The Biology of Crossing-over

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SEXUAL reproduction consists of two alternating processes: *fertilization*, by which two germ cells containing each a single set of chromosomes fuse and produce a zygote with the double number of chromosomes, and *meiosis*, by which the double number is reduced and germ cells are again formed with the single number. As Weismann first pointed out, the biological importance of these processes is that they enable the hereditary differences between the chromosomes to be recombined in the greatest number of ways to give the greatest number of different individuals and therefore the greatest scope for natural selection to act in directing evolutionary change.

In recent years we have come to know precisely how this recombination takes place, not merely in one organism, but probably in all sexually reproducing organisms. The method is both more complicated and more efficient than Weismann imagined. In the mother-cells which are to undergo meiosis, the chromosomes are present as single, instead of the usual double, threads of particles. By a combined study of ultra-violet photographs of the particles in *Drosophila*, and of the genetic effects of breaking the threads with X-rays at a series of points along their length, the particles have been identified as genes, the atomic units of heredity¹. The chromosome threads correspond, as we should expect, in pairs, and come to lie side by side in pairs, gene by gene. Their attraction is therefore specific. They then coil around one another, and this coiling proves that they have two properties that might well be expected of them. It proves that they are each in a state of torsion such as that which determines the ordinary contraction of a chromosome into a rod-shaped body at mitosis. It proves also that the threads do not slip around one another. They stick together like two threads of wool placed side by side. The attraction of their genes for one another must therefore be specific in position, that is, not merely between the genes but between the parts of the gene².

If we imitate the physical condition of the chromosomes while they are paired and coiled by placing two woollen threads under torsion side by

side, we find that they coil round one another but at the same time necessarily uncoil themselves internally. The relational and internal coiling (as we may call them) are opposite and in equilibrium. The stability of this system is attested by its use in all spinning operations.

The coiling equilibrium of the paired chromosomes is upset by their division, and we then find that the half-chromosomes, or chromatids, arising in this way are as we should expect coiled round one another. But other changes take place at almost the same time as the division and are presumably

Fig. 1.

DIAGRAM SHOWING THE SERIES OF CHANGES BY WHICH CROSSING-OVER DETERMINES CHIASMA FORMATION AND THE LATER ASSOCIATION, ORIENTATION, AND SEPARATION OF A PAIR OF CHROMOSOMES. THE CIRCLES REPRESENT CENTROMERES OR SPINDLE FIBRE ATTACHMENT CHROMOMERES.

determined by it. First, the divided chromosomes separate: they no longer attract one another. Secondly, chromatids of partner chromosomes break at opposite points and the broken ends uncoil and rejoin so that exchanges of chromatids occur between the separating chromosomes. The chromosomes, although no longer attracting one another, are held together by these exchanges, or chiasmata, which appear in varying numbers and positions in different chromosomes and in different cells.

The special mechanical situation of chromosomes dividing while they are paired thus determines the breakage and reunion which we call crossing-over. In the absence of crossing-over the partner chromosomes fall apart and are unpaired at all later stages. On this process, therefore, the later reduction in number and segregation to opposite daughter-cells equally depend (Fig. 1). Thus crossing-over, which is the only regular genetic change that the chromosomes undergo in their history, is the immediate condition of

reduction and segregation, which are the external changes essential for sexual reproduction. Special exceptions to this rule we will consider later.

Crossing-over within every pair of chromosomes is thus essential to sexual reproduction, but, leaving out this primary consequence, we can sort out its secondary biological consequences into several convenient groups.

