THE MECHANISM OF MENDELIAN HEREDITY

CHAPTER I

MENDELIAN SEGREGATION AND THE CHROMOSOMES

Mendel's law was announced in 1865. Its fundamental principle is very simple. *The units contributed by two parents separate in the germ cells of the offspring without having had any influence on each other.* For example, in a cross between yellow-seeded and green-seeded peas, one parent contributes to the offspring a unit for yellow and the other parent contributes a unit for green. These units separate in the ripening of the germ cells of the offspring so that half of the germ cells are yellow bearing and half are green bearing. This separation occurs both in the eggs and in the sperm.

Mendel did not know of any mechanism by which such a process could take place. In fact, in 1865 very little was known about the ripening of the germ cells. But in 1900, when Mendel's long-forgotten discovery was brought to light once more, a mechanism had been discovered that fulfils exactly the Mendelian requirements of pairing and separation.

The sperm of every species of animal or plant carries a definite number of bodies called chromosomes. The egg carries the same number. Consequently, when the sperm unites with the egg, the fertilized egg will contain the double number of chromosomes. For each chromosome contributed by the sperm there is a corresponding chromosome contributed by the egg, *i.e.*, there are two chromosomes of each kind, which together constitute a pair.

When the egg divides (Fig. 1, *a–d*), every chromosome splits into two chromosomes, and these two daughter chromosomes then move apart, going to opposite poles of the dividing cell (Fig. 1, *c*). Thus each daughter cell (Fig. 1, *d*) receives one of the daughter chromosomes formed from each original chromosome. The same process occurs in all cell divisions, so that all the cells of the animal or plant come to contain the double set of chromosomes.

The germ cells also have at first the double set of chromosomes, but when they are ready to go through the last stages of their transformation into sperm or eggs the chromosomes unite in pairs (Fig. 1, *e*). Then follows a different kind of division (Fig. 1, *f*) at which the chromosomes do not split but the members of each pair of chromosomes separate and each member goes into one of the daughter cells (Fig. 1, *g*, *h*). As a result each mature germ cell receives one or the other member of every pair of chromosomes and the number is reduced to half. Thus the behavior of the chromosomes parallels the behavior of the Mendelian units, for in the germ cells each unit derived from the father separates from the corresponding unit derived from the mother. These units will henceforth be spoken of as factors; the two factors of a pair are called allelomorphs of each

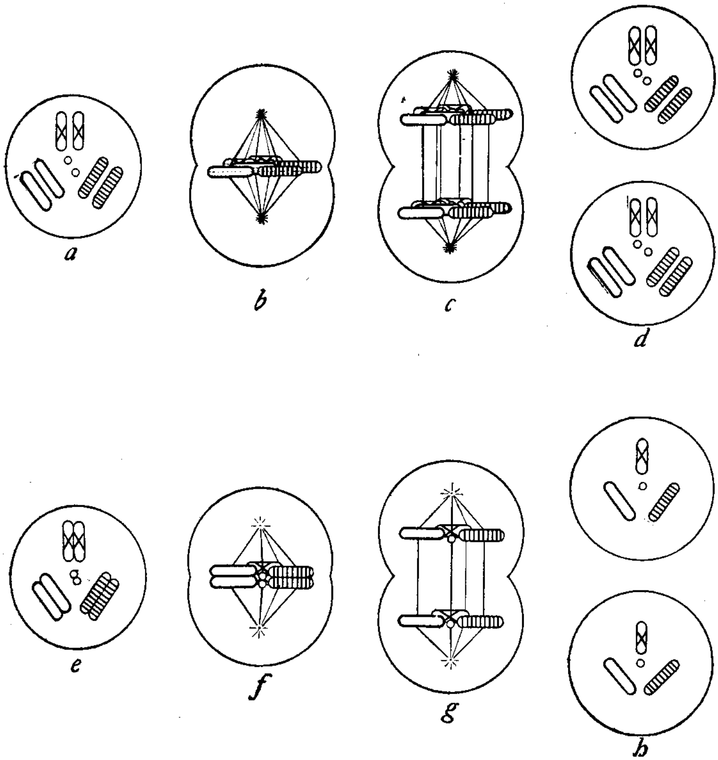


FIG. 1.—In the upper line, four stages in the division of the egg (or of a body cell) are represented. Every chromosome divides when the cell divides. In the lower line the "reduction division" of a germ cell, after the chromosomes have united in pairs, is represented. The members of each of the four pairs of chromosomes separate from each other at this division.

other. Their separation in the germ cells is called segregation.

The possibility of explaining Mendelian phenomena by means of the manœuvers of the chromosomes seems to have occurred to more than one person, but Sutton was the first to present the idea in the form in which we recognize it today. Moreover, he not only called attention to the fact above mentioned, that both chromosomes and hereditary factors undergo segregation, but showed that the parallelism between their methods of distribution goes even further than this. Mendel had found that when the inheritance of more than one pair of factors is followed, the different pairs of factors segregate independently of one another. Thus in a cross of a pea having both green seeds and tall stature with a pea having yellow seeds and short stature, the fact that a germ cell receives a particular member of one pair (*e.g.*, yellow) does not determine which member of the other pair it receives; it is as likely to receive the tall as the short. Sutton pointed out that in the same way the segregation of one pair of chromosomes is probably independent of the segregation of the other pairs.

It was obvious from the beginning, however, that there was one essential requirement of the chromosome view, namely, that all the factors carried by the *same* chromosome should tend to remain together. Therefore, since the number of inheritable characters may be large in comparison with the number of pairs of chromosomes, we should expect actually to find not only the independent behavior of pairs, but also cases in which characters are linked together in groups in their inheritance. Even in species where a limited number of Mendelian units are known, we should still expect to find some of them in groups.

