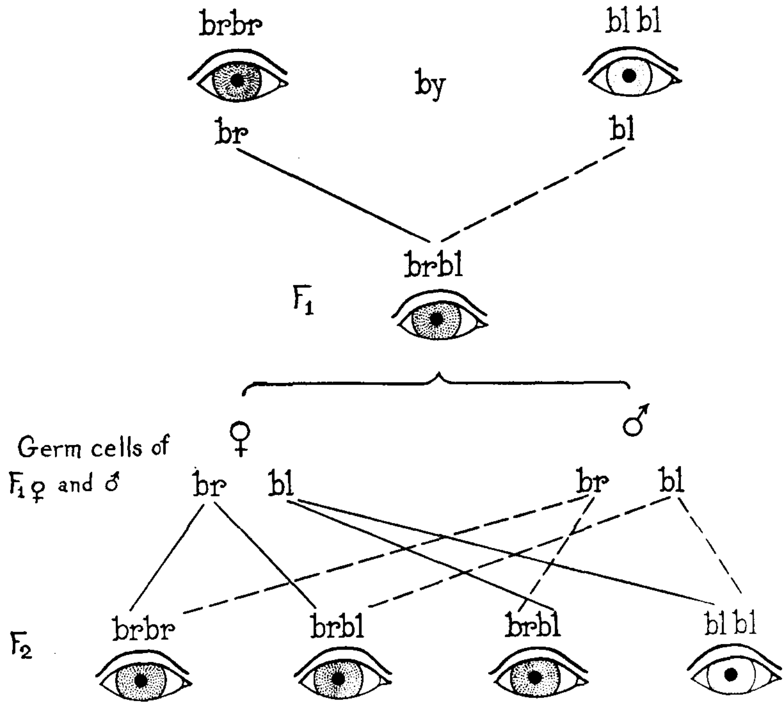

Fig. 3.

Inheritance of brown eyes (brbr) *versus* blue (blbl) eyes in man.

bred to brown give only brown, provided the browns have had only a brown ancestry. If a blue mates with a pure brown, the children are brown (Fig. 3). If two individuals that have arisen from such parentage marry, their children will be brown- and blue-eyed in the ratio of 3 to 1.

If a hybrid brown-eyed individual (F_1 brown-blue) marries a blue-eyed individual, half the children will have brown, and half will have blue eyes (Fig. 4).

There are other crosses that give, perhaps, a more striking illustration of Mendel's first law. For instance, when a red and a white-flowered four-o'clock are crossed, the hybrid has pink flowers (Fig. 5). If these pink-flowered hybrid plants self-fertilize, some of their offspring (F_2) are red like one grandparent, some of them pink like the hybrid, and others white like the other grandparent, in the ratio of 1:2:1. Here one original parental color is restored when red germ-cell meets red, the other color is restored when white meets white, and the hybrid combinations appear as often as red meets white, or white meets red. All the colored flowered plants in the second generation taken together are to the white-flowered plants as 3:1.

Eggs Sperm	blue	blue
brown	blue brown	blue brown
blue	blue blue	blue blue

FIG. 4.

A "back-cross" of a brown-eyed, F_1, individual, heterozygous for blue eyes, to the recessive type, blue eyes, giving equal numbers brown-eyed and blue-eyed offspring.

In passing it is important to note two facts. The red and the white F_2 individuals are expected to breed true, because they contain the elements for red, or for white, twice present (Fig. 6), but the pink F_2 individuals should not breed true, since they are like the first hybrid generation, and contain one red and one white element (Fig. 6). All this turns out to be true when these plants are tested.

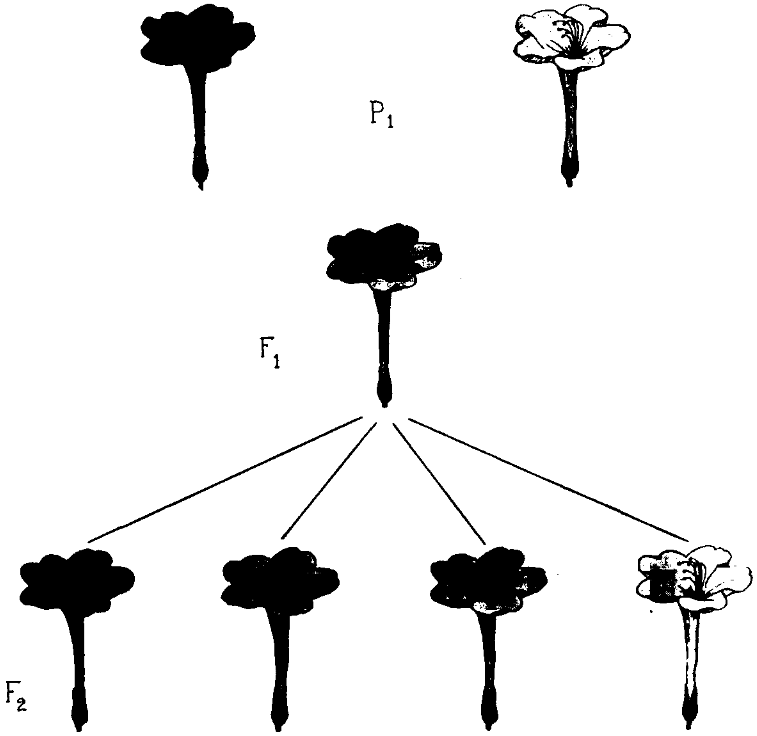

FIG. 5.

