

## Cytological Theory in Relation to Heredity.\*

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THE chromosome theory of heredity, by relating chromosome behaviour with the phenomena of inheritance, has obviously made it possible to apply the cytological method to the study of inheritance. With this profitable field before them, geneticists and cytologists have not hesitated to draw conclusions in the one field from observations made in the other, but in order to do so they have had to apply certain rules of interpretation. Their method has naturally been to assume, so far as possible, a direct relationship between cytological and genetical observations. The geneticist has therefore not only assumed that the material of every part of the chromosome has a specific genetic effect, which is a widely verified assumption; but also that the capacity of the chromosome for variation is equally specific, so that it is possible to refer to hereditary differences and to particles of chromosome alike as 'genes'. This second assumption is also widely verified; but it is subject to serious exceptions in that two different kinds of change have been shown to befall the same particle, namely, internal change and external change such as loss or re-arrangement. This constitutes no primary objection to the theory of the gene but rather indicates a necessary enlargement of its scope.

Cytologists, on the other hand, in translating their observations into genetical terms, have sought to apply the chromosome theory to the interpretation of meiosis. With the help of the simple rule that the pairing of chromosomes is a criterion of their relationship, they have set to work to examine meiosis in hybrids and in ring-forming plants (such as various species of *Oenothera*). The results of these studies have been confusing because investigators have not first examined the principles they were applying to see if they were indeed principles or merely empirical rules of special derivation and therefore of limited application. We now have evidence by which to test them.

Meiosis consists in the occurrence of two successive divisions of a nucleus in the course of which the chromosomes divide once instead of twice as they would in two ordinary mitoses. Where the distribution of the chromosomes is regular, the four daughter nuclei therefore have half the number of chromosomes of the parent nucleus (Fig. 1).

At the first division, the chromosomes come together in pairs, and a whole chromosome of each pair passes to one pole to divide at the second division of the nucleus. To express this comparatively with regard to mitosis, we may say that while two half-chromosomes (or 'chromatids') are associated in pairs at a mitosis, four are associated at the first metaphase of meiosis. A numerical reduction in the chromosomes must be attributed directly to the lack of any splitting of the chromosomes in the interval between the two divisions

of the nucleus such as ordinarily occurs. But this is readily related to the fact that each chromosome is already split into the two chromatids which have passed together to one pole. This in turn is related to the pairing of the chromosomes.

It has therefore seemed natural (since 1890) to regard the essential difference between meiosis and mitosis as consisting in the pairing of the chromosomes. Since different pairs of chromosomes pass at random to the two poles (so that  $A_1-A_2$  and  $B_1-B_2$  may give daughter nuclei  $A_1B_1$  and  $A_2B_2$  or, equally,  $A_1B_2$  and  $A_2B_1$ ), and since the chromosomes are qualitatively differentiated, it follows that those which pair and pass to opposite poles must be similar if meiosis is to yield similar reduced nuclei (Boveri). Clearly, likeness is a condition of pairing. But since the chromosomes that pair can be seen to be morphologically alike and therefore to be corresponding structures derived (so far as observation then showed) from opposite parents (Montgomery), it seemed enough to say that this pairing was due to the likeness of the chromosomes. An 'incipient' association is often to be seen at mitosis in the somatic cells. Perhaps, therefore, meiosis was the final step in the sexual process in which the maternal and paternal elements at last united.

Such is, in a general way, the 'explanation' of meiosis that is current to-day. To be sure, we now know that the association cannot be attributed to an attraction between chromosomes derived from opposite gametes, since pairing has been found in meiosis in parthenogenetic organisms,<sup>1, 2</sup> and very often between chromosomes derived from the same gamete in polyploid plants. It may also be objected that this is merely to explain *ignotum per ignotius*. But it is still taken to be a satisfactory basis for cytological, genetical, and evolutionary deduction. Incompatible observations are freely ascribed to 'mechanical' or 'physiological' conditions.

There are many recent observations of this kind. There are tetraploid plants (such as *Primula sinensis*<sup>3</sup>), the nuclei of which contain four identical chromosomes of each of the twelve types that are represented twice in the diploid. These chromosomes usually associate in fours at meiosis, as they would be expected to do if likeness were the sole condition of pairing. But nearly always one, two, or three of these groups fail to be formed and their chromosomes appear merely paired. This is not explicable on the affinity theory. The chromosomes should be either *all* in fours or *all* in pairs.

Other observations of the same type are: (1) The occurrence of unpaired chromosomes in triploids, instead of all three identical chromosomes of each type being associated (*Zea*,<sup>4</sup> *Tulipa*,<sup>5</sup> *Lilium*<sup>6</sup>). (2) The occurrence of unpaired fragment chromosomes, although these have identical mates with which they can pair (*Secale*,<sup>7</sup> *Matthiola*,<sup>8</sup> *Tradescantia*<sup>9</sup>).

