TEN YEARS OF HEREDITY[1]

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Though no one is likely to be misled by my subject into supposing that the laws of heredity have been in operation only a decade, it may not be universally appreciated that heredity is one of the oldest of biological phenomena. It is at least as old as, probably older than, organic evolution of which we have long been accustomed to speak in terms of millions of years. For, when the first living thing, if ever there was such a being, gave rise to a second, by reproduction, this second living thing was either like its parent, or different from it. If like its parent, heredity had begun. If different from its parent, it was almost certainly different in only one or a few respects, but like the parent in the rest, in which case both heredity and evolution were in operation.

The stipulated ten years to which my title refers are not, however, an arbitrary limit set for the purpose of relieving me of the necessity of covering the whole of a very large subject. They are a period which, in the development of knowledge of heredity, is naturally marked off from the numerous decades that precede. Those of you who possess a little knowledge of heredity, to whom the name of Gregor Mendel has a fascinatingly familiar sound, and in whose memory lingers the date of 1900 in which year the famous Austrian monk's long hidden experiments were again brought to light, may wonder why I should wish to describe the developments of but the latter half of the period since that rediscovery. It is true that the great interest aroused by the verification of Mendel's Law, with the multiplication of experimental work which was induced by it, was a necessary precursor of the events with which I propose to deal. But about 1910 there began a chain of discoveries, which have followed one another in unbroken series to the present time, and which have led to a conception of the operations of heredity of a degree of complexity, and withal of harmony, which even the most sanguine twenty years ago would not have ventured to predict.

[1] This lecture, delivered before the Graduate Club of the University of Michigan, was designed to present to persons without biological training, not a résumé of all important work in heredity in the period referred to, but the point of farthest advance and the principal work leading to it.

Former Lack of Analysis

Heredity had long been discussed in terms of averages. In popular discourse it was always so, children were replicas of their mothers, or were chips out of the old block, or the son of a Cholmondeley was the image of a Jones. The *ensemble* of characters was considered. Even those who were professionally engaged in the study of heredity lumped together many things now known to be partially or wholly distinct from one another, regarding them as a single trait. Stature, obviously made up of many elements, was treated as a single characteristic. Intelligence, likewise compound, was studied as if simple.

There was not wanting, it is true, even among the laity, an analytic tendency. A youth would have his father's mouth, his mother's eyes, his grandfather's complexion. But it was not until the emergence of Mendel's work in 1900, and the multiplication of investigations consequent upon that event, *that it was realized to what extent inherited traits may be separated from one another as distinct and independent units.* Eyes were inherited independently of hair, hair color independently of hair form, color independently of distribution of color, whether uniform or in patches. Unit characters became distinctly vogue. Anyone who could utter the magic expression "unit characters" and speak the name of Mendel with his first name and title, had thereby established his right to be regarded as a thoroughly modern geneticist.

Difficulties of the New Conception

All this development raised in the biological mind certain difficulties. When it was inquired how all these unit characters were manipulated independently of one another, there were obstacles—that is, when the offered explanation passed a certain point. To speak intelligibly of these difficulties it will be necessary to refer briefly to a few elementary facts of biology.

All organisms are composed of units of structure called cells. These cells regularly contain, as part of their structure, a rounded body, the nucleus, which stains deeply in most dyes and which is therefore conspicuous in most common microscopic preparations. The size of an organism is increased usually by the multiplication of cells, which is accomplished by the division of the cells already present. In the process of division, the cells develop a complicated figure in which the highly staining material of the nucleus is resolved into a number of distinct bodies called chromosomes. As the division is completed, the chromosomes lose their distinct form, producing a nucleus in which separate bodies are no longer visible; but at the next division the chromosomes appear again, in the same number as in the previous division. This number is in general constant in all cells of the same individual, and, barring some differences between the

sexes, is constant for all members of the same species. Moreover, in animals in which the chromosomes are not all of the same size or shape, *each dividing cell reveals the same number of chromosomes of each shape or size.*

Since all organisms are composed of cells, the phenomena of heredity must in some way be traceable to cells. The constancy of occurrence of the nucleus, and of a given number of chromosomes in the nucleus, early gave rise to a suspicion which later, on a foundation of fact, ripened into a conviction, that in these structures is the mechanism through which heredity is governed. If it were assumed that the factors of heredity were contained in the chromosomes, many things would be explained. Reference will be made now to only one of these things.

