SYMPOSIUM NO. 4: MEIOSIS

INTRODUCTION BY THE CHAIRMAN

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A few of you may recall that an International Congress of Genetics was held at Cornell University, Ithaca, New York in 1932. The year before, two noteworthy papers on meiosis had been published and the results were reviewed or demonstrated at the Congress. STERN and CREIGHTON with MCCLINTOCK had independently demonstrated what have become classic experiments in cytogenetic literature, i.e., new chromosome arrangements were associated with recombinant genes. Using chromosomes marked by mutant genes and morphological differences at each end they were able to demonstrate in *Drosophila melanogaster* (STERN 1931) and *Zea mays* (CREIGHTON and MCCLINTOCK 1931) that crossing over was correlated with segmental interchange between homologous chromosomes. Although this implied to some that a physical exchange of chromosome parts occurred, another view had already taken shape in the mind of another cytogeneticist of the time, JOHN BELLING (1928). He suggested that no break was necessary and proposed instead what later became known as the copy choice model in which one chromatid was used as template during a part of reproduction and the homologous chromatid served in that capacity for the remainder of the length. The new chromatid would have a new arrangement, but no breaks and rejoining need be involved. This was such an attractive idea that the hypothesis in some form held center stage for nearly thirty years. In 1961 MESELSON and WEIGLE and independently KELLENBERGER, ZICHICHI and WEIGLE (1961) disproved BELLING's attractive hypothesis. They were able to show, with radioactive and density markers, that the parental DNA (chromosome) of phage λ actually breaks and exchanges segments during some recombinant events. Some years earlier at another Genetics Congress in Montreal, Canada, I had been able to show physical exchanges between sister chromatids in mitosis (TAYLOR 1959), but no correlation with genetic recombination was possible in that system. However, by 1965 I was able to demonstrate that similar exchanges between non-sister chromatids could be observed by autoradiography with ^{3}H-thymidine when appropriately labeled chromatids of the grasshopper Romalea passed through meiosis. Still, no correlation could be made with behavior of genetic markers, but exchanges occurred at about that frequency expected on the basis of the number of observed chiasmata. If the assumption is made that all chiasmata are physical evidence of exchanges between homologous chromatids, a one-to-one correlation is indicated. That presumption had never been firmly established, but you will recall that a battle raged for many years between

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the proponents of the classic theory, namely, that chiasmata are the result of alternate separation of sister and non-sister chromatids at diplotene, led by KARL SAX in the later years, and the proponents of the partial chiasma-type or one-plane hypothesis proposed by JANSSENS (1909, 1924) and championed by DARLINGTON (1932, 1937) in that grand period of cytogenetics during the 1930's. The controversy was perhaps never resolved to everyone's satisfaction, but by 1955 when BROWN and ZOHARY studied the frequency of chiasmata in *Lilium formosanum* the case for the one-plane, chiasmatype hypothesis appeared overwhelming. The frequency of first and second division segregation of short and long chromatids as opposed to equal chromatids was in accord with the hypothesis that each chiasma seen at diplotene or diakinesis represents a crossover if segregation of centromeres is regularly reductional at division I. The autoradiographic studies on meiosis in the grasshopper (TAYLOR 1965) verified that assumption by showing that centromeres segregate reductionally at division I. In addition, diplotene configurations produced by a paracentric inversion in Lilium and pericentric inversion in maize (ZOHARY 1955) was also in accord with the idea that sister chromatids remained together at diplotene and that each chiasma represents a crossover. Later papers by NODA (1960), by KAYANO (1960), by JAIN and BASAK (1963), by ZEN (1961), also supplement the evidence for the chiasmatype hypothesis presented and defended on the basis of similar evidence by DARLINGTON (1935, 1937) and by MATHER (1938) many years before.