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The only difference between these fragments and the other chromosomes which pair regularly appears to be their smaller size. If the triploids are examined, it is similarly found that the chromosomes which fail to associate regularly in threes are the small ones (*Hyacinthus*<sup>10</sup>). Therefore, not only *likeness* but also *size* bears some relation to the pairing of chromosomes.

If now we turn to consider the structures of the paired chromosomes at meiosis we find a variety of form that shows, at first sight, neither a rule in itself nor any clear relationship with ordinary mitosis. The two processes must be studied in their development in order to be seen in relationship.

The prophase of mitosis is characterised by a linear contraction of two threads, associated side by side, to become the two cylindrical rods which constitute the metaphase chromosome. At meiosis we find at the earliest stage a difference. The threads observed are single. They soon come together in pairs side by side and reproduce the conditions observed at the prophase of mitosis very closely indeed. But on account of their pairing they are present at this pachytene stage in half the number found at the prophase of a mitosis in the same organism. Evidently, therefore, the single threads at the earlier stage were chromosomes still undivided although in the earliest visible stage in mitosis they have already divided.

After an interval, splits appear in the pachytene thread, separating it into two threads, each of which is now seen to be double. But instead of these splits passing right along the paired chromosomes and separating them entirely, it is found, when they meet, that the double threads that separate in one part are not the same pair of threads that separate in another. The separated pairs of threads therefore change partners, and the points at which they change partners (there are often several distributed along the paired chromosome) are called 'chiasmata'. This stage is diplotene (Fig. 1).

Between diplotene and metaphase there is further linear contraction, and the structure of the paired chromosomes may remain the same in regard to the relationships of the four threads of which they are composed: that is, the chiasmata may remain stationary. But they may undergo a change which consists in the opening out of the loop that includes the spindle-attachment, at the expense of the adjoining loops, as though the spindle-attachments of the chromosomes were repelling one another. In other words, the chiasmata appear to move along the chromosome towards the ends: finally, the chromatids are associated in pairs with changes of partners only at the ends. Such changes of partners are called 'terminal chiasmata', and the frequency of the end-to-end unions at metaphase corresponds with the frequency of the chiasmata seen earlier, when they were still interstitial, in small chromosomes (fragments) which only have one chiasma at most.<sup>11</sup> Further, in organisms with large chromosomes it is still possible to see the change of

partner: at the end the association is double; it is between the ends of two pairs of chromatids, not merely between the ends of one pair of chromosomes.

These observations point to the chiasmata being the immediate cause of pairing between chromosomes. How can such a hypothesis be tested? It

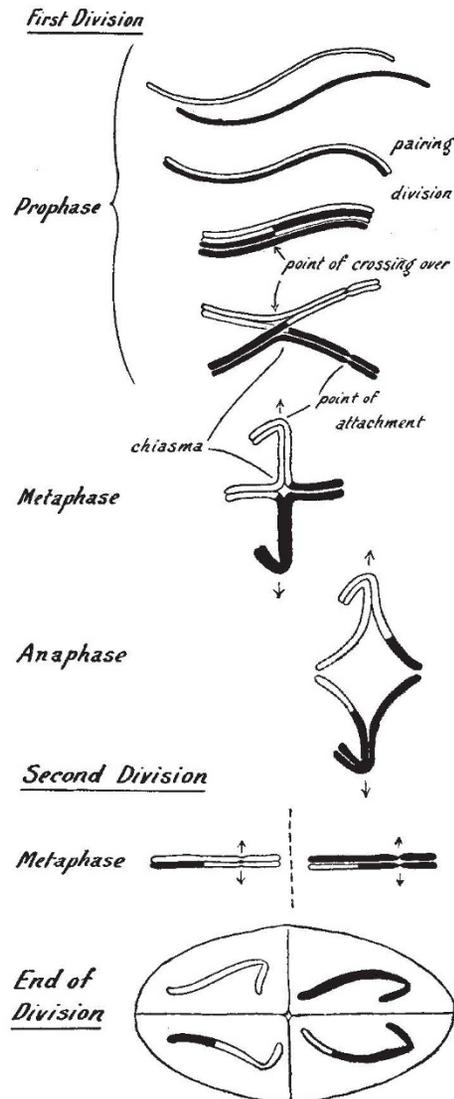


FIG. 1.—Diagram to show the development of one pair of chromosomes at meiosis, and their relationship on the assumption that crossing over is the cause of chiasma formation. The four stages of prophase shown are: (1) leptotene, (2) pachytene before division, (3) pachytene after division, (4) diplotene to diakinesis.