One of the new features of discussion of heredity was the attention devoted to unit characters. How were these characters operated as units, independently of one another? Chromosomes provided the answer. It must be understood that in all the higher animals and plants, *no parent contributes all of its chromosomes to any one offspring, but only half of these chromosomes.* In the development of the germ cells a peculiar cell division called the reduction division takes place in which *the chromosomes separate into two groups, one group being enclosed in the one daughter cell, the other group in the other cell.*

Chromosomes and Recombination of Characters

In the composition of these groups of chromosomes, there is a wide range of different possibilities. In some cases, the chromosomes may be

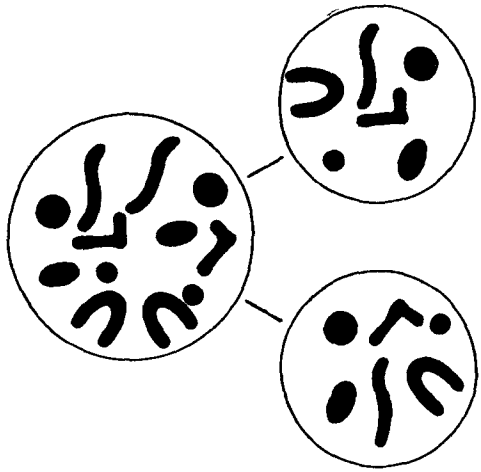

Figure 1. Diagram of a cell in which the chromosomes are capable of arrangement in pairs, the two chromosomes of each pair being precisely alike in all respects. Such a cell, in maturation, divides into two cells, each with half the number of chromosomes, and each exactly like the other in all hereditary factors. The shapes of the chromosomes are not actual, but only a diagrammatic representation of the likenesses and differences in their hereditary composition.

capable of assortment in pairs, as in figure 1; that is, there are two chromosomes in each cell that are exactly alike, two other chromosomes that are exactly alike but different from the first pair, and so on. In such a case, by separating the members of each pair, two groups of chromosomes may be made up which are identical. In such a case, therefore, *two germ cells with exactly the same hereditary possibilities are produced,* and the parent may contribute precisely the same hereditary traits to every one of its progeny. Moreover, it can transmit to each of its offspring every hereditary trait of which it is possessed.

In other individuals, on the contrary, every chromosome of a cell may differ in one or more respects from every other chromosome, as in figure 2.

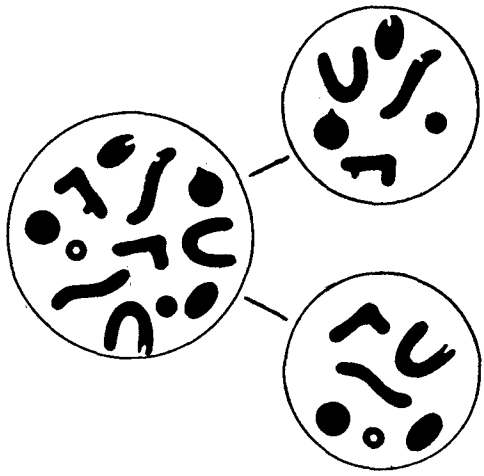

Figure 2. Diagram of a cell in which the chromosomes may be arranged in pairs, but the chromosomes of one pair are not exactly alike. The chromosomes of a pair may be alike in most respects, but different in one or more features. Such a cell, in maturation, divides into two cells which are alike in the main but differ in certain hereditary factors. The precise hereditary composition of each cell therefore depends on how the chromosomes are distributed to the two cells.

In such a case, in the reduction division at which only half the chromosomes are conveyed to each daughter cell, it is not possible to produce two cells that are identical. *Each chromosome in each of these two cells is different from every chromosome in the other cell.* Moreover, the parent is here contributing, with respect to certain characteristics, only half of its hereditary potentialities to any one of its offspring.

Between these extremes, in which, on the one hand, the parent hands on all its hereditary traits to all of its offspring, and, on the other hand, transmits only half of its possibilities with respect to certain features to any one offspring, there are all intermediate grades. The result depends

on how the chromosomes are separated into two groups. In that cell division in which each daughter cell receives only half the total number of chromosomes, it appears to be a matter of chance, subject to certain restrictions, how the half number shall be made up. If I have not made this procedure clear, the following analogy will be useful. If it is proposed to divide by chance a group of buttons, or poker chips, if that be a more familiar figure, of a variety of colors, into two groups of six each, it is obvious that the groups of six may be very unlike; also, that if the same dozen buttons be divided into two groups again, the second division may be very unlike the first. If these buttons represent chromosomes, and their colors stand for hereditary traits, it is clear that these traits may be distributed in very different ways to different offspring.

The chromosomes, then, because they act to some extent independently of one another, *offer an explanation of the independence of unit characters*—provided only that the things which produce these characters are in the chromosomes. There are other reasons, equally good, perhaps better, for believing that the hereditary factors, as they are called, are in the chromosomes, but this additional evidence may pass.