A cross between a red-flowered four-o'clock (Mirabilis Jalapa) and a white-flowered four-o'clock, giving pink in F_1, and one red, two pink, one white in F_2.

So far the results tell us no more than that something derived from one parent separates, in the germ-cells of the hybrid, from something brought in by the other parent. The results might be interpreted, on this evidence alone, to mean that red-flowered and white-flowered plants behave as wholes or entities in inheritance.

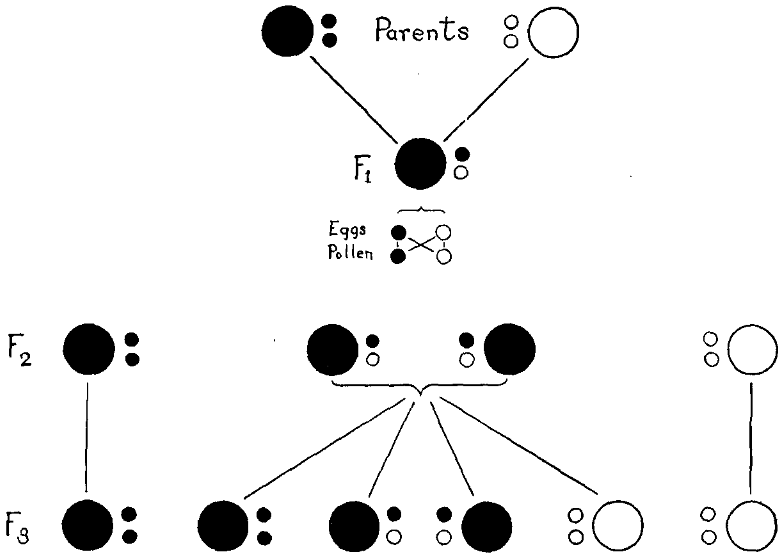

FIG. 6.

Diagram to illustrate the history of the germ-cells in the cross between red and white four-o'clock (Fig. 5). The small black circles stand for red-producing genes and the small white circles for white-producing genes.

Another experiment, however, throws further light on this question. Mendel crossed peas whose seeds were yellow and round with peas whose seeds were green and wrinkled. Other crosses had shown that yellow and green constitute a pair of contrasted characters giving a 3 to 1 ratio in the second generation, and that round and wrinkled constitute another pair.

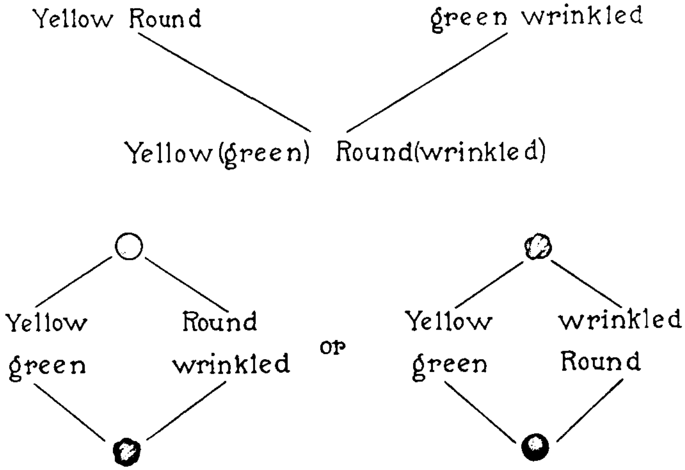

FIG. 7.

Diagram to illustrate the inheritance of two pairs of Mendelian characters, *viz.*, yellow-round and green-wrinkled peas. In the lower part of the diagram the four classes of F_2 peas are shown, *viz.*, the two original classes, yellow-round and green-wrinkled, and the two recombination classes, yellow-wrinkled and green-round.

The offspring were yellow and round (Fig. 7). When selfed, they produced four kinds of individuals, yellow round, yellow wrinkled, green round, and green wrinkled in the ratio of 9:3:3:1.

Mendel pointed out that the numerical results found here can be explained, if the separation of the elements for yellow and for green is independent of that for round and wrinkled. This would give four kinds of germ-cells in the hybrid, yellow round, yellow wrinkled, green round, and green wrinkled (Fig. 8).

If the fertilization of the four kinds of ovules by the four kinds of pollen grains is at random, there will be sixteen combinations possible. Remembering that yellow dominates green, and that round dominates wrinkled, these sixteen combinations will fall into four classes, that are in the ratios of 9 : 3 : 3 : 1.