In 1906 Bateson and Punnett made the discovery of linkage, which they called gametic coupling. They found that when a sweet pea with factors for purple flowers and long pollen grains was crossed to a pea with factors for red flowers and round pollen grains, the two factors that came from the same parent tended to be inherited together. Here was the first case that gave the sort of result that was to be expected if factors were in chromosomes, although this relation was not pointed out at the time. In the same year, however, Lock called attention to the possible relation between the chromosome hypothesis and linkage.

In other groups a few cases of coupling became known, but nowhere had the evidence been sufficiently ample or sufficiently studied to show how frequently coupling occurs. Since 1910, however, in the fruit fly, Drosophila ampelophila, a large number of new characters have appeared by mutation, and so rapidly does the animal reproduce that in a relatively short time the inheritance of more than a hundred characters has been studied. It became evident very soon that these characters are inherited in groups. There is one great group of characters that are sex linked. There are two other groups of characters slightly greater in number. Finally a character appeared that did not belong to any of the other groups, and a year later still another character appeared that was linked to the last one but was independent of all the other groups. Hence there are four groups of characters in Drosophila. A partial list of these groups is given in the following table:

Group I	Group II	Group III	Group IV
Abnormal	Antlered	Band	Bent
Bar	Apterous	Beaded	Eyeless
Bifid	Arc	Cream III	
Bow	Balloon	Deformed	
Cherry	Black	Dwarf	
Chrome	Blistered	Ebony	
Cleft	Comma	Giant	
Club	Confluent	Kidney	
Depressed	Cream II	Low crossover	
Dotted	Curved	Maroon	
Eosin	Dachs	Peach	
Facet	Extra vein	Pink	
Forked	Fringed	Rough	
Furrowed	Jaunty	Safranin	
Fused	Limited	Sepia	
Green	Little crossover	Sooty	
Jaunty I	Morula	Spineless	
Lemon	Olive	Spread	
Lethal 1	Plexus	Truncate intens.	
Lethal 1a	Purple	Trident	
Lethal 2	Speck	White head	
Lethal 3	Strap	White ocelli	
Lethal 3a	Streak		
Lethal 4	Tip		
Lethal 5	Trefoil		
Lethal 6	Truncate		
Lethal 7	Vestigial		
Lethal B			
Lethal Sa			
Lethal Sb			
Lethal Sc			
Miniature			
Notch			
Reduplicated			
Ruby			
Rudimentary			
Sable			
Shifted			
Short			
Skee			
Spoon			
Spot			
Tan			
Truncate intens.			
Vermilion			
White			
Yellow			

The four pairs of chromosomes of the female of Drosophila are shown in Fig. 2 (to the left). There are three pairs of large chromosomes and one pair of small chromosomes. One of the four is the pair of sex chromosomes (X chromosomes). In the male, Fig. 2 (to the right), there are likewise three pairs of large chromosomes and a smaller pair. The two sex chromosomes in the male are here represented as differ-

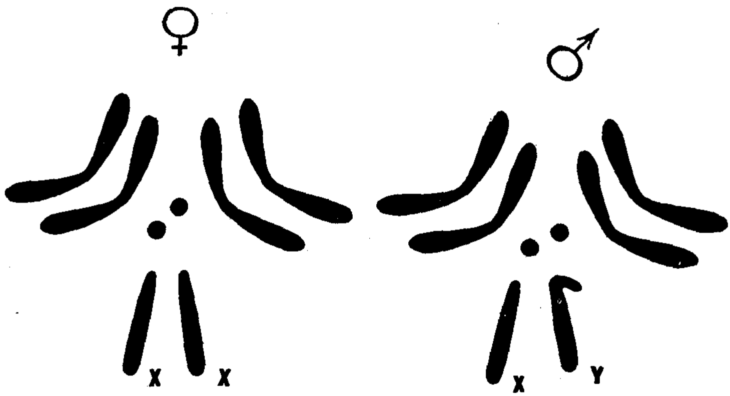


FIG. 2.—Diagram of female and of male group (duplex) of chromosomes of Drosophila ampelophila showing the four pairs of chromosomes. The hook on the Y chromosome is a convention. The members of each pair are usually found together, as here.

ing from each other in shape. In the diagrams the Y chromosome is represented as hook shaped, but this is intended only as a convention. It is true that in the case of non-disjunction where the Y chromosome has been transferred to the female it has this hook shape, but as yet it has not been possible to identify the Y chromosome as hook shaped in the male. Stevens' work had seemed to show that the X chromosome is attached to another chromosome and that there is no Y chromosome. In the earlier papers on Drosophila this relation of the chromosomes was assumed to be correct and the female was represented as XX and the male as XO.

In Drosophila, then, there is a numerical correspondence between the number of hereditary groups and the number of the chromosomes. Moreover, the size relations of the groups and of the chromosomes correspond. The method of inheritance of the factors carried by these chromosomes will now be considered more in detail.

The Inheritance of one Pair of Factors

The inheritance of a single pair of characters may be illustrated by the following examples from Drosophila, one from each of the four groups.

The mutant stock called vestigial is so characterized because it has only small vestiges of the wings. If a fly with vestigial wings is mated to the wild type with long wings (Fig. 3, P_1), the offspring will have long wings (Fig. 3, F_1). If these hybrid flies of the first generation (the first filial generation, or F_1) are mated to each other, their offspring (or F_2) will be of two sorts: some will have long wings and others will have vestigial wings. There will be three times as many flies with long wings as flies with vestigial wings. This is the Mendelian ratio of 3:1 that appears when a single pair of characters is involved.