Individuality of the Chromosomes

All this conception of the operations of heredity, in relation to the chromosomes, was arrived at before the ten year period of which I am eventually to speak. But certain difficulties are inherent in the conception. The number of chromosomes in the cells of an animal is strictly limited. In man, one author fixes the number at 48, another at 24. In other animals there is better agreement, and the number is as low as four, or even two. In man, even the largest number suggested, 48, must be much smaller than the number of traits which he inherits. If this be true, *the representatives of several traits must reside in the same chromosome.*

The difficulty involved in this situation was that *the chromosomes were believed to be individuals.* That is, the chromosomes which become distinguishable at one cell division were held to be the same identical chromosomes, part for part, as were observable at the preceding cell division; and chromosomes occurring in one individual were believed to be identical with those of its parents. There were many facts concerning the shapes of the chromosomes, and their behavior at various times, which lent support to the view that they are persistent individual objects.

Were this regularly true, *two hereditary traits represented by something in the same chromosome would necessarily behave as a single characteristic.* They could not be independently assorted, when the chromosomes were separated into two groups in the reduction division in the production of germ cells, but would go together. Traits represented in different chromosomes would be independently assorted, but those in a single chromosome would act as a unit.

Requirements of Proof of Linkage

Whether this condition actually existed in any animal or plant was for a long time not known. *To determine whether inherited traits were ever bound together in groups required an animal in which differences in a considerable number of characteristics existed in different individuals.* It required also a careful study of such an animal or plant to determine whether the traits were wholly independent, or were grouped. Early in the revival of Mendelism, an association of certain hereditary traits with sex was demonstrated, but indications of an association of hereditary traits with one another were long delayed. The number of traits whose inheritance was understood, in any one species, was too small.

Then came the year 1910. In that year a fly was born— or hatched. It belonged to the small brownish gray species which is seen every summer day hovering about fruit stands or garbage pails. This species had been bred for years in a number of laboratories, notably those of Columbia University by Professor T. H. Morgan and his students. Then one afternoon, in a bottle, appeared the fly of which I speak, which differed from all others in the bottle, and from all of its ancestors for many generations, in having white eyes. Flies of this species regularly have red eyes. Since 1910, other eye colors have appeared, vermilion, cherry, eosin, buff, tinged, blood and purple being the names applied to some of them. Other flies were produced which had unusual wings—short, blunt, crumpled, or missing, curled up, curved down like an inverted bowl of a spoon, or spread at an angle. Other parts of the body likewise presented variations. The spines became forked, or reduced in number. Extra legs were produced. The color of the body became yellow or black in certain individuals. Physiological changes not producing any observable structural differences have also been detected. All told, over two hundred such modifications have been discovered in this one species of fly since 1910. Most of these characteristics were found to be definitely inherited. Fortunately, many of these altered flies were quite healthy, were easily reared, and have been carefully studied. *The fruitfly was obviously the organism by which the individuality of the chromosomes and their relation to heredity could be tested.*

Early Demonstrations of Linkage

This test came gradually. It was found that these characteristics were not wholly independent of one another. Thus, white eye and yellow body-color were very closely associated with one another. When a white-eyed and yellow-bodied fly was crossed with a normal red-eyed and gray-bodied fly, their offspring in certain subsequent generations, in certain cases should have shown all combinations of the two eye colors and the two body colors with equal frequency. That is, if the four traits were inherited independently of one another, white eye and gray body

should have been combined in one individual as often as white eye and yellow body. But they were not; white eyes and gray bodies were found together in only about one-fiftieth as many cases as would have been expected. White eye was nearly always associated with yellow body in these crosses.

It was discovered, also, that white eye color was associated in the same way, though less closely, with sable body color, with club shaped wings, and a number of other characteristics. Moreover, if white eye color was thus bound up with a certain characteristic, yellow body color was also associated with the same characteristic. And all characteristics that were thus associated with white eye and yellow body were found to be linked—that is the word Morgan uses—with one another. *All these traits behave, to some extent, as a unit. They are not absolutely bound together, but they hang together more frequently than the chance assortment of chromosomes, or colored buttons, or poker chips, would lead one to expect.*

Independent Linkage Groups

Approximately forty of the more than two hundred new characteristics that have arisen in this fly in the past ten years may safely be said to belong to the group that is linked with white eye color and yellow body. Long before all of these had been discovered—indeed, when only a few of them were known—certain other new traits had come into existence which were definitely *not* linked with white eye. One of these was a short crumpled wing which has been called vestigial. In crosses which involve vestigial wing and white eye at the same time, the occurrence of vestigial wing in the individuals of subsequent generations bears no relation to the occurrence of white eyes in the same individuals. The chances are even, in such crosses, that a fly with a vestigial wing will have white eyes in as large a proportion of cases as will a fly with normal wings. Likewise, there is no relation between vestigial wings and yellow body color. Nor is there any association between vestigial wings and any other characteristic in the entire group that is linked with white eyes and yellow body. Clearly, vestigial wing is not a member of that group.

