CHAPTER 5

GENES AND CHROMOSOMES

For many years the standard authority on the chromosomes was Wilson's *The Cell in Development and Inheritance*. The second edition of this work was published in 1900; it gives a full account of the state of knowledge and of current theories about chromosomes at the time of the discovery of Mendel's paper.

The constancy of chromosome number for a species was known, and it was known that this number was usually even, equal numbers coming from the egg and from the sperm. It was known that each chromosome divides longitudinally at each somatic division, and that this division is initiated by an equal division of each visible granule along the length of the chromosome. It was also known that the reduction in chromosome number is accomplished by the last two divisions before the production of the mature gametes (in animals) or gametophytes (in plants). Further, it was generally supposed that the chromosomes are the bearers of the essential hereditary material.

There were, however, a number of things, now part of common biological knowledge, that were not known. It was generally supposed that, when the chromosomes reappear at the end of the resting stage, they first do so as a single continuous thread, or spireme, which then breaks into the number of chromosomes characteristic for the particular species. It had been postulated by Rabl and by Boveri that the chromosomes "do not lose their individuality at the close of division, but persist in the reticulum of the resting nucleus." Although Weismann adopted this view, Wilson felt that it was far from proved. The details of chromosome reduction at meiosis were not at all clear, chiefly because the two-by-two pairing in meiotic prophase was not recognized. The whole idea of definite pairs of chromosomes was missing. It was not recognized that there are different kinds of chromosomes in a single cell. In short, one chromosome was

tacitly assumed to be essentially like any other in the species, and in Weismann's writings this assumption was explicitly made.

It was supposed that the bivalent chromosomes in the first meiotic division were condensed from a single continuous spireme and were therefore attached end to end from the beginning; the reduction in number must therefore arise from a transverse division. There were, however, good descriptions indicating that these bivalents divided by means of two successive *longitudinal* divisions in some species; this appeared as a paradox, since it seemed to contradict the view that the reduction is a qualitative one, and not merely quantitative.

These matters were gradually cleared up by the cytologists. That the chromosomes occur in distinct pairs, which can sometimes be recognized by their sizes and shapes, was first indicated by Montgomery in 1901 and was shown conclusively (in a grasshopper) by Sutton in 1902. Both authors showed that one member of each pair was maternal in origin, the other paternal; this interpretation was very soon generally accepted. But both men still thought that the two members of a pair were attached end to end.

The interpretation of the bivalents in the first meiotic division as resulting from side-by-side pairing of separate chromosomes was suggested by Winiwarter in 1901, as a result of his studies of the ovaries of the rabbit. He discussed the difficulties just outlined and concluded that such side-by-side pairing was the simplest way of reconciling the apparent contradictions. This view was not at once generally accepted but slowly gained ground as more and more cytologists saw figures consistent with it. It was not important in the earliest work on the relation between genes and chromosomes but, as will appear, was essential for later developments.

In 1902 Boveri issued a remarkable paper on the results of polyspermy in the fertilization of the eggs of the sea urchin. He showed that, if an excess of sperm is used, two sperm may enter a single egg. Each sperm centriole then divides, and 3-poled or 4-poled spindles result. These eggs may divide into three or four cells at the first cleavage division. The three haploid sets of chromosomes (one from the egg and one from each sperm) divide and pass to these daughter cells more or less at random, so that most cells receive abnormal numbers of chromosomes. These cells usually divide normally for a few divisions, but the resulting embryos are quite abnormal, often appearing to be mosaics, with some portions reasonably normal and others aborted or quite abnormal.

If the four cells resulting from the first two cleavages of a normally fertilized (monospermic) egg are separated, each will give a normal

(though small) embryo. Boveri found that if the three or four cells produced by the first cleavage of dispermic eggs were separated, they would sometimes develop into normal embryos—but never would all of the cells from any one egg do so. He showed that this result could not be explained by the number of chromosomes present, since in cells that failed to develop this was often greater than the haploid number—and a single complete haploid set was already known, from other experiments, to be enough for normal development. The results can only be explained on the assumption that the chromosomes differ in their effects on development, and that a cell will not give rise to a normal embryo unless it has at least one complete haploid set of chromosomes.

The paper has a footnote, in which Boveri points out that he, like Weismann, had previously supposed that the chromosomes of an individual were equivalent one to another. This view he now finds untenable, and therefore Weismann's interpretation of chromosome reduction at meiosis must now be revised. This same footnote contains a statement that may be freely translated thus: "I shall consider in another place these and related problems, such as the connection with the results of the botanists on the behavior of hybrids and their offspring." Before this further discussion appeared, the whole matter was clearly analyzed by Sutton, but there can be no doubt that Boveri was near to the solution.