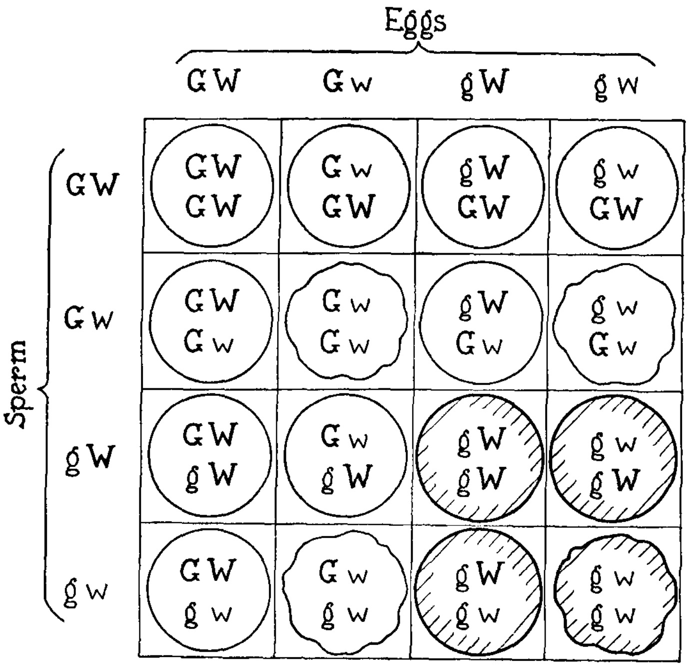

FIG. 8.

Diagram illustrating the sixteen F_2 recombinations (from yellow-round and green-wrinkled peas) that result when the four kinds of eggs and the four kinds of pollen grains of the F_1 hybrid come together.

The results of this experiment show that it can no longer be assumed that the whole parental germ-materials are separated in the hybrid; for yellow and round that went in together have, in some cases, come out separated. Similarly for green and wrinkled.

Mendel also showed that when three, and even four, pairs of characters enter a cross their elements are independently assorted in the germ-cells of the hybrid.

It might, then, have seemed justifiable to extend this conclusion to as many pairs of characters as enter any particular cross. This would mean that there are as many independent pairs of elements in the germinal material as there are possible characters. Subsequent work has shown, however, that Mendel's second law of independent assortment has a more restricted application, since many pairs of elements do not assort freely, but certain elements that enter together show a tendency to remain together in succeeding generations. This is called linkage.

Linkage.

Mendel's paper was recovered in 1900. Four years later Bateson and Punnett reported observations that did not give the numerical results expected for two independent pairs of characters. For instance, when a sweet pea *having purple flower-color and long pollen grains* is crossed to one with red flowers and round pollen grains, the two types that go in together come out together more frequently than expected for independent assortment of purple-red and round-long (Fig. 9). They spoke of these results as due to repulsion between the combinations purple and long and red and round, that came from opposite parents. Today these relations are called linkage. By linkage we mean that when certain characters enter a cross together, they tend to remain together in later generations, or, stated in a negative way, certain pairs of characters do not assort at random.

It would seem, then, so far as linkage holds, that there are limits to the subdivision of the germinal material. For example in the vinegar fly, Drosophila melanogaster, there are known about 400 new mutant types that fall into only four linkage groups.

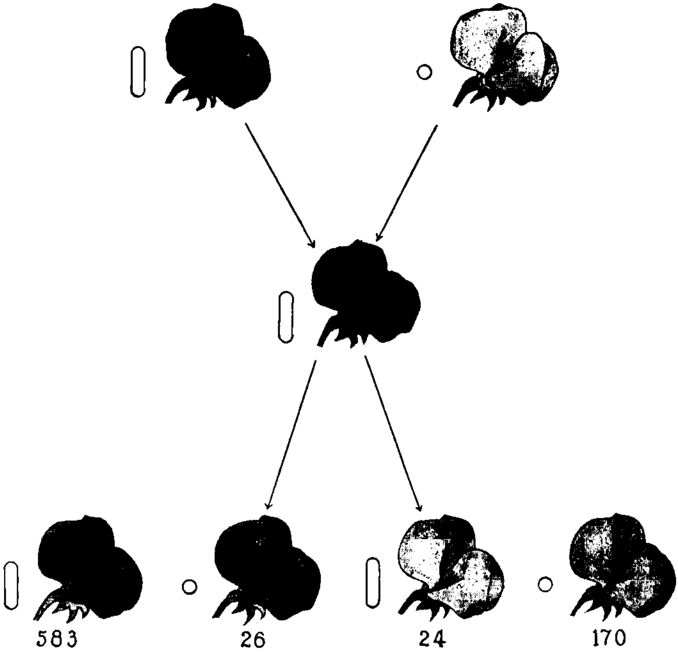

FIG. 9.

Cross between a sweet pea with purple flowers and long pollen grains and one with white flowers and round pollen grains. In the lower line the four classes of F_2 individuals appeared in the proportions given.

One of these groups of characters of Drosophila is said to be sex-linked, because in inheritance the characters show certain relations to sex. There are about 150 of these sex-linked mutant characters. Several of them are modifications of the color of the eye, others relate to its shape or its size, or to the regularity of the distribution of its facets. Other characters involve the body color; others the shape of the wings, or the distribution of its veins; others the spines and hairs that cover the body.

A second group of about 120 linked characters includes changes in all parts of the body. None of the effects are identical with those of the first group.

A third group of about 130 characters also involves all parts of the body. None of these characters are the same as those of the other two groups.

There is a small fourth group of only three characters: one involves the size of the eyes, leading in extreme cases to their total absence; one involves the mode of carriage of the wings; and the third relates to the reduction in size of the hairs.

The method of inheritance of linked characters is given in the following example. A male Drosophila with four linked characters (belonging to the second group), black body color, purple eyes, vestigial wings, and a speck at the base of the wings (Fig. 10), is crossed to a wild type female with the corresponding normal characters, that may be called gray body color, red eyes, long wings, and absence of speck. The offspring are wild type. If one of the sons[1] is now crossed to a stock female having the four recessive characters (black, purple, vestigial, speck), the offspring are of two kinds only, half are like one grandparent with the four recessive characters, and the other half are wild type like the other grandparent.