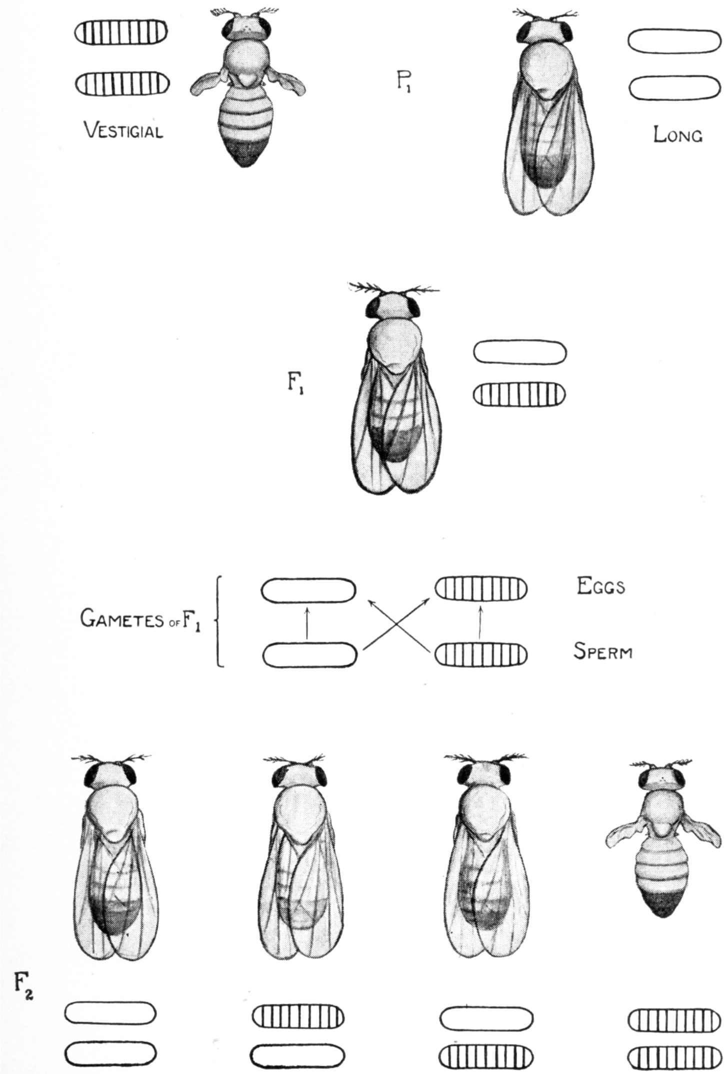
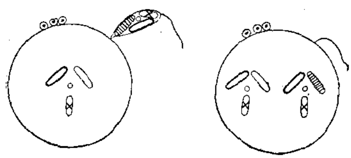


Fig. 3.—Vestigial winged by long winged (wild type) fly. The second chromosome that carries the recessive factor for vestigial is cross-barred, the corresponding chromosome of the normal is plain.

If the factors for vestigial wings are carried by a pair of chromosomes (the cross-barred chromosomes in Fig. 1) then at the ripening of the germ cells (eggs and sperm) such a pair of chromosomes will come together (Fig. 1, *e*) and then separate (Fig. 1, *g*); so that each germ cell (Fig. 1, *h*) will have one such chromosome and not the other.

If such a sperm cell fertilizes an egg of the wild fly that contains a similar group of chromosomes, ex-



A *B*

FIG. 4.—Diagram to illustrate the fertilization of an egg by a sperm *A*. One chromosome in the egg differs from the corresponding (homologous) chromosome in the sperm. The fertilized egg (zygote) with the double (duplex) number of chromosomes in *B*.

cept that the corresponding chromosome carries the factor for long wings (Fig. 4, *A*), the result will be to produce a fertilized egg (Fig. 4, *B*) in which one member of the pair of chromosomes in question comes from the mother and carries the factor for long, and the other comes from the father and carries the factor for vestigial wing. Since this egg with both factors present produces a fly with long wings, the vestigial character is said to be recessive to the long; or conversely the long is said to be dominant to the vestigial character.

When the eggs and the sperm of hybrid flies of this origin come to maturity, the homologous chromosomes conjugate in pairs, as shown diagrammatically in Fig. 5, *b*. The chromosomes then separate (Fig. 5, *c* and *d*) at the time of division of the cell, and one of the resulting daughter cells gets the chromosome bearing the vestigial, and the other daughter cell gets the homologous chromosome, bearing the long factor. Hence, there will be two kinds of eggs in the female and two kinds of spermatozoa in the male. When two such hybrid flies mate with each other, any

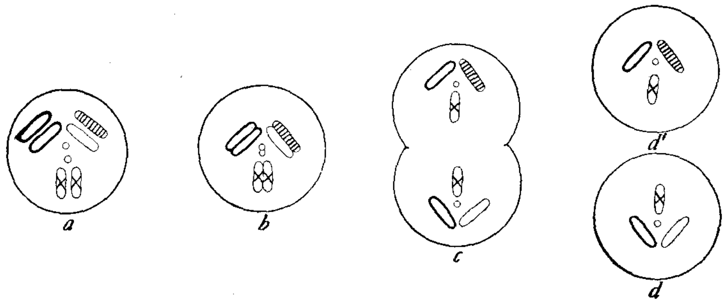


FIG. 5.—Diagram to illustrate in a heterozygous individual the conjugation and segregation of the chromosomes during "reduction."

sperm may meet and fertilize any egg. The possible combinations that result, and the frequency with which they occur, are shown in the next diagram (Fig. 6).