First we must take the simple effect of crossing-over in recombining parts of chromosomes, the effect which has been made the basis of genetic analysis in *Drosophila*. Without crossing-over, each chromosome would be a permanent individual, varying and being selected as an individual like a plant clone or any other asexually reproducing organism. With crossing-over, the individual unit of variation and selection will be the unit of crossing-over, which in practice is the gene. Cytological observation has therefore shown that

FIG. 2.
DIAGRAM SHOWING THE SERIES OF CHANGES BY WHICH A PAIR OF CHROMOSOMES, DIFFERING IN REGARD TO THE INVERSION OF A SEGMENT, HAVE CROSSING-OVER IN THAT SEGMENT WITH THE CONSEQUENT FORMATION OF ONE DICENTRIC AND ONE ACENTRIC CHROMATID.

the gene structure established by crossing-over experiments in *Drosophila* is applicable to all sexually reproducing organisms. The sizes of the genes and their physiological activity or inertness will be different in different organisms, but their methods of inheritance, variation and selection will be essentially similar. We may expect, for example, that, as in *Drosophila*, chromosomes or parts of chromosomes in which crossing-over is reduced or suppressed will mutate to an inert state in which they will continue until by chance breakage they are lost³.

One respect in which species differ most significantly is in the amount of crossing-over taking place in their whole chromosome complements. This is one factor affecting the amount of total recombination that will take place among the genes at meiosis. The other factor is the number of pairs of chromosomes themselves. By adding

this number to the average total frequency of chiasmata in the mother-cell, we can obtain a *recombination index* which will be a measure of the average total number of independently segregating gene-blocks in the species. This index is 6 in male *Drosophila melanogaster*, 12 in the female, 36 in *Zea Mays* and about 75 in man⁴. It is clear that these enormous differences will affect the character of variation in a species, though in what way it remains for us to find out.

One general property of the recombination index may be noted. A low index has a positive selective value. This may be shown in the following way. The chiasma frequency is under genotypic control; it is therefore capable of selection and is usually as low as is consistent with regular pairing of the chromosomes. On the other hand, it is much easier to increase chromosome numbers, both by doubling individual chromosomes and whole sets, than it is to reduce them. Nevertheless we have to-day a very large proportion of organisms with low chromosome numbers. More than half the angiosperms have twelve pairs of chromosomes or fewer. It follows that while some recombination is a great advantage, too much is a disadvantage. Presumably a certain stability in combination gives the maximum efficiency in the selection of different combinations. In this regard Fisher has remarked⁵ that there is more crossing-over in Nature than would seem desirable. The reason is now clear: each pair of chromosomes has to have at least one chiasma in order to undergo meiosis.

There is another genetic effect of crossing-over that is entirely different from that of recombination; namely, its effect in certain kinds of structural hybrids. Most organisms that have not been closely inbred are structural hybrids of one kind or another. The commonest kind is the inversion hybrid, which has a segment of a chromosome inverted relative to its partner. When crossing-over takes place within such a segment two new chromatids are produced, one joining the two centromeres of the chromosomes and the other joining their two ends and lacking any centromere (Fig. 2). When the bivalent formed in this way attempts to divide, the 'dicentric' chromatid forms a bridge between the daughter nuclei, and the 'acentric' one, incapable of movement, is lost. The bridge may break anywhere along its length, so that new chromatids are produced having some genes in excess and others lacking. Thus the primary structural change of inversion gives rise to secondary changes such as reduplication and deficiency. These are changes of 'balance', and rank with intra-genic changes and position changes as one of the three effective means of variation. The original variation becomes the basis of future variability. This does not mean that variation

within an endogamous group will be cumulative. Equilibrium is presumably reached by the effect of structural change in decreasing fertility, or a new system is established by the breaking up of the group into two smaller genetically isolated groups, that is, by the fission of the species. This property of genetic isolation brings us to the last important relationship of crossing-over.

So long as we have a structurally homozygous stock with crossing-over taking place at intervals between all the varying genes, no stable combination of variants can be maintained without elimination of cross-overs and loss of fertility. Optimum adaptation always demands such a combination, for adaptation depends on the integration of the whole gene system. The most generally recognized way of securing stable combinations is by geographical or ecological isolation. In the same way inter-sterility may secure a genetic isolation of two types of combination. All these methods depend on an isolation of zygotes. But an equally important method is the isolation of chromosomes or parts of chromosomes by structural change. When a small inversion or translocation occurs in one chromosome of a species, crossing-over is restricted or abolished between this changed segment and its normally arranged partner. Any gene differences occurring within this segment are held together in a more or less permanent combination. A new unit, a new order of integration, is established in this way.