Two sets of contrasted (or allelomorphic) linked genes went into this cross. When the germ-cells in the male hybrid matured, one of these sets of linked genes went into half of the sperm-cells and the corresponding allelomorphic set into the wild type half of the sperm-

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[1] It is necessary to make this reservation as to the *male* Drosophila, because in the female these same characters are not *completely* linked.

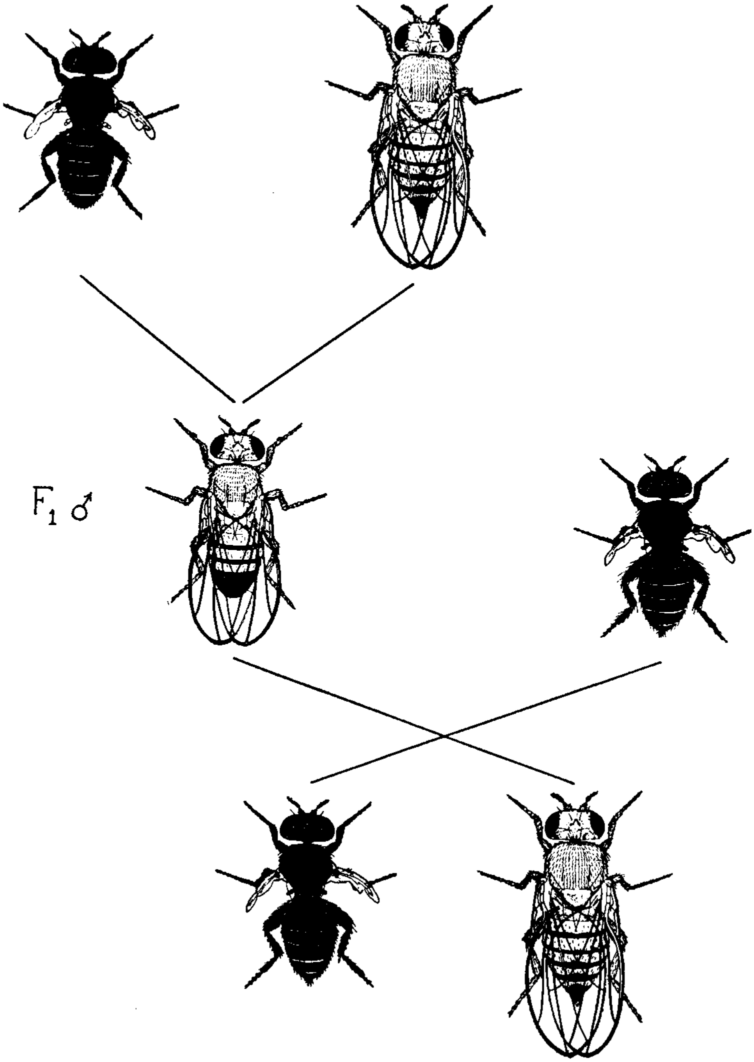

FIG. 10.

The inheritance of four linked, recessive characters, *viz.*, black body color, purple eyes, vestigial wings, and speck, *versus* their normal allelomorphs of the wild type fly. The F_1 male is "back-crossed" to a female of the multiple recessive stock, giving in the second generation (shown below) only the two grand parental combinations.

cells. This was revealed, as described above, by crossing the hybrid (F_1) male to a female pure for the four recessive genes. All of her mature eggs contain one set of four recessive genes. Any egg fertilized by a sperm with one set of the dominant wild type genes should give a wild type fly. Any egg fertilized by a sperm with the four recessive genes (which are the same as those in the female here used) should give a black, purple, vestigial, speck fly. These are two kinds of individuals obtained.

Crossing-Over.

The members of a linked group may not always be completely linked as in the case just given. In fact, in the F_1 female from the same cross, some of the recessive characters of one series may be interchanged for wild type characters from the other series, but even then, since they remain united more often than they interchange, they are still said to be linked together. This interchange is called crossing-over, which means that, between two corresponding linked series, there may take place an orderly interchange involving great numbers of genes. Since an understanding of this process is essential to what follows, a few examples of crossing-over may be given.

When a male Drosophila with the two recessive mutant characters, yellow wings and white eyes, is mated to a female with the wild type characters, gray wings and red eyes, the daughters and sons have gray wings and red eyes (Fig. 11). If one of the daughters is mated to a male with the two recessive characters, yellow wings and white eyes, there are four kinds of offspring. Two kinds are like the grandparents, that is, they have yellow wings and white eyes, or gray wings and red eyes. Together they constitute 99 per cent of the offspring. The characters that went in together have come out together in a much higher percentage than expected from Mendel's second law, *viz.*, the law of free assortment. In addition to the two classes, there are two other kinds of flies in the second generation (Fig. 11), one with yellow wings and red eyes, and the other with gray wings and white eyes. Together they constitute 1 per cent of this generation.