As shown in this diagram, a spermatozoon bearing the factor for long wings fertilizing an egg bearing the same factor produces a fly pure for long wings; a spermatozoon bearing the factor for long wings fertilizing an egg bearing the factor for vestigial wings produces a hybrid fly that has long wings. Hence we say the long dominates the vestigial character.

Similarly, a spermatozoon bearing the factor for vestigial wings fertilizing an egg bearing the factor for long wings produces a hybrid with long wings; a spermatozoon bearing the factor for vestigial wings

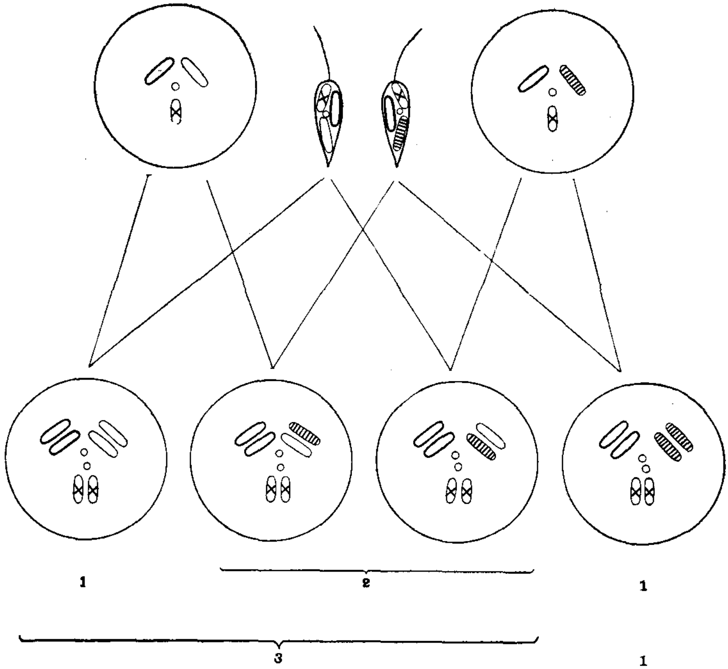


FIG. 6.—Diagram to illustrate how by the random meeting of two kinds of sperm and two kinds of eggs the typical 3:1 ratio results.

fertilizing an egg bearing the factor for vestigial wings produces a fly pure for vestigial wings.

Since the sperm and the eggs meet at random there should be 1 pure long, to 2 heterozygous long, to 1 vestigial; or putting together all flies with long wings, 3 long to 1 vestigial. Three to one is the characteristic Mendelian ratio when one pair of characters is involved.

In another mutant stock, ebony, the body and wings are very dark in contrast to the wild fly whose color is "gray." Gray is used to designate the color of the wild fly, whose wings are gray, but whose body is yellowish with black bands on the abdomen. If ebony is crossed to gray the offspring (F_1) are gray but are somewhat darker than the ordinary wild flies. When these hybrids are inbred they give (F_2) 1 gray, to 2 intermediates, to 1 ebony. The group of intermediates in the second generation (F_2) can not be separated accurately from the pure gray type. If they are counted as gray, the result is three grays to one ebony.

Since ebony and gray assort independently of long and vestigial, as will be shown later, the factor for ebony must be supposed to be carried by a chromosome of a different pair from the one that carries vestigial. Since this chromosome behaves in the same way as does the one that bears the vestigial factor, the scheme used for vestigial will apply here also.

Another mutant stock is characterized by small eyes, and since in the extreme form it may lack one or both eyes entirely (Fig. 7), the name "eyeless" has been given to this mutant. When this stock is bred to wild flies the offspring have normal eyes. These inbred give three normal to one eyeless fly. As shown in the table on page 6, this character belongs in still another, the fourth, group, and its mode of inheritance is explicable on the supposition that it lies in the fourth pair of chromosomes.

For an adequate understanding of the inheritance

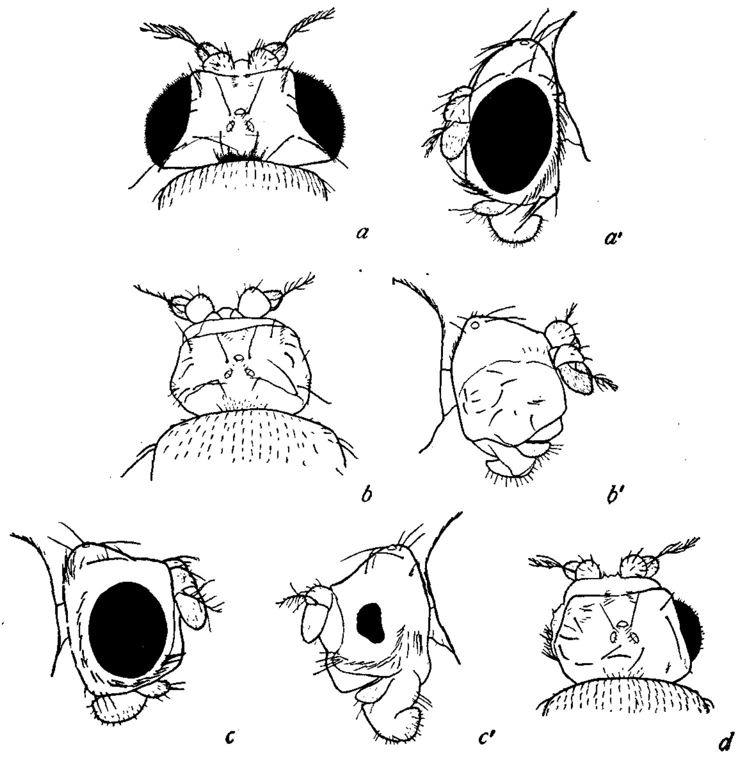


FIG. 7.—Normal eyes of Drosophila *a*, *a'*. Eyeless *b–d; b*, *b'* top and side view of head of fly without eyes; *c*, *c'* right and left eyes of another fly; *d*, small eye on right side, none on left.