It is through this special type of unit that three important types of discontinuity arise in Nature. The simplest type is that by which two groups which remain interfertile diverge within a species. It is probably the basis of the discontinuity between *Avena fatua* and *Triticum Spelta* and their allied forms, which differ essentially in a group of genes lying in a part of one chromosome. A second type is that by which the sex-determining chromosomes (X and Y) come to be distinguished. Originally one pair of genes in these chromosomes determines the sex difference by their segregation. Later other genes become associated with them in two groups which show no crossing-over. Their crossing-over may be suppressed structurally by an inversion or some other similar change. It may also be suppressed genotypically, and here we come to the exceptions in which crossing-over does not take place at meiosis at all. This situation arises in the heterozygous sex in certain insects where a new pairing mechanism is introduced instead of chiasmata. It is only one sex, however, that is affected, and this shows us that in the last resort it is not chiasmata which are indispensable for meiosis but crossing-over which is indispensable for the species. The exclusion of one sex from crossing-over has a special effect on one chromo-

some, the Y-chromosome. Where sex is determined by the segregation of X and Y, the Y, being confined to the heterozygous sex, is permanently excluded from crossing-over. The result of this is shown in evolutionary series when we compare different animals. First the Y becomes inert as in *Drosophila*, later it becomes smaller as in the Mammalia, finally it is lost as in many Orthoptera³. The intermediate stages show different transitions according to the positions in which crossing-over is localized before its eventual suppression. In whatever way crossing-over may lapse, a group discontinuity arises between the two sex-determining chromosomes. This discontinuity differs in its effect from that arising between species merely in that the two types it distinguishes are mutually adapted for sexual reproduction⁶.

The third type of discontinuity occurs in plants. It is that which arises between chromosomes in establishing a permanent hybrid of the *Oenothera* type. Here an interchange of segments between two different chromosomes is the origin of the system. It operates by suppressing crossing-over between the middle segments of the chromosomes, and when all the members of the complement are affected by the interchanges and are held together in a single ring at meiosis, only two types of gamete are produced, and all the chromosomes of one type are prevented from crossing-over with those of the other in their middle segments. Thus complex differences arise owing to the isolation not of zygotes nor of parts of one pair of chromosomes but of parts of all the chromosomes of the gamete, a gametic isolation. The differences between the two gametes are of the same order as the differences between two species.

Other mechanisms occur in the dog roses and with certain kinds of parthenogenesis whereby, as in *Oenothera*, a large part of the genes are prevented from recombining. With such systems stability has been achieved at the expense of variability, and we have arrived at what we may call a sub-sexual method of reproduction.

In these various ways and in many others the study of crossing-over shows us that this simple and universal mechanical property underlies most of the important relationships with which we are concerned in genetics. Variation and adaptation, hybridity and discontinuity, sex-determination and species-formation operate and develop according to the varying occurrence or suppression of crossing-over. Crossing-over is the primary variable in the evolution of genetic systems.

¹ Muller, H. J., and Prokofyeva, A. A., *Proc. Nat. Ac. Sci.*, **21**, 16-26 (1935).

² Darlington, C. D., *J. Genet.*, **31**, 185-212 (1935).

³ Darlington, C. D., "Recent Advances in Cytology" (London, 1937).

⁴ Koller, P. C., *Proc. Roy. Soc. Edin.*, **57**, 194-214 (1937).

⁵ Fisher, R. A., "The Genetical Theory of Natural Selection" (Oxford, 1930).

⁶ Muller, H. J., *Amer. Nat.*, **66**, 118-138 (1932).