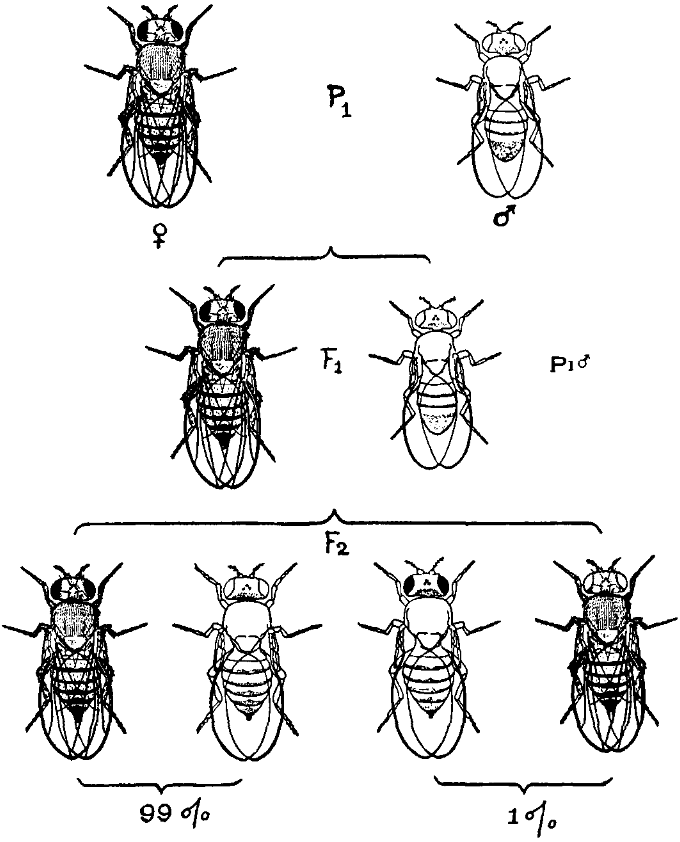

FIG. 11.

The inheritance of two recessive sex-linked characters, *viz.*, white eyes and yellow wings and their "normal" allelomorphs, *viz.*, red eyes and gray wings.

They are the crossovers, and represent interchanges between the two linkage groups.

A similar experiment can be made in which the same characters as before are differently combined. If a male Drosophila with yellow wings and red eyes is mated to a

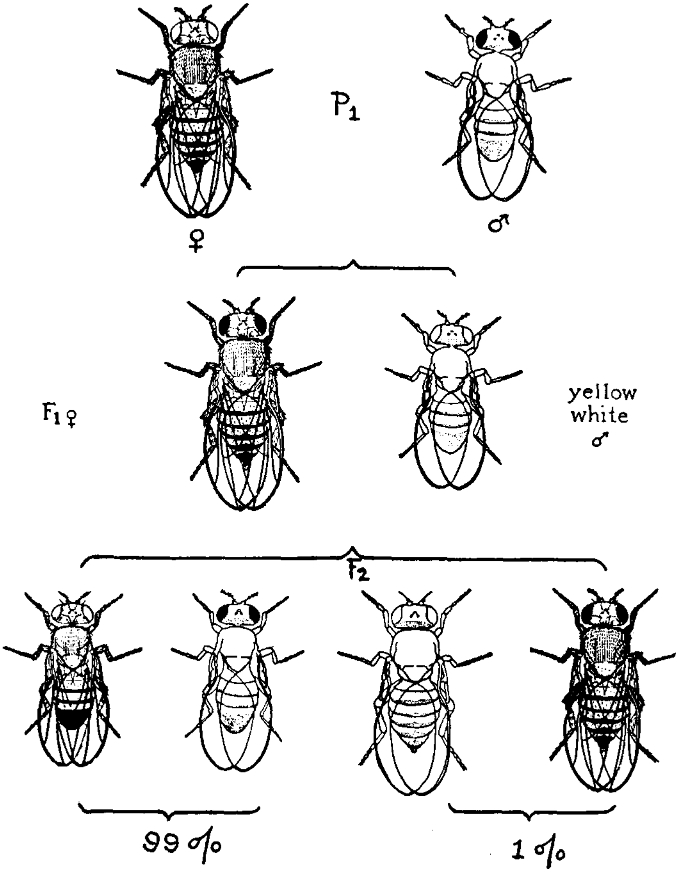

FIG. 12.

The inheritance of the same two sex-linked characters of Fig. 11, but in reciprocal combinations, *viz.*, red eyes and yellow wings, and white eyes and gray wings.

female with gray wings and white eyes the daughters have gray wings and red eyes (Fig. 12). If one of the daughters is mated to a male with the two recessive mutant characters, yellow wings and white eyes, there are four kinds of flies produced. Two of these are like the two grandparents, and constitute 99 per cent of the output. Two are new combinations, or crossovers, one with yellow wings and white eyes and the other with gray wings and red eyes. Together they make up 1 per cent of the second generation.

These results show that the same amount of crossing-over takes place irrespective of the way in which the combinations of the same characters enter the cross. If the two recessives enter together, they tend to hold together. This relation was called coupling by Bateson and Punnett. If one of the recessives enters from one parent and the other recessive from the other parent, they tend to come out separately (each in combination with the dominant that went in with it). This relation was called repulsion. It is clear, however, from the two crosses that have just been given, that these relations are not two phenomena, but expressions of the same one, namely, that the two linked characters that enter a cross, quite irrespective of their dominance or recessiveness, tend to hold together.