Another character that is independent of white eye color is black body color. In crosses which should test any such supposed relation, the distribution of black color of the body among the individuals is wholly unrelated to the white color of the eye. Black body occurs with equal relative frequency in individuals with red eyes and white eyes. Black body color is also independent of any other characters of the group linked with white eye color. But black body color *is* associated with vestigial wing. If a cross is made involving an individual with both vestigial wing and black body, then in generations produced by appropriate crosses among the descendants, black body and vestigial wing will occur together

much oftener than apart. That is, flies having both black body and vestigial wing will be relatively much more numerous than flies having black body and normal long wing; and much more numerous than flies with vestigial wing and normal gray body. Vestigial wing and black body color are clearly linked with one another.

With these two traits are also linked a number of others that concern the wings, the body, the eyes, etc. All characteristics linked with black body or with vestigial wing are, when tested in appropriate crosses, found to be linked with one another. They form a distinct second group, every member of which is linked to some extent with every other member. This group contains about as many characters as does the first group linked with white eyes. It must be made entirely clear that, while all the traits of this second group are linked with one another, none of them is in any way linked with any character of the first group to which white eye and yellow body belong.

There is still a third group of characters, and a fourth group quite small in numbers, which are made up, as are the first two, of characters that tend to hang together, once they start together. All members of the third group hang together more than mere chance would permit; and all members of the fourth group are in like manner associated with one another more frequently than can be attributed to accident. But no trait of the third group is in any way bound with any trait of the first, second or fourth groups. And no trait of the fourth group is linked to any extent with any member of any of the first three groups. *Three of these groups are rather large, that is, include numerous characters, one is quite small.*

Chromosomes and the Linkage Groups

You will have guessed long since that the reason assigned for the linkage of these various traits is that the hereditary factors responsible for them are located in the same chromosomes. All characteristics of the first group are produced by something in the same chromosome. All characteristics of the second group are likewise represented by something in *one* chromosome. But that chromosome is a different one from the chromosome that produces the characteristics of the first group. *Each of these groups owes its existence as a group to one chromosome, which is a different chromosome for each group.*

In this connection you will care to know something about the chromosomes of this fly. Fortunately they are well known. Each cell has eight of them (figure 3), but when, in the formation of germ cells, the reduction division divides these into two groups, there are only four in each germ cell. *Three of these chromosomes are large, and one quite small, and three of the linkage groups of characters are large, and one small.*

Assuming that the hereditary factors for one group are all in one chromosome, and that that is the cause of their linkage with one another,

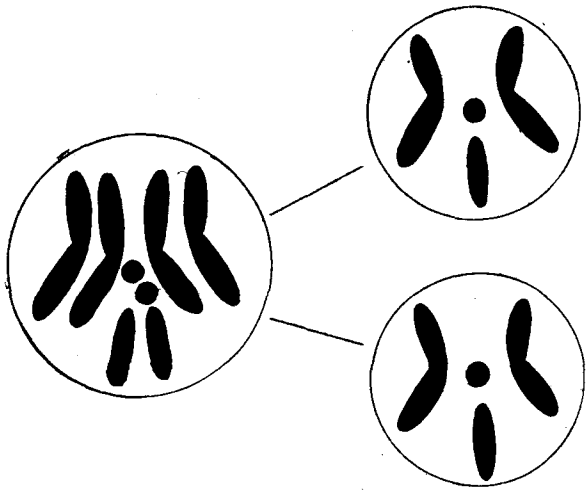

Figure 3. The chromosomes of the female fruitfly *Drosophila melanogaster*. In the body cells and immature germ cells there are eight chromosomes, two each of four kinds. In maturation, at the reduction division, the number is reduced to four, one of each of the four kinds. Three of the chromosomes are large, and one is small.

what becomes of the idea of individuality of the chromosomes? It must be modified, of course. As previously pointed out, the characteristics of each group are not absolutely bound together, they merely occur together more frequently than chance would permit in the case of *independent* characteristics. That is, once they are transmitted from parent to offspring in conjunction with one another, they separate from one another thereafter less frequently than would be expected. But if their factors are in the same chromosome, how can they separate at all?