of factors in the first group it will be necessary to consider the distribution of the sex chromosomes (Fig. 8). In the female of Drosophila there are two X chromosomes (XX). After the conjugation and separation of the X chromosomes in the female there is one X chromosome left in each egg. In the male there is one X chromosome and another chromosome, its mate, called the Y chromosome. Hence in the male there are two classes of spermatozoa: one containing X, the other Y. If a Y-bearing spermatozoon should

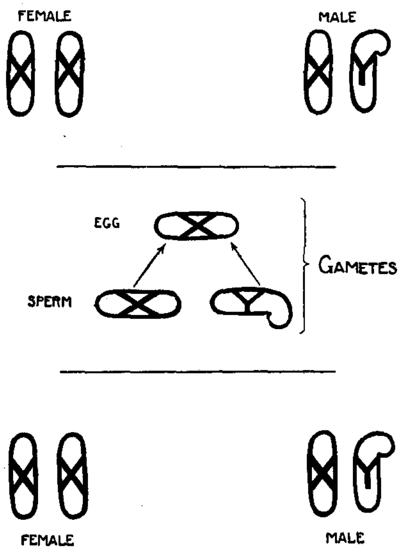


FIG. 8.—Diagram to show the history of the sex chromosomes from one generation to the next.

fertilize an egg the result will be an XY individual, or male. It is evident that the Y chromosome is found only in the males, while an X chromosome passes not only from female to female, but also from female to male and from male to female.

As will be shown now, certain factors follow the distribution of the X chromosomes and are therefore supposed to be contained in them. These factors are said to be sex linked.

The inheritance of white eyes may serve as an illustration for the entire group of sex linked characters. If a white-eyed male is bred to a red-eyed female (wild type) (Fig. 9), the sons and daughters (F_1) have red eyes. If these are inbred the offspring (F_2) are three reds to one white, but the white-eyed flies are all males. If we trace the history of the sex chromosomes we can see how this happens.

In the red-eyed mother, each egg contains an X chromosome bearing a factor for red eyes. In the white-eyed father, half of the spermatozoa contain an X chromosome which carries a factor for white eyes, while the other half contain a Y chromosome which carries no factors (Fig. 9). Any egg fertilized by an X-bearing spermatozoon of the white-eyed father will produce a female that has one red-producing X chromosome and one white-producing X chromosome (Fig. 9). Her eyes are red, because red dominates white. Any egg fertilized by a Y-bearing spermatozoon of the white-eyed father will produce a son (Fig. 9) that has red eyes, because his X chromosome brings in the red factor from the mother, while the Y chromosome does not bring in any dominant factor. At the ripening of the germ cells in the F_1 female the number of chromosomes is reduced to half. There result two kinds of eggs, half with the red-bearing and half with the white-bearing X (Fig. 9). Similarly in the male there will be two classes of sperm, half with the red-bearing X chromosome,

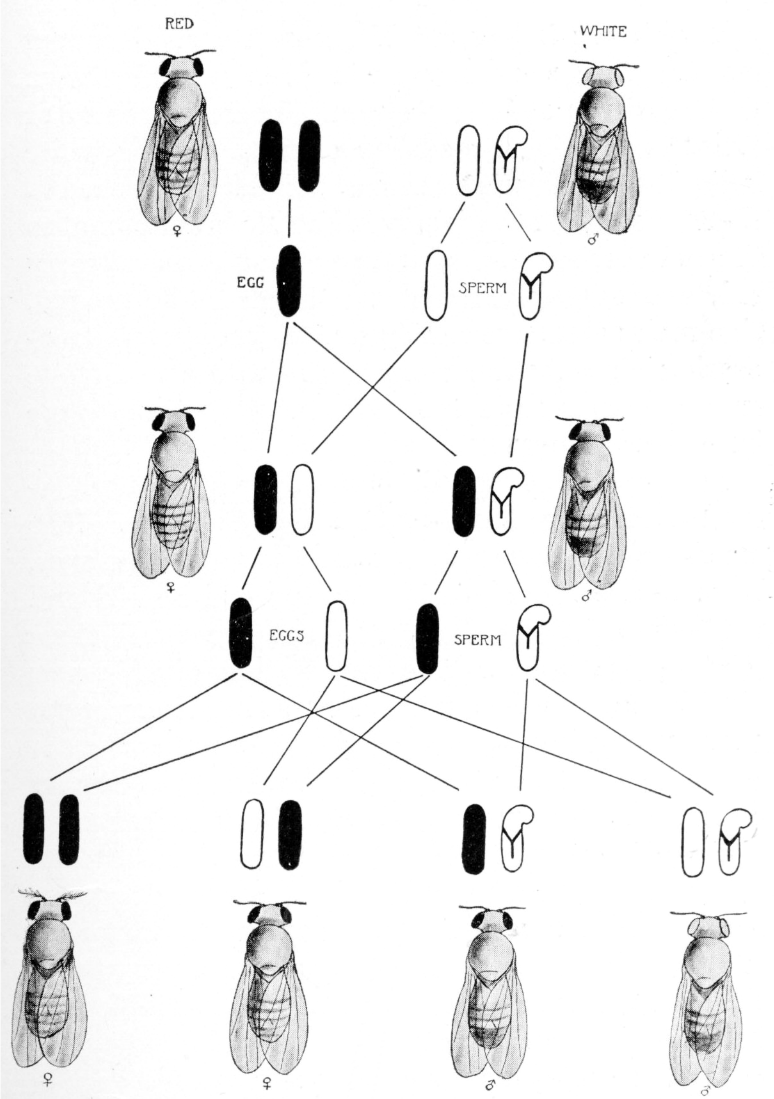


FIG. 9.—Red-eyed female by white-eyed male (D. ampelophila). This is the reciprocal of the cross shown in Fig. 10.

