SOME OBSERVATIONS ON THE STUDY OF THE GENETIC CONTROL OF MEIOSIS IN *DROSOPHILA MELANOGASTER*[1]

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TO date, the genetic dissection of meiosis in Drosophila has involved the collection and analysis of mutants that adversely affect the fidelity of the meiotic process—that is, mutants that result in the production of a chromosomally abnormal population of gametes. The array of meiotic mutants recorded in *D. melanogaster* now involves 40 loci and includes genes influencing the rate of recombination, the distribution of exchanges along the chromosome, recombination in males, the regularity of homologous centromere separation at anaphase I, the regularity of sister centromere separation at anaphase II, the ability of chromosomes to move to the anaphase poles, and the behavior of chromosomes in gametes and immediately upon fertilization.

The selection of meiotic mutants by criteria of impaired fidelity implies certain biases in the kinds of mutants that are studied and in the kinds of meiotic processes that can be examined. In the first place, in order to be detected a meiotic mutant must be viable and fertile. This excludes the serious impairment of any function that meiosis shares with mitosis (e.g., spindle formation) and also excludes the abolition of any meiotic event necessary for the completion of meiosis or gametogenesis. Secondly, because a meiotic mutant must be conveniently analyzable by cytogenetic techniques, polygenic effects (although frequently encountered) and single-gene effects of very small magnitude have not been investigated.

Despite these limitations, meiotic mutants are relatively easy to find. Thus, among 118 second and third chromosomes collected from natural populations, 15 mutants that affected meiosis in females were recovered (SANDLER *et al.* 1968), one such mutant was recovered from among 30 second and third chromosomes treated with EMS (SANDLER 1971), and 11 meiotic mutants affecting females were recovered among 209 EMS-treated X chromosomes (BAKER and CARPENTER 1972). To these may be added the fortuitous recovery over the years of ten cases starting with the first meiotic mutant observed, *c(3)G* (GOWEN and GOWEN 1922).

TABLE 1

The female meiotic mutants of Drosophila melanogaster

Mutant*	Location	Major phenotype†		Major references‡
		Exchange	Nondisjunction	
mei-9, mei-9b	1-5	decreased	increased AI	BAKER and CARPENTER (1972)
mei-38	1-(not located)	normal or lower	increased AI	BAKER and CARPENTER (1972)
mei-41, mei-195	1-(not located)	decreased	increased AI	BAKER and CARPENTER (1972)
mei-99	1-(not located)	normal or lower	increased AI	BAKER and CARPENTER (1972)
mei-160	1-(not located)	normal or lower	increased AI	BAKER and CARPENTER (1972)
mei-218	1-57	decreased	increased AI	BAKER and CARPENTER (1972)
mei-251	1-(not located)	decreased	increased AI	BAKER and CARPENTER (1972)
mei-352	1-(not located)	decreased	increased AI	BAKER and CARPENTER (1972)
nod	1-36	normal	increased AI	BAKER and CARPENTER (1972); CARPENTER (1973)
mei-B	2-(not located)	decreased	not tested	BRIDGES (1929); LINDSLEY et al. (1968)
mei-S332	2-95	normal	increased AII	SANDLER et al. (1968); DAVIS (1971)
mei-L1	2-(not located)	decreased	increased	LINDSLEY and PEACOCK (unpublished)
mei-W68	2-(not located)	abolished	increased	BAKER (unpublished)
abo	2-44	decreased	increased AI	SANDLER et al. (1968); MANGE and SANDLER (1973)
mei-S282b	2-(not located)	increased	not tested	SANDLER et al. (1968); PARRY (1973)
mei-S282	3-5	decreased	increased AI	SANDLER et al. (1968); PARRY (1973)
mei-T3	3-(not located)	not tested	increased	SANDLER et al. (1968)
c(3)G17, c(3)G68, mu	3-57	abolished	increased AI	GOWEN (1933); HALL (1972)
cand	3-100	normal or lower	increased AI	STURTEVANT (1929); DAVIS (1969)
mei-S332b	3-(not located)	increased	not tested	SANDLER et al. (1968); LINDSLEY et al. (1968)
mei-S51	2-3-(synthetic)	decreased	increased AI	SANDLER et al. (1968); ROBBINS (1971)

* Not listed are the case of eq (SHULTZ, 1934), two only partially resolved mutants reported by SPIELER (1963), eight similarly incompletely analyzed cases reported by SANDLER et al. (1968), and a putative temperature-sensitive case reported by WRIGHT (1973).