Other characters give different percentages of crossing-over. For example, when a male Drosophila with the two mutant characters, white eyes and miniature wings (Fig. 13), is mated to a wild type fly with red eyes and long wings the offspring have long wings and red eyes. If one of the daughters is mated to a male with white eyes and miniature wings the offspring are of four kinds. The two grandparental types constitute 67 per cent and the two cross-over types 33 per cent of this generation.

A still higher percentage of crossing-over is given in the following experiment. A male with white eyes and forked bristles is mated to a wild type female (Fig. 14). The offspring have red eyes and straight bristles. If one of the daughters is mated to a male with white eyes and forked bristles, there are four kinds of individuals pro-

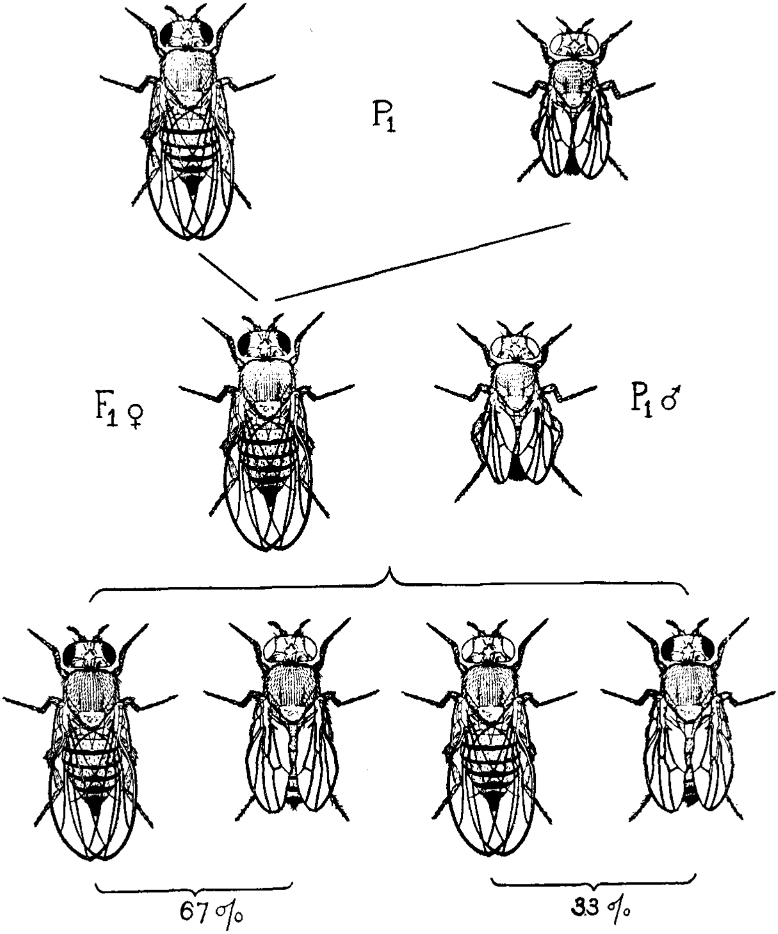

Fig. 13.

The inheritance of two sex-linked characters, white eyes and miniature wings, and red eyes and long wings.

duced. The grandparental types constitute 60 per cent and the crossovers 40 per cent of this second generation.

A study of crossing-over has shown that all possible percentages of crossing-over occur, up to nearly 50 per cent. If exactly 50 per cent of crossing-over took place,

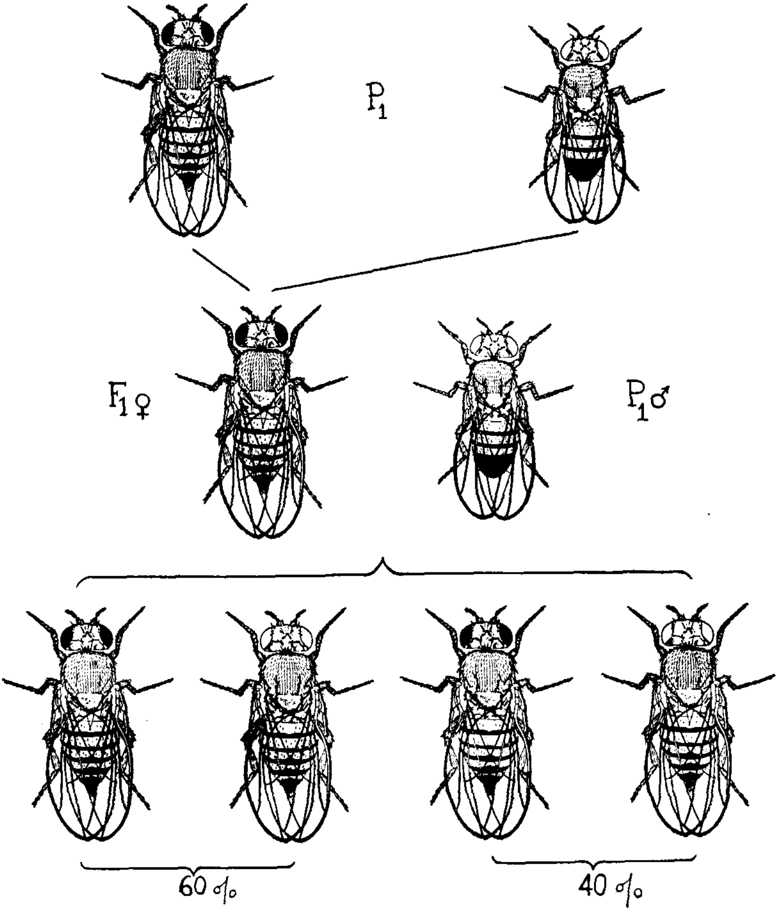

FIG. 14.