is found that given pairs of chromosomes have a constant range in the number of chiasmata formed. For example, in the *M* chromosome of *Vicia Faba*<sup>12, 11</sup> from 3 to 13 chiasmata are found at the metaphase, with a mean of 8.1. The *M* chromosome, which is much shorter has a range of 1 to 6, with a mean of 3.0. If we suppose that small chromosomes arising by fragmentation have a chiasma frequency proportionate to their length as compared with their larger neighbours, then we can predict from

observations of their size and of the observed frequency of chiasmata in the large chromosomes what their frequency of pairing will be, on this hypothesis. Thus, in the variety "Yellow" of *Fritillaria imperialis* it was found that the chiasmata frequency was 2.58 in the large chromosomes. The fragments were about one-ninth of the length of the large chromosomes. They should therefore have chiasmata in a frequency of 2.58/9 per pair, or 0.29. This means that they should pair in 0.29 cases (neglecting the frequency of one pair forming two chiasmata, which should be slight). They were observed to pair in 0.22 of cases.<sup>11</sup> Here is an example of the type of observation which is susceptible of statistical analysis and supports this hypothesis.

Now, if we admit chiasmata as the condition of chromosome pairing, a considerable simplification is possible in stating the relationship of mitosis and meiosis. Throughout the prophase of mitosis, the threads are held together by an attraction in pairs. The same rule applies to meiosis, for the evidences of failure of pairing of fragments, of odd chromosomes in triploids, and of the four chromosomes of a type in tetraploids all point to the chromosomes having no present attraction at metaphase. They are merely held together by the chiasmata—that is, by the attraction between the pairs of half chromosomes and the exchanges of partners amongst them; and this attraction exists equally at mitosis.

This being so, we must look to the earliest stage of prophase to find the essential difference between the two types of nuclear division. It evidently lies in the time at which the chromosomes split into their two halves. At mitosis, it is probable that this has already happened before the chromosomes appear at prophase. At meiosis, it does not happen until pachytene (possibly at the moment at which the diplotene loops appear). The prophase of meiosis therefore starts too soon, relative to the splitting of the chromosomes. If we consider that there is a universal attraction of threads in pairs at the prophase of any nuclear division, as we see it at mitosis, it follows that this condition is fulfilled by the pairing of chromosome threads when they are still single, and their separation at diplotene when they have at last come to divide. The decisive difference would therefore appear to be in the singleness of the early prophase threads in meiosis. This singleness may be attributed to one or both of two causes: (i) a delayed division of the chromosomes, (ii) a precocious onset of prophase. The second of these seems the more likely explanation, on account of the short duration of the pre-meiotic prophase in some animals. Either assumption would account for the most characteristic of all secondary features of meiosis, namely, the exaggerated linear contraction of the chromosomes, paired or unpaired, if the time relationship of metaphase to the division of the chromosomes remains the same. This hypothesis of precocity<sup>13</sup> may be tested by the observation of a correlation between irregularities in meiosis and (a) abnormality in the timing of meiosis, and

(b) diminished contraction of the chromosomes at metaphase.

The first of these tests is applicable to many organisms with occasional suppression of reduction; the aberrant nuclei enter on the prophase of meiosis either earlier or later than the normal nuclei.<sup>14, 15, 16, 17</sup> When they are too early, it may be supposed that a premature division of the chromosomes has precipitated the prophase; when too late, it may be supposed that the prophase has been delayed. In either case, the chromosomes would no longer be single at early prophase and the condition of their pairing would be lost.

Such a cause of failure of pachytene pairing may be expected to be distinguishable by its effect on the contraction (the second kind of test). For when failure of metaphase pairing is not due to an upset in the timing of prophase but merely to failure of chiasma formation, we might expect normal meiotic contraction; this is the case in maize.<sup>18</sup> Where the prophase has been delayed, we might expect an approach to mitotic conditions; this is the case in *Matthiola*.<sup>19, 20</sup> Other critical evidence in favour of the hypothesis has already been quoted in these columns.<sup>21</sup>

By trying to define in this way the relationship of meiosis to mitosis, we find out what is essential and therefore universal in meiosis, and what is unessential and secondary. Only when the direct interpretation of events in the nucleus is clear (as it now seems to be) can we attempt their genetical interpretation on a satisfactory basis.

Two examples of the genetical interpretation of chromosome behaviour at meiosis are of immediate importance. It has been shown in every organism that has been adequately tested that crossing-over can occur between corresponding parts of the paired chromosomes at meiosis, actually between the chromatids, so that crossing-over in the region between *C* and *D* in a pair of chromosomes *ABCDE* and *abcde* will give four kinds of chromatid: *ABCDE*, *ABCde*, *abcDE*, and *abcde* (Fig. 1). We may suppose that this crossing-over has no relation with anything observable cytologically; that it takes place when the chromosomes are intimately associated at pachytene and has no connexion with later behaviour. This view can only be taken when other possibilities are eliminated. We may also assume that crossing-over has some relationship with chiasmata, either as a cause ('chiasmotypy')<sup>22, 23</sup> or as a consequence, through breakage and reunion of new threads.<sup>10, 9</sup> The last possibility has been eliminated by the statistical demonstration that terminal unions correspond in frequency with interstitial chiasmata,<sup>11</sup> and that the number of terminal chiasmata increases *pari passu* with the reduction of interstitial chiasmata.<sup>3, 4, 20</sup> The first possibility, that the chromosomes fall apart as they come together, and that the exchanges of partners at chiasmata are therefore due to exchanges in linear continuity or crossing-over between the chromatids, has been demonstrated in two ways.