† Applies to all the chromosomes in the complement.

‡ The review by BAKER and HALL (in press) considers most of these mutants in detail; general discussions of many of them are found in NICOLETTI (1968) and LINDSLEY et al. (1968).

Although easily obtained and relatively numerous, the number of loci detectable by these methods is probably exhaustible because among the 37 mutants here enumerated, there are two X-linked loci with two mutant alleles each (BAKER and CARPENTER 1972) and c(3)G with at least two (HALL 1972) and possibly three (GREEN 1970) mutant alleles. A list of meiotic mutants affecting females in Drosophila is given in Table 1 along with the map position, gross effects and major references for each.

In contrast to meiotic mutants affecting the female, mutants affecting the fidelity of meiosis in the male are relatively rarely detected. Thus in tests of magnitude comparable to those discussed above, only four mutants representing three loci have been obtained, to which may be added three loci collected fortitously. In addition, BAKER and CARPENTER (1972) report recovering some twenty chromosome-specific X-linked mutants all with essentially the same phenotype.

The absence of crossing over in Drosophila melanogaster males suggests that conclusions about meiosis in males are of less general interest than those concerning the more conventional meiosis in females; consequently we will confine our attention to genes controlling female meiosis. A discussion of meiotic mutants in Drosophila males will be found in the review of BAKER and HALL. It is, nevertheless, of interest that in Drosophila ananassae, a species closely related to D. melanogaster, meiotic crossing over does take place in males. HINTON (1970 and personal communication) has shown that the capacity for crossing over is under the control of at least three loci for which natural populations are polymorphic. Males that are homozygous for recessive alleles at two of these loci and carry at least one dose of the dominant allele of the third locus produce levels of crossing over on the order of one-tenth that observed in females; other genotypes produce little or no crossing over in males and all genotypes produce comparable levels in females.

The array of effects produced by female meiotic mutants suggests that the genetic controls of meiosis and mitosis differ mainly or exclusively in those (perhaps relatively few) genes that are involved in the meiosis-I-specific events of pairing, meiotic exchange and separation of homologs. The lines of supporting evidence are five. (1) All existing meiotic mutants in fact affect only meiotis-I-specific events. (2) The only meiotic mutant, c(3)G, examined for mitotic crossing over eliminates meiotic exchange but does not affect mitotic recombination (LE CLERC 1946). (3) Meiosis in males differs from meiosis in females apparently primarily or only in meiosis I and all the meiotic mutants except mei-S332 affect only one sex. (4) The exception, mei-S332, results in the precocious separation of sister centromeres in meiosis and consequent equational nondisjunction in both sexes; it is therefore, an abnormality in a process unique to meiotic anaphase I that occurs in both sexes—that is, only in that division do sister centromeres regularly fail to separate. (5) Abolition of meiotic processes shared by the two sexes should often be detected as single mutations that result in sterility in both sexes; such mutations, however, are very rare or nonexistent (LINDSLEY and LIFSCHYTZ 1972) suggesting that meiotic processes shared by both sexes also affect mitosis and are therefore lethal.

We now consider the genetic control of these events, peculiar to meiosis I in females, revealed by meiotic mutants. The first generality we may note is that when a meiotic mutant results in a decrease in recombination—that is, in an increase in the frequency of tetrads that have not undergone exchange—then those no-exchange tetrads exhibit irregular segregation characterized by frequent nondisjunction and chromosome loss. It is likely, however, that the irregular segregation is the consequence of the normal controls of disjunction acting in the anomalous circumstance of reduced recombination, and that, therefore, recombination-defective meiotic mutants can each be characterized by a single lesion in the control of meiosis.