In 1900 Correns had already raised the question of where the Mendelian segregation occurs and had discussed it in several papers, the fullest account being in 1902. He knew, from his experiments with maize hybrids, that the embryo and the endosperm of a given seed are alike. It follows that the three maternal nuclei involved in the double fertilization are alike, as are the two from the pollen. He concluded that segregation is accomplished at latest by the time the megaspore is produced, and that it occurs in the anther at some time before the final division that produces the two sperm nuclei in a single pollen grain. On the other hand, the earliest time it can be supposed to occur is after the sexual organs are formed, as both the ovaries and the anthers of heterozygous plants produce both kinds of gametes. Since the ratio of dominant to recessive gametes is so very close to 1 : 1, he concluded that segregation must come very late in the development—in order to avoid chance (or selective) differences in multiplication of the products. He was, of course, also aware that the last two sporophyte divisions (that is, the meiotic ones) are of a different type and lead to haploid nuclei. He therefore concluded that segregation occurs in these two divisions in the ovule.

In the anther he recognized that the same reasoning would lead to the view that the meiotic divisions were also those that produce segregation.

This should mean that the pollen grains of a heterozygote were of two kinds, in equal numbers. He tested this deduction. He found two flower colors in Epilobium that gave Mendelian results and were associated with differences in the color of the cell sap of the pollen grains. He examined the pollen of the heterozygote and found it to be uniform in color. An exactly similar result was found in one of the poppies. He concluded that segregation had not yet occurred, and that it must therefore occur in the first pollen division, which separates the tube nucleus from the generative nucleus—the latter then dividing to produce the two sperm nuclei. Strasburger made the suggestion (which we now know to be correct) that the color of the pollen grains is determined by the composition of the plant that produced them, not by the gene content they have just acquired. Correns admitted this possibility but argued, reasonably, that this was a special hypothesis made up to save another hypothesis, and he preferred to avoid such a procedure.

In this same paper, Correns discussed the relation of the genes to the chromosomes. He supposed that the genes were carried by the chromosomes, and he drew a diagram that looks very much like the beads-on-a-string type that later became familiar. One string was labelled *A, B, C,* and so on; on another, closely apposed string *a* was placed opposite *A, b* opposite *B,* and so on. But this was supposed to represent a single mitotic chromosome, which divided in the plane of the paper at each division, except at the time of segregation, when it divided at a right angle to the paper to yield strands *ABC* and *abc*. He also figured what looks now like crossing over, supposing that the pairs of genes could rotate about the long axis of the chromosome, so that *ABc* and *abC* (or *AbC* and *aBc,* and other combinations) could be produced. This was to explain independent assortment ("Mendel's second law").

While this scheme related the genes to the chromosomes, it was wrong in many critical points. There was no explanation of how a single mitotic chromosome came to have maternal and paternal halves; the segregation division was not identified with meiosis; and independent assortment was not related to independent segregation of nonhomologous pairs of chromosomes.

Cannon pointed out in 1902 that there is a close parallelism between Mendelian segregation and chromosome reduction and concluded that this is because the genes are in the chromosomes. Like Correns, he seems to have thought that all the paternal chromosomes went to one pole at meiosis and all the maternal ones to the other; he offered no explanation for independent assortment. De Vries, in 1903, also discussed these

questions, and he seems likewise to have supposed that the paternal and maternal chromosomes were separated as groups at meiosis. He accounted for independent assortment by postulating that, at meiosis, the members of individual gene pairs could be freely exchanged between homologous chromosomes (as Correns had supposed) and so would segregate at random.

Guyer, in 1902 and 1903, also understood the situation. The 1902 paper did not mention Mendel, and both were largely concerned with the cytology of sterile hybrids. Guyer did, however, understand that random assortment between different pairs of chromosomes would give independent assortment of genes, although both Wilson and Sutton thought that he had missed this latter point.

Thus there were several people who were close to the correct interpretation at this time, but the first clear and detailed formulation was that of Sutton. W. S. Sutton (1877–1916) was a student of McClung, whose work on the sex chromosomes will be discussed later. Sutton was working with him at the time that McClung first suggested the relation of the X chromosome to sex determination (1901), but Sutton was a graduate student under Wilson at Columbia University when he wrote his two important papers (1902 and 1903). He never finished his graduate work, but did later receive an M.D. degree, and became a practicing surgeon [see biography by McKusick (1960) for more details].

As was pointed out above, the first of Sutton's papers contained the earliest detailed demonstration that the somatic chromosomes (of a grasshopper) occur in definite distinguishably different pairs of like chromosomes. He knew of the earlier work of Montgomery on pairing and of Boveri's paper (also published in 1902) on dispermic eggs. The paper closed with the statement: "I may finally call attention to the probability that the association of paternal and maternal chromosomes in pairs and their subsequent separation during the reducing division . . . may constitute the physical basis of the Mendelian law of heredity."

The 1903 paper contains a full elaboration of this hypothesis, including the view that the different pairs of chromosomes orient at random on the meiotic spindles,* thus accounting for the independent segregation of separate pairs of genes seen by Mendel. He suggested, following Fick and Montgomery, that in those cases where both meiotic divisions had been described as longitudinal, the initial pairing had been side by side rather than end to end, as he supposed it to be in insects. The

* The cytological demonstration of the random assortment of different pairs of chromosomes was made by Carothers in 1913.

paper contains a discussion and criticism of the 1902 accounts by Cannon and by Guyer, referred to previously.

With this paper, this phase of the history is finished. The conclusions were not at once generally accepted, but they could not be disregarded and stand today as essentially correct. At last, cytology and genetics were brought into intimate relation, and results in each field began to have strong effects on the other.