The inheritance of two sex-linked characters, white eyes and forked bristles, and red eyes and normal bristles.

the numerical result would be the same as when free assortment occurs. That is, no linkage would be observed even though the characters involved are in the same linkage group. Their relation as members of the same group could, nevertheless, be shown by their common linkage to some third member of the series. If more than 50 per cent crossing-over should be found, a sort of inverted linkage would appear, since the cross-over combinations would then be more frequent than the grandparental types.

The fact that crossing-over in the female of Drosophila is always less than 50 per cent, is due to another correlated phenomenon called double crossing-over. By double crossing-over is meant that interchange takes place twice between two pairs of genes involved in the cross. The result is to lower the *observed* cases of crossing-over, since a second crossing-over undoes the effect of a single crossing-over. This will be explained later.

The Simultaneous Interchange of Many Genes in Crossing-Over.

In the examples of crossing-over just given, two pairs of characters were studied. The evidence involved only those cases of crossing-over that took place once between the two pairs of genes involved in the cross. In order to obtain information as to how frequently crossing-over takes place elsewhere, *i.e.*, in the rest of the linkage group, it is necessary to include pairs of characters that cover the entire group. For example, if a female with the following nine characters of Group I, scute, echinus, cross-veinless, cut, tan, vermilion, garnet, forked and bobbed, is crossed to a wild type male, and if the F_1 female (Fig. 15) is back-crossed to the same multiple recessive type, the offspring produced will give a record of every crossing-over. If crossing-over had taken place

FIG. 15.
Diagram of two allelomorphic series of linked genes. In the upper line the approximate location of nine, sex-linked recessive genes is indicated. In the lower line the normal allelomorphic genes are indicated.

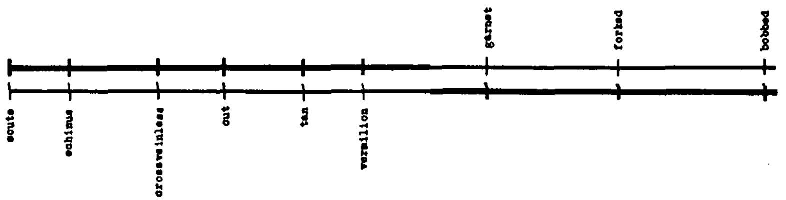

FIG. 16.
Diagram to show crossing-over between garnet and vermilion, *i.e.*, near the middle of the series shown in Fig. 15.

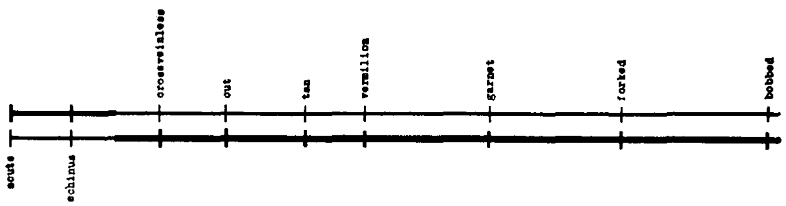

FIG. 17.
Diagram to show crossing-over between echinus and cross-veinless near the left end of the series. See Fig. 15.

FIG. 18.
Double crossing-over between the two series of genes indicated in Fig. 15. One crossing-over is between cut and tan and the other between garnet and forked.

near the middle of the series (between vermilion and garnet), the result would be that shown in Fig. 16. Two complete halves have interchanged.

In other cases, crossing-over may take place near one end (for example, between echinus and cross-veinless). The result is like that shown in Fig. 17. Only the short ends of the two series have interchanged. The same kind of process occurs whenever an interchange takes place. Whole series of genes are interchanged, although as a rule the interchange is noticed only between the genes on each side of the crossing-over.

When simultaneous crossing-over occurs at two levels at the same time (Fig. 18) very many genes are also involved. For example, in the series just given one crossing-over is supposed to take place between cut and tan, and another crossing-over between garnet and forked. All the genes in the middle of the two series have been interchanged. This would pass unobserved were there no mutant genes in the region to indicate the fact that two crossings-over had taken place, since the two ends of both series remain the same as before.

The Linear Order of the Genes.

It is self-evident that if two pairs of genes should be near together, the chance that crossing-over occurs between them is smaller than if they are further apart. If two other genes are still further apart the chance of crossing-over is correspondingly increased. We may utilize these relations to obtain information as to the "distance" at which any two pairs of elements lie with respect to each other. *With this information we can construct charts* of the series of elements in each of the linkage groups. This has been done for all the linkage groups of Drosophila. Such a chart (Fig. 19) gives the result as far as carried out.