In tetraploid *Hyacinthus* and *Primula* associations occur with such a spatial relationship that

they can only be interpreted as the result of crossing-over.<sup>3, 25</sup> In ring-forming *Enothera*,<sup>28</sup> chiasmata occur interstitially between a pair of chromosomes associated terminally with two others to give a 'figure-of-eight'. Such an arrangement also can arise only on the assumption of crossing-over. These demonstrations confirm Belling's interpretation of the *Hyacinthus* trivalents, which was not in itself indisputable.<sup>5</sup> Whether the observations are of universal application (the simplest assumption) or not, can only be shown by cytological tests of organisms which have been studied genetically.

A second problem is that of ring formation. Since, on the present hypothesis, the pairing of chromosomes at metaphase is conditioned by the formation of chiasmata at prophase between parts of chromosomes of identical structure, it follows that ring formation (where one chromosome pairs in different parts with parts of two others) must always be due to different arrangement of parts, that is, different structure, in the chromosomes contributed by opposite parents.<sup>26, 27, 9</sup> Thus the relationship of the chromosomes of two organisms can always be specified from the observation of the pairing behaviour of the chromosomes at

meiosis in the hybrid. It is therefore possible to study differences of such a magnitude as will sterilise a hybrid and are therefore not susceptible of genetical analysis. This method is now being widely applied.

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### Landscape at the Royal Academy.

IN "Cape St. Vincent" (669) we have an example of the work of the late W. L. Wyllie in which the revered veteran showed undiminished mastery of his craft. The rush of the Atlantic rollers as they mount and comb on nearing the headland will recall to many, besides the present writer, a notable incident on the voyage from England to the East.

In "Moonlight: Scilly Isles" (90), Mr. Julius Olsson renders with his usual skill one of the most beautiful aspects of the coastal scenery of Great Britain, and the spark of the beacon on the headland both focuses the attention of the eye and adds to the emotional appeal of the picture. In "Sunlight" (130), Sir Hughes Stanton depicts a promontorial town of the Mediterranean coast silhouetted against sea and sky, a picturesque relation of architecture and Nature for which we must seek foreign shores. The austerities of Spanish landscape have attracted Mr. Sydney Lee ("The Ox Cart", 79), Mr. Guy Kortright ("Spanish Cactus", 243), and Mr. Oliver Hall ("A Town of Southern Spain", 414). In the case of several pictures which embody either the golden glow and dark shadows of evening or lurid light and sombre clouds of storm, the artists have enhanced both the height and depth of tone and colour by a frame of black and gold. Notable examples of this judicious device are "The Storm" (80) by Mr. Philip H. Padwick, "Evening in the Mountains" (268) by Mr. William Clarkson, and "Mountains near Beddgelert" (281) by Mr. Oliver Hall.

In the fine study of "Amiens" (258) by Mr. Terrick Williams, the shadowed cathedral owes

its immensity to the foreground of small houses, caught by sunlight, on the quay. It is an intriguing fact that impressiveness of size should bear so little relation to that which the astronomer calls the 'apparent magnitude' of an object. A notable example of the dependence of the impression of size upon grouping is afforded by Windsor Castle, which when seen above the houses of the Borough assumes the appearance of a walled town crowning the hill.

In "The Estuary" (301) by Mr. Arnesby Brown, we have one of the characteristic landscapes of the British coast, with fine effects of atmosphere. Towering clouds fill the larger part of the picture, the horizon of the land and sea lying very low in the field of view. Underlying this practice or device of pictorial composition is the singular fact that although the eye is keen to note any lateral divergence from the vertical, it receives no warning sensation of a considerable departure from level outlook. Hence great sky views are not so much determined by the circumstance of there being more sky, as by a natural grouping which lures the eye to an upward outlook.

In "Northleach" (479), Mr. William A. Rixon gives us a faithful picture of Arcadian England; the harvest field and church tower, undulating landscape, and rounded masses of spreading trees, with soft white clouds floating overhead. We may travel the world over but only in England will such a scene be found. This is our particular heritage, which we should cherish and preserve.

In Room X., devoted to Water-Colours and Tempera, Mr. Cecil A. Hunt, in "Glen Brittle, Isle of Skye" (933), has rendered with poetic feeling a