Evidence for this is that the irregular segregation associated with these meiotic mutants shares the following characteristics with that observed in nonmutant genotypes in which recombination is mechanically restricted by structural heterozygosity: (1) irregular segregation is confined exclusively or almost exclusively to no-exchange tetrads; (2) nondisjunction occurs at the first meiotic division; (3) no-exchange nonhomologous chromosomes disjoin from one another at anaphase I—that is, the simultaneous nondisjunction of nonhomologous chromosome pairs is not independent but rather exhibits the size-dependent pattern of separation expected from a normally functioning distributive system. The distributive system (see GRELL 1969 for a review) is defined as the mechanism responsible for the disjunction at anaphase I of chromosomes that have not undergone exchange. It is special in that disjunctional partners are chosen not on the basis of sequence homology but on the basis of size similarity. Thus, no-exchange nonhomologous chromosomes of similar size can disjoin from one another regularly at the first meiotic division.

If recombination-defective meiotic mutants can each be characterized by a single lesion in exchange, then we may inquire how they can be functionally subdivided. So far, four criteria have emerged. First, recombination can be either increased or decreased. Only decreases in exchange have been adequately studied. Second, the decrease in exchange can be uniform along a chromosome arm or nonuniform. When the decrease is nonuniform, it is observed that it is always most marked distally; exchange in the most proximal regions often approaches or exceeds control values. The basis of this particular nonuniformity is as yet only speculative. Third, variations in exchange may or may not be accompanied by changes in the coefficient of coincidence, a measure of the relative frequencies of tetrads with no, one, or more than one exchange. Finally, fourth, some recombination-defective meiotic mutants abolish the response to the interchromosomal effect on exchange, some exhibit an interchromosomal effect, and in one case the interchromosomal effect is strikingly accentuated. The term interchromosomal effect (see LUCCHESI and SUZUKI 1968 for a review) describes the observation that structural heterozygosity in one chromosome pair is associated with changes, usually increases, in the amount of recombination in other chromosome pairs. This increase in recombination is most marked in proximal regions and is usually accompanied by an increase in the coefficient of coincidence.

Following an argument of BRIDGES (1915), it would seem possible to employ

the coefficient of coincidence to separate mutants affecting exchange preconditions (such as the establishment of synapsis) from mutations affecting the probability of the exchanges themselves. A change in one or more preconditions for exchange should influence both the amount of recombination and the coefficient of coincidence, while a change only in the probability of exchange itself would influence the amount of recombination but leave the coefficient of coincidence unaltered. By this criterion, only the meiotic mutants *mei-9* (BAKER and CARPENTER 1972) and *abo* (MANGE and SANDLER 1973) appear to affect exchange directly. Of these two mutants, at least *abo* responds to the interchromosomal effect, while among the others there is at least one insensitive, and one extra-sensitive example. Thus far, therefore, there are three distinguishable categories of recombination-defective meiotic mutant in *D. melanogaster* females: exchange mutants, precondition mutants insensitive to the interchromosomal effect and precondition mutants that respond to the interchromosomal effect.