As a graduate student I became very interested in meiosis, and during my early career as a biologist I considered devoting my entire life's work to the solution of some of the central problems associated with the meiotic divisions and genetic recombination. My principal effort, in initiating the experiments on production of ^{3}H-thymidine as a label for DNA and studying the segregation of tritium-labeled chromosomes in mitosis, was directed toward the larger problems of segregation and recombination in meiosis. Unfortunately, the solutions to these problems were not immediately forthcoming from the ability to label DNA and produce autoradiographs with resolution needed to study crossing over. It seemed a simple step from observing the segregation of chromatids in mitosis and the study of sister chromatid exchanges to similar applications in meiosis. Actually, problems were anticipated, but the years which elapsed before any results worthy of publication were obtained attest to the technical problems which have faced all who have tried to use labeling and autoradiography to study meiosis. However, a few facts have been obtained which limit the hypotheses which can still be considered. First of all, chromosomes were demonstrated to be stable physical entities, as genetic studies had indicated. The DNA of even the largest chromosomes remains essentially intact during the long prophase of the first meiotic division. The number of exchanges is very close to the number predicted on the basis of chiasma frequency. Sister chromatid exchanges are few in number, if not absent, in the grasshopper and perhaps in some other organisms. These statements are made with the reservation that some uncertainties concerning the effects from irradiation by the incorporated tritium during the long meiotic prophase have not been properly resolved.

Tritiated thymidine has also been useful for timing events in meiosis. The first instance was the resolution of the problem of when chromosomes are reproduced or, in particular, when the DNA is synthesized. It turned out, contrary to many earlier ideas, that nearly all replication occurred before meiotic prophase in a premeiotic S phase which proved to be rather extended compared to the S phase of somatic cells in higher animals. In mouse spermtocytes S phase was indicated to be 14 hours compared to 5–6 hours for somatic mitotic cycles (MONESI 1962). The difference is more extreme in the newt, Trituris, where premeiotic S phase requires about 10 days compared to about 12 hours for somatic cells in culture (CALLAN and TAYLOR 1968; and CALLAN 1972). Perhaps a small amount of synthesis is delayed until prophase (HOTTA, ITO and STERN 1966). However, there appears to be some difference of opinion as to whether this represents a delay in replication of a small amount of the genome or a repair replication. Perhaps one of our speakers today will clarify that problem area.

Another use of ^{3}H-thymidine has been in the timing of replication in relation to other events in meiotic prophase. HENDERSON (1966) used this approach to show that heat treatments could be effective in changing the frequency of chiasmata several days after premeiotic DNA synthesis was complete. Several similar studies have given additional useful information on the timing of events related to pairing, chiasma formation and genetic recombination (ABEL 1965, 1968; PEACOCK 1968).

A second area of progress involves the study of mutations affecting the meiotic process and spore or sperm maturation. One of our speakers will bring us up to date on the progress with yeast as the experimental material. In another symposium later this week LINDSLEY and SANDLER (1974) will report on mutants affecting the meiotic process in Drosophila. The genetic dissection of many processes has been fruitful in the past, and its use with the very complex and difficult meiotic system is certainly promising.

The elegant micromanipulations of chromosomes in living cells which BRUCE NICKLAS will describe for us has given new insight into problems of segregation and other chromosome movements during meiosis. The games he and his colleagues play with chromosomes are not only instructive, but highly amusing, and verify in a very dramatic way the fun associated with innovative research. Another approach to chromosome movements and pairing that has been interesting and instructive has come about through the use of the allopolyploids available to us in the cultivated wheats. Here a genetic control of segregation has been localized to a particular component of the genome and its usefulness will be described today by RALPH RILEY.

In spite of all these promising leads, three central problems which were delineated and appreciated many years ago are still with us, namely (1) the mechanism of homologous pairing in zygotene; (2) the mechanisms of chiasma formation and crossing over; and (3) the basis of segregation, i.e., the affinity of sister chromatids after diplotene, the terminalization of chiasma and the affinity of homologous chromatids and the related manipulations of bivalents characteristic of the first meiotic division.

I will only remind you that meiosis is still a potential battleground where dead

hypotheses litter the field or rest uneasily in shallow graves, ready to emerge and haunt any conscientious scientist who tries to consolidate a victory for any particular thesis. However, today we may do just that; we zero in on several of these old problems. I do not presume to give any clues or steal any thunder from our speakers, although I dare say it is unlikely that any of these old ghosts can be laid to rest forever.

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