Breaking the Linkage Groups

To make the proposed answer to this question clear it must be stated that when this separation does occur, there is a fairly even exchange. That is, when white eye is separated from yellow body with which it had been associated, some other eye color takes its place and is thereafter as closely linked with yellow body color as was the white eye color before. This is always the case. *Whenever a trait is removed from association with another trait, its place is taken by a trait related to the same part of the body.* Eye color is exchanged for eye color; one form of wing is replaced by another form of wing.

This exchange is made possible, presumably, because of the approximate duplication of the chromosomes in each cell. It has already been pointed out that the chromosomes of a cell may be such that they are exactly alike, two by two (figure 1). But even where the chromosomes are all

different from one another (figure 2), nevertheless they can be arranged in pairs of twins such that the members of one pair differ from one another in only one or a few features, but are alike in a host of others. One of them may, for example, include a representative of vestigial wing, the other of the normal long wing, but be alike in everything else. Or they may differ with respect to color of body and color of eye, and be alike in all other respects. The two chromosomes have to do with the same parts of the body, and no other chromosomes of the cell are concerned with those traits in the same way. The chromosomes are truly capable of arrangement in pairs of twins.

Mechanism of Crossing-over

This arrangement in pairs is not purely a figurative one, it is at certain times an actual bodily one. At a certain time in the formation of the germ cells, these chromosomes come together side by side. What they look like in this operation, is known in relatively few forms. In one of these the chromosomes are long slender threads, and the two twins twist about one another in loose spirals (figure 4). This is not an isolated case. It is

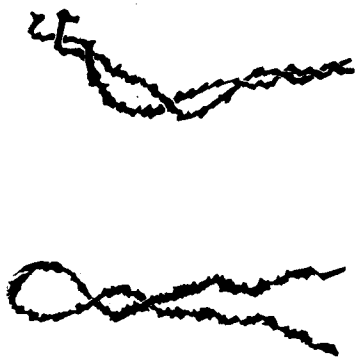

Figure 4. Some of the chromosomes of Batracoseps twisting about one another in spiral form prior to the reduction division. The chromosomes thus twisting together contain factors for the same hereditary characters. Whether they untwist in the reduction division, or separate in some other fashion, is not known from observation. (*Modified from Janssens.*)

not impossible that, in many or most animals, the twin chromosomes twist about one another at this stage of development. Later they separate from one another in some fashion at what we have called the reduction division. How this separation takes place is not known from direct observation, but several possibilities exist. The chromosomes may *unwrap completely* and be the same chromosomes as before they twisted. *Or they may adhere at points, and the two sides of the spiral in that region exchange places.* This is a very important conception, put forward by Professor Morgan and his students, but before it can be developed certain other considerations must be presented.

The hereditary factors contained in a chromosome are, Professor Morgan believes, *arranged in linear order*, like beads on a string (figure 5). Every cell in an animal's body has a chromosome in which these "beads" are the same as those of one chromosome in each of the other cells of the

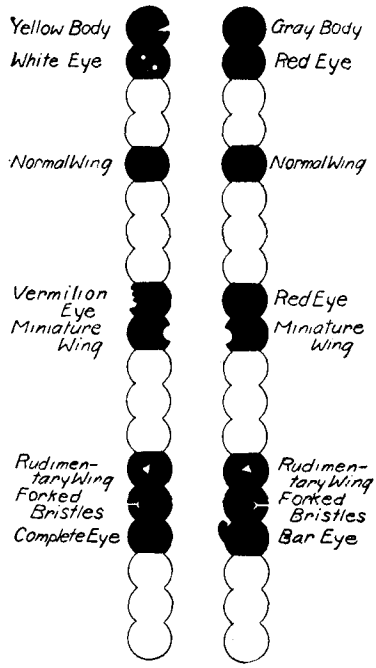

Figure 5. Diagram of a pair of chromosomes of the female fruitfly *Drosophila melanogaster*. The hereditary factors are arranged in a single row in each chromosome. Both chromosomes have hereditary factors for the same characters. The factors for one character are placed at the same level in both chromosomes, so that when the chromosomes meet in a pair the two homologous genes are side by side. Not all the known factors are represented. (*From Principles of Animal Biology, by Shull, La Rue and Ruthven. McGraw-Hill Book Co.*)

body. In the same cell with it is another chromosome in which the hereditary factors are precisely the same, or at least they concern the same parts of the body. The hereditary factors in these two chromosomes are held to be *arranged in the same order, and to lie at the same level.* So that, if the chromosomes are placed side by side, or twisted about one another, *the two hereditary factors for the same part of the body are side by side.*

If two such chromosomes twist about one another, as has been described, and then in separating are not unwrapped carefully, they may exchange hereditary factors. If in one of these chromosomes were a factor for white eye and one for sable body color (figure 6), some distance apart so that the breaking point occurred between them, the linkage that formerly existed between these two characteristics would be broken. Where they

