CHAPTER 6

LINKAGE

With the work of Sutton, the relation of the chromosomes to segregation and to independent assortment became clear. But there was a difficulty, already recognized in 1903 by Sutton and by de Vries: It must be supposed that there are more separately Mendelizing genes than there are chromosomes in the cells. That is to say, there are not enough chromosomes to make it possible to identify each gene with one whole chromosome. De Vries pointed out that this difficulty could be avoided by supposing that genes were freely exchanged between homologous chromosomes at meiosis—the process that he appealed to as an explanation of independent assortment. Boveri made a similar suggestion in 1904. The real solution showed that the principle of independent assortment is not as regularly applicable as was then thought. The discovery and analysis of *linkage*, increasing knowledge of the nature and behavior of the sex chromosomes, and more detailed cytological study of the meiotic prophases finally led to a resolution of the difficulty.

The first report of linkage was that of Correns (1900). He crossed two strains of Matthiola (stocks), one of which had anthocyanin in the petals and seeds, and also had hoary leaves and stems; the other had white flowers and seeds, and smooth leaves and stems. The F_1 had colored flowers and seeds and was hoary. In F_2 he expected to find many types, resulting from independent segregation of three pairs of genes, but actually recovered only the two parental combinations, in the ratio 3 : 1. He suggested that the flower color and seed color might be due to the same pair of genes, but interpreted the relation between color and hoariness as being due to the absence of recombination between two different pairs of genes. He knew of the existence of smooth strains with colored flowers and of hoary strains with white flowers, which confirmed the view that there were two pairs of genes. Later work by Tschermak and by Saunders has shown that the genetic situation is very complex, there being at least four (and probably more) genes in which the various known

strains differ. But the most probable interpretation of Correns' original experiment is that he was dealing with two effects of a single gene, and that the different combinations of colors and hoariness that he knew existed are due to mutant genes not present in the strains used in his experiments. This was a degree of genetic complexity unimagined at that time. In any case, he did not recover any recombinations and so thought only of *complete* linkage.

Incomplete linkage was first reported in the sweet pea by Bateson and Punnett (1905), the two gene pairs concerned distinguishing purple flowers from red, and long pollen grains from round ones. The two dominants (purple and long) were contributed by the same parent, and the phenomenon was called "coupling"; the other situation, where one dominant and one recessive of a linked pair come from each parent, was called "repulsion" when it was discovered later by the same authors. Early examples of both types were studied by rearing F_2 cultures, which made the estimation of the frequency of recombination difficult and inexact. Bateson and Punnett concluded that the frequencies found in the early examples fell into a regular series which included a ratio of 7 parental : 1 recombination type and one of 15 : 1. That is to say, the series was supposed to be $(2^n - 1) : 1$, the first member (where $n = 1$) representing independent segregation, with other ratios, such as 3 : 1, 31 : 1, and so on, being expected.* Later work, using test-cross methods on many kinds of plants and animals, has of course shown that there is no tendency for recombination values to fall into any such series; but this supposition led Bateson to formulate the "reduplication" hypothesis that played a large part in later discussions. This hypothesis, though now discredited, must be described.

According to the reduplication hypothesis, segregation does not occur at the time of meiosis but somewhat earlier, and not necessarily at the same time for each pair of genes. The cells that are finally produced, each with a single set of genes, then multiply at different rates to give the observed ratios. It is not easy to see why this scheme was developed, since there is nothing in it that seems related to the $(2^n - 1) : 1$ series, nor is there any independent evidence for the complex and symmetrical pattern of divisions that it requires.† The hypothesis is related to Bateson's

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* Bateson and Punnett did not present this algebraic formulation nor specifically include the 1 : 1 case in the series, but this seems to be the simplest way of stating their scheme.

† Bateson, an embryologist by training, was impressed by the circumstance that sometimes the two cells arising from the cleavage of a fertilized egg give rise to the right and left sides, respectively, of the embryo. The mirror-image symmetry of these

reluctance to believe that segregation occurs at the meiotic divisions. It was found early that, in some plants (for example, Matthiola, Oenothera) the pollen does not always transmit all the kinds of genes that the eggs of the same individual do. As will appear later (Chapter 10), this is because certain genes prevent the functioning of pollen that contains them—a view to which Bateson was never reconciled. To him these cases were proof of the occurrence of segregation in some division at or before the setting apart of the germinal tissue of the anther—and hence of the inadequacy of the chromosome interpretation of segregation and linkage.

The first suggestion of the relation of a particular character to a particular chromosome was made in 1901, when McClung postulated that the so-called accessory chromosome (now known as the "X chromosome") is male determining. This body was first described by Henking (1891) in the male of the bug Pyrrhocoris. For a long time it was considered doubtful that it was a chromosome, and its uncertain nature and function were the reason for giving it the designation "X." Henking showed that it divides at only one of the meiotic divisions, with the result that it is present in two of the four sperm arising from each primary spermatocyte and absent in the other two. Other investigators (especially Montgomery) confirmed this description for other Hemiptera, and McClung and Sutton found the same relations in several grasshoppers. Sutton, at McClung's suggestion, studied the female; unfortunately the material was difficult and the chromosome number was large, with the result that he counted 22 in the female as compared to the 23 clearly present in the male. Therefore the X was interpreted by McClung as producing maleness, and the supposed significance of the two kinds of sperm was the reverse of the true one.

The correct relation was shown in 1905 for a beetle (Tenebrio) by Stevens; in this case there was also a Y present, smaller than the X, and she showed clearly that the female is XX, the male XY. This result was immediately confirmed by Wilson (also in 1905) for Hemiptera and was soon shown for Orthoptera, Diptera, Homoptera, Myriapoda, and, with less certainty, for various other kinds of animals.