half with the indifferent Y chromosome. Random meeting of eggs and sperm will give the result shown in the lower line of the diagram. There will be a 3 : 1 ratio, as in other Mendelian crosses, but the white individuals in F_2 will be males. The factor for red in the F_1 male will always stay in the X chromosome, so that all the female-producing spermatozoa will carry red, and consequently all F_2 females will be red. The males will have red eyes if they receive the red-bearing chromosome from their mother and white eyes if they receive the white-bearing chromosome from their mother.

The reciprocal cross is made by mating a white-eyed female to a red-eyed male (Fig. 10). The daughters will have red eyes and the sons white eyes. If these are inbred their offspring will be red and white in equal numbers, and not the usual three reds to one white. The explanation of this new ratio is at once apparent as soon as the history of the sex chromosomes is studied.

The two X chromosomes in the white-eyed mother carry the factor for white eyes. After ripening, each egg carries one white-bearing X chromosome. The single X chromosome of the female-producing spermatozoon of the red-eyed father carries the factor for red eyes; the male-producing spermatozoa carry the Y chromosome which, as stated above, is indifferent. Any egg fertilized by a spermatozoon containing the red-bearing X chromosome will produce a red daughter, because red dominates white. Conversely, any egg fertilized by the Y-bearing male-producing sper-

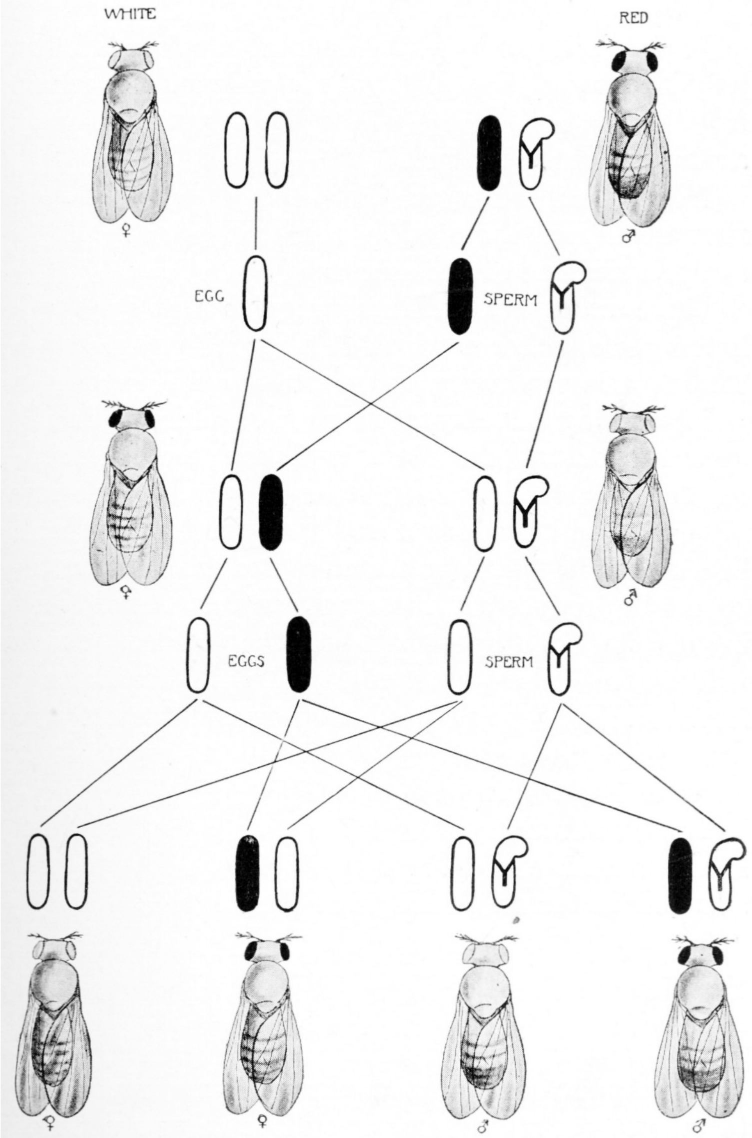


Fig. 10.—White-eyed female by red-eyed male (D. ampelophila). The factors for these characters are carried by the X chromosomes, the factor for red by the black X, and the factor for the white by the plain X. The history of the chromosomes is shown in the middle of the diagram.

matozoon will produce a white-eyed son, because the only X chromosome that the son contains is derived from his mother, both of whose X chromosomes carry a white-producing factor.

When these red-eyed daughters and white-eyed sons are inbred the possible combinations are shown in the lower line of the diagram (Fig. 10).