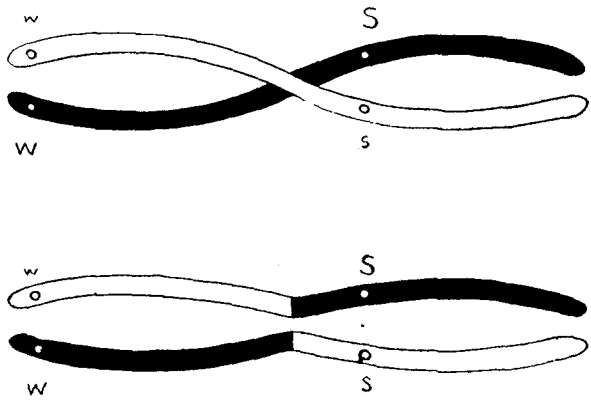

Figure 6. Crossing-over between two chromosomes containing factors for eye color and body color. One chromosome has factors for white eye (*w*) and sable body (*s*); the other has factors for red eye (*W*) and gray body (*S*). If these chromosomes adhere and break at some point between the pairs of factors, after the reduction division one chromosome contains factors for white eye (*w*) and gray body (*S*), the other has factors for red eye (*W*) and sable body (*s*).

had formerly necessarily passed to the same individual, they would now necessarily pass to different individuals. There is also much to prove that the chromosomes may break twice, or at three places instead of only one. If one of the two chromosomes that twist about one another (figure 7) has

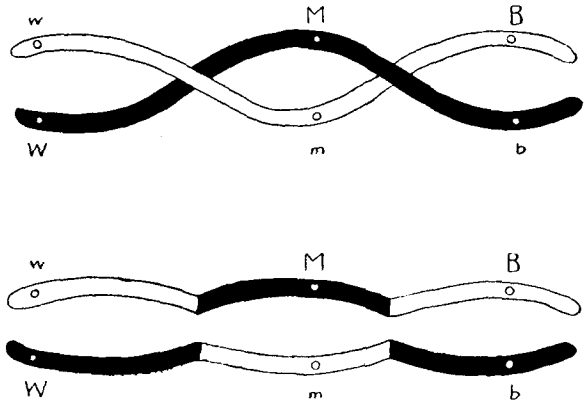

Figure 7. Double crossing-over in a pair of chromosomes. The chromosomes adhere and break at two points in their length, so that after the reduction division each chromosome is made up of three fragments, two from one of the original chromosomes, one from the other. In the original chromosomes the factors *w*, *m* and *B* were linked, as were also *W*, *M* and *b*. After the crossing-over, *w*, *M* and *B* form one linked group, *W*, *m* and *b* the other. See text for explanation of the symbols.

in it factors for white eye (*w*), miniature wing (*m*), and bar eye (*B*), the other the contrasted normal characteristics which are red eye (*W*),

long wing (*M*), and round eye (*b*), and these chromosomes break at two points as they separate from one another, two of the three linked characters may be still linked together, but the third separated from them. The separation of a hereditary factor from another with which it was linked is called crossing-over.

Whether a pair of twisted chromosomes shall break at one point or another is, with certain restrictions, held to be a matter of chance. If they break between the factors for black body and vestigial wing, those factors will be released from linkage with one another; that is, crossing-over between these two characteristics occurs. These chromosomes may break at any number of places *not* between the factors for black body and vestigial wing, and the two traits will remain linked as before.

Mapping Chromosomes

Inasmuch as breakage presumably occurs at different places in haphazard fashion, *crossing-over between two traits is likely to occur often if their factors are far apart on the chromosome.* Conversely, *if the factors are very near together they are seldom separated.* It is very easy, by making appropriate crosses, to pick out immediately those individuals in which certain characteristics, usually associated, have been separated, and hence in whose chromosomes breaking has occurred in a given region. By counting these individuals one may ascertain whether crossing-over between vermilion eye and club wing, for example, is frequent or rare; and can judge, therefore, whether the factors for these characteristics are far apart or near one another. By means of such experiments, it has been shown that white eye and yellow body seldom separate; they do so in only one out of a hundred chances, whereas they should cross over fifty times out of a hundred if they were independent of one another. Black body and vestigial wing, on the contrary, separate much more frequently, that is, about seventeen times out of a possible hundred. White eye and yellow body must therefore be very close together, black body and vestigial wing must be rather far apart. On the basis of such computations entire chromosome maps have been prepared. Such maps have been in existence for years, having been gradually developed, and altered as new evidence is procured. An abridged map of one of the chromosomes of the fruitfly is given in figure 8.