These relations were sometimes interpreted on the basis that the sex chromosomes were not the cause of the differences between males and females, but were merely a kind of secondary sexual character, resulting from some other more basic sex-determining mechanism. The only

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two halves seemed to him to give a clue as to the nature of heredity—a point to which he returned again and again. This idea seems to have been one source of the reduplication hypothesis.

strong argument in favor of the XY system as the sex-determining mechanism was that it gave a simple way of getting the 1 : 1 sex ratio. But it was known that other situations occur in which fertilized eggs give rise only to females, and unfertilized eggs give rise to either sex. In the group of aphids and phylloxerans, where this occurs, the chromosomes are not too difficult to study, and the work of von Baehr, Stevens, and Morgan soon showed that there were a series of unusual cytological phenomena that constituted a clear confirmation of the XY sex-determining mechanism (see Chapter 13).

Sex-linkage was first reported by Doncaster and Raynor in 1906, in the currant moth (Abraxas); in 1908 Durham and Marryatt demonstrated it in canaries. But in both instances, the results indicated that the female was the heterozygous sex, as was also soon shown in fowl by several workers. Since these results concerned both moths and birds, it seemed that they must be generally applicable; and since the cytological demonstration of the heterozygous nature of the male had likewise been made in many groups of animals, it was also evidently a general condition. This contradiction led to much discussion and speculation, which became pointless with the later discovery of sex-linkage of the type with the male heterozygous by Morgan in 1910 for Drosophila, (and in 1911 for man), and the cytological demonstration of female heterozygosis in moths by Seiler in 1913.

In 1909 there appeared an important paper by Janssens on the cytology of the meiotic divisions in salamanders, especially in Batrachoseps. Janssens raised two questions: Why *two* meiotic divisions both in animals and in plants, when one would appear to suffice for a qualitative chromosome reduction; and how are we to explain the existence of more pairs of genes than the haploid number of chromosomes? He believed that he had found the answers to both of these questions in his chiasmatype theory.

Janssens presented evidence indicating that the longitudinally paired meiotic chromosomes each undergo a longitudinal split, giving a quadripartite structure made up of two daughter strands of each original member of the pair, as others had previously supposed. At the first meiotic division, two strands pass to each daughter cell. Janssens believed that he could show that there had occasionally been an exchange between two of these strands, giving the now-familiar chiasma formation. This accounted for the necessity for two meiotic divisions, since only two of the four strands underwent an exchange at any one level. He also supposed that the two strands involved in an exchange were not, or at least need not always be, sister strands—which meant that there had been an exchange

between homologous chromosomes. This in turn ". . . ouvre le champ à une plus large application cytologique de la théorie de Mendel."

It was at this point that Drosophila entered the scene, so a digression on the history of its use is in order here.

There is a reference in Aristotle to a gnat produced by larvae engendered in the slime of vinegar—this must have been Drosophila. The genus was described and named by Fallén in 1823. It is perhaps to be regretted that his inappropriate name (dew lover) takes precedence over the more descriptive Oinopota (wine drinker), which was used by some early entomologists. The most-studied species, *D. melanogaster*, was described in 1830 by Meigen, and again, under the name *D. ampelophila* (which appears in some of the early genetic literature), by Loew in 1862. This species probably arose in southeastern Asia, but has long been common in all tropical regions; it was introduced into the United States before 1871, probably when bananas began to be imported.

The first person to cultivate Drosophila in the laboratory seems to have been the entomologist, C. W. Woodworth. Through Woodworth, Castle learned of the advantages of the animal; and it was through Castle's work that it became known to other geneticists.*

In 1910 Morgan reported the sex-linked inheritance of white eyes in Drosophila, thus resolving the contradiction outlined earlier. Further mutant types were soon found, and one of these (now known as rudimentary) was also found to be sex-linked. Here, then, were two pairs of genes that must be supposed to lie in the X chromosomes, and Morgan saw that one could now test the question causing such wide discussion: Is there recombination between genes that lie in the same pair of chromosomes? The result of crosses between white and rudimentary (1910) showed that recombination did occur, because four types of eggs were produced by females heterozygous for both characteristics. This was a major advance, for it removed the most serious difficulty in the way of accepting the chromosome interpretation of Mendelian inheritance.

It happens that white and rudimentary lie far apart in the X chromosome, with the result that there was no obvious linkage between them; but in the following year, linkage between sex-linked genes was observed by Morgan in several cases—first and most strikingly between yellow body color and white eyes. The possibility that linkage might result from genes lying in the same chromosome had been suggested by Lock in 1906, in his elaboration of de Vries' idea that exchange of mate-

* A more detailed account of the early laboratory studies, with names and dates, may be found in my biography of Morgan (Sturtevant, 1959).

rials between homologous chromosomes could account for independent segregation; but this had remained merely an interesting suggestion.*

Morgan then applied the chiasmatype hypothesis of Janssens to the results and postulated that linkage is due to the genes concerned lying in the same chromosome pair. The term *crossing over* was introduced, and it was concluded that closely linked genes lie close to each other, more loosely linked ones farther apart. Here, then, in 1911, was the essence of the chromosome interpretation of the phenomena of inheritance. There followed a period of great activity—the usual consequence of a major scientific breakthrough. The next chapter will be concerned with this development.

* One of the genes involved in the case described by Lock concerned date of flowering in peas and did not lead to clearly separable classes. While his data indicated linkage, they were not amenable to exact analysis.