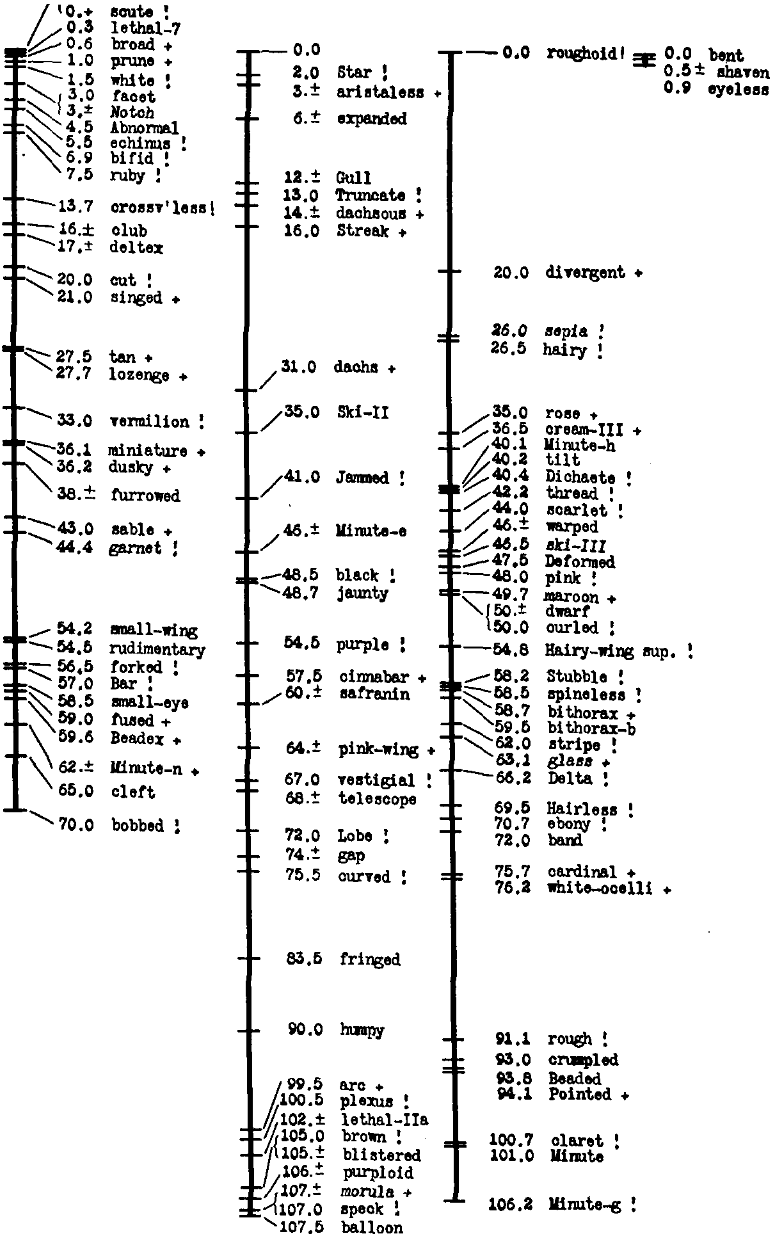

FIG. 19.

Map or chart of the four series, I, II, III, IV, of linked genes of Drosophila melanogaster. The "map distance" is given in the numerals to the left of each character.

In the preceding illustrations of linkage and crossing-over, that have been given, the genes are represented as lying in a line—like beads on a string. The numerical data from crossing-over show, in fact, that this arrangement is the only one that is consistent with the results obtained, as the following example will serve to illustrate.

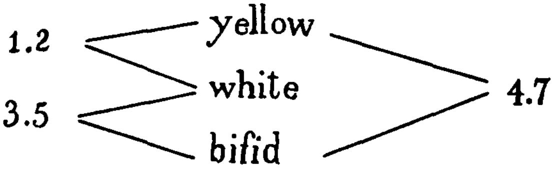

FIG. 20.

Diagram illustrating the linear order of three sex-linked genes, *viz.*, yellow wings, white eyes, bifid wings.

Suppose that crossing-over between yellow wings and white eyes occurs in 1.2 per cent of cases. If we then test white with a third member of the same series, such as bifid wings, we find 3.5 per cent of crossing-over (Fig. 20). If bifid is in line and on one side of white it is expected to give with yellow 4.7 per cent crossing-over, if on the other side of white it is expected to give 2.3 per cent of crossing-over with yellow. In fact, it gives one of these values, namely, 4.7. We place it, therefore, below white in the diagram. This sort of result is obtained whenever a new character is compared with two other members of the same linkage group. The crossing-over of a new character is found to give, in relation to two other known factors, either the sum or the difference of their respective cross-over values. This is the known relation of points on a line, and is the proof of the linear order of the genes; for no other spatial relation has yet been found that fulfills these conditions.

The Theory of the Gene.

We are now in a position to formulate the theory of the gene. *The theory states that the characters of the individual are referable to paired elements (genes) in the germinal material that are held together in a definite number of linkage groups; it states that the members of each pair of genes separate when the germ-cells mature in accordance with Mendel's first law, and in consequence each germ-cell comes to contain one set only; it states that the members belonging to different linkage groups assort independently in accordance with Mendel's second law; it states that an orderly interchange—crossing-over—also takes place, at times, between the elements in corresponding linkage groups; and it states that the frequency of crossing-over furnishes evidence of the linear order of the elements in each linkage group and of the relative position of the elements with respect to each other.*

These principles, which, taken together, I have ventured to call the theory of the gene, enable us to handle problems of genetics on a strictly numerical basis, and allow us to predict, with a great deal of precision, what will occur in any given situation. In these respects the theory fulfills the requirements of a scientific theory in the fullest sense.