As new characters appear in this species, experiments are performed to determine in which chromosome their factors are, by determining with which other characters they are linked. And when that chromosome has been discovered, the place in it occupied by the new factor is next to be found. In locating the new factor, it may be necessary to alter the supposed place of certain other factors. That has happened time and again, for at first the location can be only tentative.

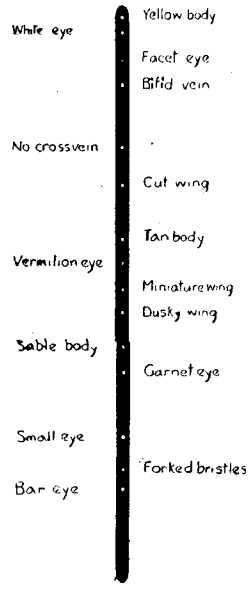

Figure 8. Abridged map of one of the chromosomes of the fruitfly *Drosophila melanogaster*, showing approximately the distances between the factors. The distances are determined by the number of times crossing-over occurs between the hereditary factors. Attention is especially called in the text to the distance between the factors for vermilion eye and sable body, and that between garnet eye and forked bristles.

Linear Order of Factors

While crossing-over can be easily demonstrated, it is admittedly pure hypothesis that it is accomplished by twisting of the chromosomes. It is also pure hypothesis that the factors are arranged in linear order, and that the amount of crossing-over between any two depends on the distance between them. However, any hypothesis is valuable in proportion to the number of things it explains, and a hypothesis that explains many things and is contradicted by nothing, has traveled a long way toward proof. Judged by these criteria, let us examine the situation of the hypothesis of the linear order of the hereditary factors and the twisting of the chromosomes.

First, assume that the amount of crossing-over between two characters, A and B, has been determined, and that from this amount the supposed distance between the factors for A and B, in terms of some arbitrary unit of measurement, has been computed. Suppose also that the distance between B and a third factor C has been similarly determined. If these determinations are actually computations of distances, then these two calculations fix the distance also between A and C, and it should be possible

to predict how great a proportion of crossing-over should occur between A and C, before the experiments to test it have been performed.

These predictions, when applied to short distances, have proven remarkably accurate. For example, as has been stated, in the first chromosome, breaking of the chromosome between the factors for yellow body and white eye occurs in about one per cent of possible cases. Crossing-over between white eye and bifid wing vein has been computed to occur in about five per cent of possible cases. If the map of this chromosome has been properly constructed (figure 8), crossing-over between yellow body and bifid wing vein should occur in about six per cent of cases. Within a small fraction of a per cent, this prediction is verified by experiments directly testing it. Similar verification has been obtained in numerous other groups of factors, and in no case where only small distances are involved have there been any serious discrepancies.

Errors in Long Distances

The fact that only in cases where small distances are computed is the correspondence between prediction and fact very close may at first seem to weaken the evidence in favor of the theory. On the contrary, *lack of close correspondence between prediction and discovery where long distances are concerned, is an important part of the confirmation of the theory.* I have already pointed out that the same two chromosomes, when they meet, may break at several points. Suppose that, in this case, the two chromosomes differed from one another in only two factors, white eye and bar eye (see figure 7, *w* and *B*), and that there were no identifying factor between them. If, in these premises, crossing-over should occur at two points between the factors for white eye and bar eye, the two factors would nevertheless be in the same chromosome after the chromosomes separated, and the experiment would not reveal the fact that crossing over had occurred at all. Crossing-over might occur four times, or six times, or any *even* number of times, and the two factors would still be left in the same chromosome. When the two factors are separated by long distances, multiple crossing-over between them is likely to occur, *and only a part of it is detected.* Such factors would appear, by the usual computations, to be much nearer one another than they actually are. When a new factor is discovered, its location may be tentatively determined with reference to some other well known factor. If it turns out to be rather far from the factor first chosen as a zero point, the test may be repeated with another known factor which is probably near it. It has invariably happened that these later computations increase the distance as determined from the first long-distance test. That is simply because, in the second computation which concerns only a short distance, the investigator is discovering *all* the cases of crossing over, instead of only a fraction of them, and the dis-

tance is necessarily made to appear greater. So regularly has it happened that first computations of long distances have had to be increased as intermediate short distances are determined that the investigator is now able to guess with considerable accuracy how much a long distance diverges from the truth, and to fix with a good deal of precision the probable location of a new factor before the second computation is made. Lack of precision in the calculation of long distances is not, therefore, a weak point in the argument. Indeed, *there would be something the matter with the theory if long distances could be determined as accurately as short ones.*