There will be two kinds of eggs, one containing a red-bearing, the other a white-bearing, X chromosome. The female-producing spermatozoa will contain a white-bearing X chromosome; the male-producing spermatozoa will contain a Y chromosome. A red-bearing egg fertilized by a female-producing spermatozoon will produce a red-eyed female; a white-bearing egg fertilized by a female-producing spermatozoon will produce a white-eyed female. A red-bearing egg fertilized by a male-producing spermatozoon will produce a red-eyed male; a white-bearing egg fertilized by a male-producing spermatozoon will produce a white-eyed male. The resulting ratio is 1 red to 1 white, in both sexes.

The distribution of the chromosomes explains how in one cross the Mendelian ratio of 3 :1 obtains, and also how in the reciprocal cross there is a 1:1 ratio.

The Inheritance of Two or More Independent Pairs of Factors

The application of the chromosome hypothesis to crosses between races that differ in two pairs of factors is illustrated by the following example (Fig.

11). If a vestigial gray fly is mated to a long-winged ebony fly, all the offspring (F_1) will have long wings and gray (or slightly darker) body color. If these hybrids (F_1) are inbred, offspring (F_2) will be produced in the ratios:

9 Flies with *long* wings and *gray* body color.
3 Flies with *vestigial* wings and *gray* body color.
3 Flies with *long* wings and *ebony* body color.
1 Fly with *vestigial* wings and *ebony* body color.

In the diagram (Fig. 11) two pairs of chromosomes, the second and the third pairs, are represented by the following conventions: The cross-barred chromosomes, each of which carries a factor for vestigial, are the second pair. The third pair, that contains the factors for ebony, is represented as black. The third pair of chromosomes in the vestigial fly is "normal" in respect to ebony. Correspondingly the second pair of chromosomes in the ebony fly is "normal" in respect to vestigial.

Each germ cell of the vestigial-gray parent will contain one chromosome with the factor for vestigial and one for gray, and each germ cell of the long-winged ebony parent will contain one chromosome with the factor for long and one for ebony. The hybrid (Fig. 11) will contain, therefore, a pair of chromosomes, one of which carries vestigial, the other long; and will also contain another pair, one of which carries ebony, the other gray.

In the maturation of the germ cells of the hybrid, the members of each pair separate from each other as shown in Fig. 11 in the gametogenesis of F_1.

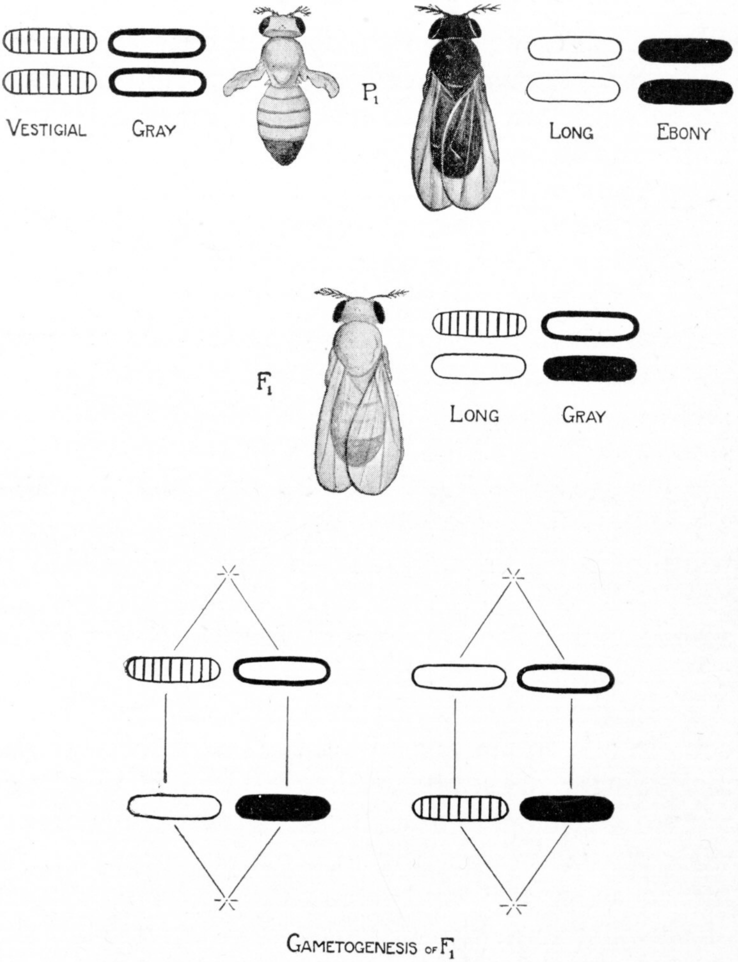


FIG. 11.—Vestigial gray by long ebony fly, to illustrate the inheritance of two pairs of characters. The factor for vestigial is carried by the second, the factor for ebony by the third chromosome pair. In the lower part of the figure the two modes of separation, of the two pairs of chromosomes involved here, are represented. Four kinds of gametes result. These four kinds combine at random in fertilization, so that 16 classes are produced in F_2, as shown in the next figure.

The two pairs of chromosomes "assort" on the spindle in either one of the two ways shown in the diagram; resulting in four and only four kinds of gametes.

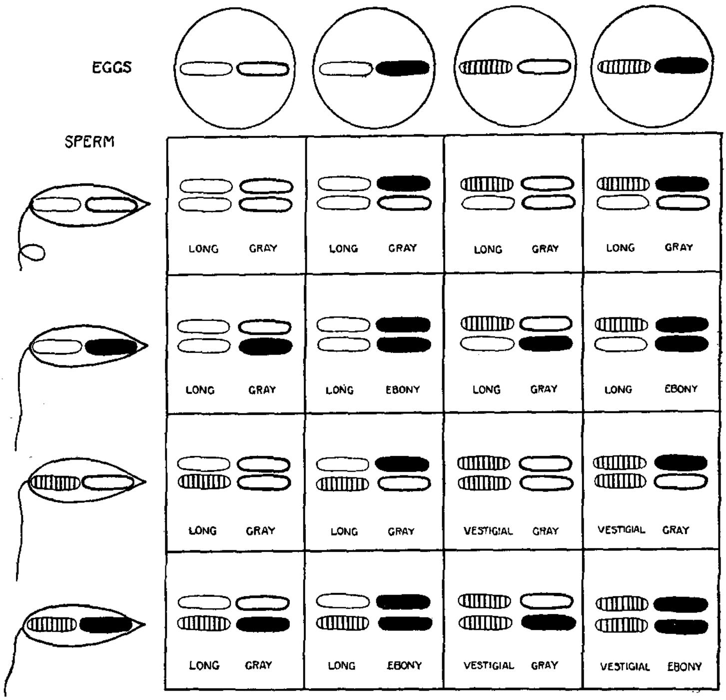


FIG. 12.—Diagram to show the 16 possible kinds of permutations of the four kinds of gametes of Fig. 11. Along the top line are four kinds of eggs; along the left side are four kinds of sperm; in the squares are the combinations formed by the meeting of each kind of egg with each kind of sperm, giving 9 long gray; 3 long ebony; 3 vestigial gray; 1 vestigial ebony.

The process just described takes place both in the male and in the female. Consequently there will be four kinds of eggs and four kinds of spermatozoa.

Chance meeting between these will give the results shown in the next diagram (Fig. 12).

In *the table (Fig. 12) the four kinds of eggs are* represented at the head of the four vertical columns, and the four kinds of spermatozoa at the left of each horizontal row. In the squares the combination of each kind of sperm with each kind of egg is represented, giving the ratio of 9 long gray: 3 vestigial gray: 3 long ebony: 1 vestigial ebony.

The F_2 expectation may, of course, be derived more directly as follows: There will be 3 long to 1 vestigial. These longs will be both gray and ebony in the ratio again of 3 to 1; hence 9 long gray to 3 long ebony. Correspondingly, the vestigials will be both gray and ebony, in the ratio of 3 to 1; hence 3 vestigial gray to 1 vestigial ebony. The result is the same as before.

If one of two independent pairs of characters is sex linked, the same scheme holds in those cases where the recessive sex linked character enters through the grandfather, but the ratio is different when the recessive sex linked character enters through the grandmother (viz., 3 :3 :1 :1), as is to be expected from the mode of inheritance of white eyes taken alone;[1] and here, too, the result conforms fully to the chromosome scheme.

Three factors can be worked out by means of the

[1] For example, taking white and red alone the ratio of the F_2 is 1 : 1. But among the reds the ratio of gray to ebony will be 3 : 1 and among the whites will be 3 : 1. Hence the result 3 red gray, 1 red ebony, 3 white gray, 1 white ebony.

chromosomes as readily as one or two. It will not be necessary to give the full analysis, for it will be easily understood from the scheme already given. If a fly with vestigial wings is crossed to an ebony, eyeless fly three pairs of factors are involved that lie in different chromosomes. The F_1 flies are normal, for there is in the hybrid a normal mate for each of the three recessive factors. The possible recombinations are shown in the next diagram, Fig. 13. There

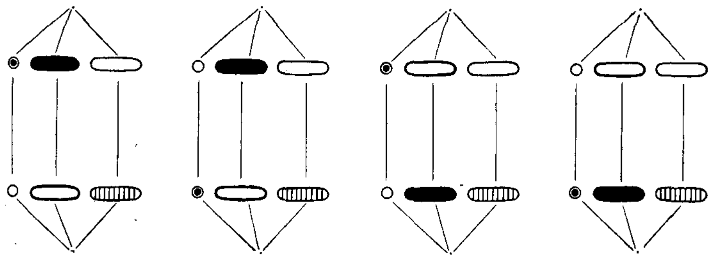


Fig. 13.—Diagram to show the segregation of the three pairs of chromosomes. Eight combinations are possible, giving 8 kinds of germ cells, with 64 possible re-combinations.

are four different positions for the chromosome pairs on the spindle, leading to eight kinds of germ cells. By chance meetings of the eight kinds of sperm with the eight kinds of eggs there will result 8 types as follows:

27 Long, gray, normal eye (wild type).
9 *Vestigial*, gray, normal eye.
9 Long, *ebony*, normal eye.
9 Long, gray, *eyeless*.
3 *Vestigial*, *ebony*, normal eye.
3 *Vestigial*, gray, *eyeless*.
3 Long, *ebony*, *eyeless*.
1 *Vestigial*, *ebony*, *eyeless*.

The same manner of treatment will work for more than three pairs of chromosomes; the number of kinds of germ cells increases in geometrical ratio. In most animals and plants the number of chromosomes is higher than in Drosophila, and the number of pairs of factors that may show independent assortment is, in consequence, increased. In the snail, Helix hortensis, the half number of the chromosomes is given as 22; in the potato beetle 18; in man, probably, 24; in the mouse 20; in cotton 28; in the four-o'clock 16; in the garden pea 7; in corn 20; in the evening primrose 7; in the nightshade 36; in tobacco 24; in the tomato 12; in wheat 8. If 20 pairs of chromosomes are present there will be over one million possible kinds of germ cells in the F_1 hybrid. The number of combinations that two such sets of germ cells may produce through fertilization is enormously greater. From this point of view we can understand the absence of identical individuals in such mixed types as the human race. The chance of identity is still further decreased since in addition there may be very large numbers of factors within each chromosome.