Points of Cross-Over Never Near Together

The theory of linear arrangement of the factors, and of the twisting of the chromosomes, carries with it certain corollaries. It is scarcely possible that crossing over at one point of a chromosome is entirely independent of crossing over at other points in the same chromosome. Thus, if two chromosomes break at two points, a chunk is removed from the middle of each chromosome and transferred to the other. The size of this chunk is probably not entirely free of limitations. It extends from one point of crossing over to the other. How near or how far apart these breaks can be may depend on how tightly the chromosomes are twisted, or at how frequent intervals they adhere intimately to one another. No upper limit is set to the distance between cross-overs, but a lower limit is certainly to be expected. The size of a piece of chromosome that can be removed, by this method, to another chromosome presumably can not fall below a certain minimum. That means that *if breaking occurs at one point, it is not likely to occur at a nearby point at the same time.*

Fortunately, owing to the large number of factors now known in some of the chromosomes, this interference of crossing over at one point with crossing over at a nearby point can be tested. Thus, in one of the chromosomes (figure 8) the factors for vermilion eye and sable body color are at such a distance from one another that crossing over between them occurs once in ten times—in ten percent of cases. In a nearby region of this chromosome are two other factors, one for garnet eye, the other for forked bristles, so placed that crossing over occurs between them in twelve per cent of possible cases. If the breaking of the chromosome in one point has no bearing upon its breaking at another point, any chromosome that is severed between vermilion and sable should have twelve chances in a hundred of breaking also between garnet and forked. But experiments on a large scale show that, if crossing over occurs in the vermilion-sable region, it occurs also in the garnet-forked region in only a little over one case (1.2 to be more precise) out of a hundred. In like manner, if the various breaks of the chromosome are wholly independent of one another, out of a hundred chromosomes that have broken between

garnet and forked, ten should also be found to have broken between vermilion and sable. As a matter of fact, only one of the hundred breaks in the latter region. *Crossing over in one of these regions obviously interferes with crossing over in the other region.*

These two regions are near one another. The reason for the interference may be attributed, whether correctly or not, to the closeness or looseness of the spiral winding of the chromosomes about each other. When the two chromosomes adhere at one point, unless they are very tightly wound, they are not likely to adhere at another point except at some distance. If this explanation is the correct one, interference of crossing over should be most marked when the two regions are near one another, less marked when the regions are farther apart. That has indeed proven to be the result. Regions farther apart than these have been tested for simultaneous crossing over, and the degree of interference has decreased as the distance between the regions tested increased, up to a certain limit. This limit was reached when the two regions studied were far enough apart to account for about 46 per cent of crossing over between them. When regions farther apart than this were studied, then interference became greater again.

Variation in Frequency of Crossing-over

The idea that the frequency of crossing-over within a certain region depends upon the tightness with which the chromosomes twist has found expression in the explanation of another phenomenon. When this frequency of crossing over is determined by experiments, the results usually have a considerable degree of uniformity. The amount of crossing between vermilion and sable, for example, has never diverged very much, in an experiment involving large numbers of individuals, from ten per cent. However, certain strains of these flies have been found in which the ratio of crossing over differs very considerably from that found in other stocks. It is fairly uniform within the aberrant stock, but is different from other strains. This capacity for, let us say, a smaller amount of crossing over is, furthermore, transmitted to the offspring as a permanent family character. One interpretation put upon this phenomenon has been that some inherited feature, doubtless of a physiological nature, causes the chromosomes, when they meet in pairs, to wrap more loosely, about one another; or perhaps merely to adhere less frequently.

Further elaborations of this hypothesis of linear order of the hereditary factors, and of the twisting of the chromosomes, would be available if desired. Perhaps, however, the purpose which this lecture is designed to serve has been fulfilled. If it has shown that *the study of heredity has undergone a very considerable change in the past decade*, it has accomplished one of its aims. If instead of composing you to slumber it has convinced you

that the modern study of heredity is no longer a subject with which to lull oneself into an afternoon nap, it has attained another of its objects. I have not conducted you quite to the limits of present knowledge. Certainly we have not been anywhere near the confines of speculation. The discussion should have shown that in recent years the complexity of fact and theory in heredity has enormously increased. The progress made in this period is, I believe, *unquestionably proportionately greater than has been made in the same period in either physics or chemistry*. Biology, in at least this one division of it, has taken a long stride toward destroying the significance of that relative term by which the sciences of physics, chemistry, astronomy, etc., are so often fondly designated by their followers, namely, the "exact sciences." So complex now are the known phenomena of heredity, and yet in such close agreement are the multitude of facts of experiment and observation with the chain of hypotheses developed to explain them, that one who would contemplate the harmony of the universe may now reasonably strain his ear to catch, not the music of the spheres, but the concert of the chromosomes.

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