If this conclusion is correct, however, there are two preplexing observations. First, as the fourth chromosomes do not normally undergo exchange and yet disjoin regularly, even in cells in which some other pairs of chromosomes have failed to undergo exchange (GRELL 1969), fourth-chromosome disjunction should be normal in exchange mutants but could be abnormal in precondition mutants (NOVITSKI 1964). In fact, all recombination-defective mutants so far investigated produce frequent fourth-chromosome exceptions. This implies that recombination-defective meiotic mutants are more complex than here considered, or that they all interfere with the establishment of preconditions or that our understanding of the rules governing the distributive system (that is, the segregation of chromosomes in the absence of exchange) is incomplete. Secondly, following the argument of BRIDGES that interference is a consequence of constraints operating in the establishment of the conditions for exchange, one might expect that mutations that further constrain the establishment of such conditions would reduce coincidence and recombination concomitantly. The observation is that those recombination-defective mutants which have been shown to affect coincidence exhibit increased coincidence. It is difficult to imagine how a precondition mutant can have effects of opposite sign on these two parameters; however, discordant responses of coincidence and recombination have also been observed with maternal age and heterozygosity for heterologous inversions (RENDEL 1958) and BAKER and HALL imply a rationalization based on mutant effects on the spatial distribution of exchanges. It seems likely that some mutants could reduce the activity of components of the meiotic phenotype to the point where meiosis becomes extremely sensitive to variations in both the internal and external environment; in these mutants intercellular heterogeneity will lead to the correlated occurrence of abnormal meiotic events in the least normal cells and of normal meiotic events in the most nearly normal cells in the population. The correlated occurrence of exchanges could lead to inflated estimates of coincidence; however, in one case where this possibility was explicitly tested (PARRY 1973), the results were negative.

Turning now to disjunction, the meiotic mutants that adversely affect the

fidelity of segregation but do not affect recombination frequencies make possible several inferences about the genetic control of the separation of homologous chromosomes in meiosis I. First, and most straightforward, is the case of *mei-S332* described above. This appears to be a gene whose wild-type function is to prohibit the equational separation of centromeres at anaphase I. It may well be that this is the latest meiotic process that can be studied by the methods employed thus far.

Secondly, it seems clear that an exchange is not a sufficient condition, even given a normal mitotic apparatus, for effecting meiotic disjunction. Thus, in some cases under the influence of *nod*, and very often under the influence of ca^{nd}, recombinant chromosomes segregate abnormally.

Thirdly, it now appears that the distributive system is under genic control that is partially, if not entirely, separable from the genetic control of the separation of homologs that have undergone exchange. In particular, the meiotic mutant *nod* is defective in distributive disjunction but not, at least to any great extent, defective in the process of disjunction of exchange homologs. This same mutant permits the inference that distributive disjunction has at least two components—the establishment of a plane of separation that is independent of *nod*, followed by the actual separation itself which requires nod^+ (CARPENTER 1973).

Finally, one of the characteristics of the distributive system is the recognition of disjunctional partners on the basis of similarity in overall chromosome size. The meiotic mutant *mei-S51*, while genetically complex, seems at the least to involve a defect in the process whereby chromosomes that will disjoin distributively recognize one another.

It is expected that additional mutants detected by those criteria already used and the further analysis of such mutants along the lines described here will be important in further specifying the nature of the genetic control of pairing, recombination, and the disjunction of homologs. It seems, however, worthwhile inquiring about ways in which the resolution of the genetic control of meiosis might be expanded beyond the limits inherent in the methods used thus far.

One class of meiotic mutant that would increase our range of inquiry and that could be detected with only minor changes in technique has been found among mutants affecting meiosis in the male but has not yet been recovered among meiotic mutants with effects in the female. This is a class of mutation with normal meiotic control signals but abnormal responding sites. In females they should differ from the meiotic mutants discussed above in that they should result in anomolous meiotic behavior only of the chromosome or chromosome region in which they are located. Indeed, in Neurospora the recessive allele *cog* has been interpreted as this kind of defect (ANGEL, AUSTIN and CATCHESIDE 1970); the level of recombination in the *his-3–ad-3* interval, which is under the control of the unlinked locus *rec-2*, responds to the *rec-2* constitution only when the interval carries cog^+ in at least one of the homologous chromosomes.

A second, and ultimately perhaps the most important, extension of our understanding of the genetic control of meiosis should come from combining results from different organisms, utilizing the special technical advantages of each. While combining results from different forms is always a hazardous procedure,

the cytological similarities in meiosis in most organisms provide a morphological basis for comparing different forms and suggest that meiosis, and by inference its genetic control, is evolutionarily conservative so that reasoning from organism to organism in this instance may be more helpful than confusing. Thus, a fraction of fungal mutants defective in sporulation can be expected to affect meiotic processes; for example, BRESCH, MÜLLER and EGEL (1968), report the isolation of a number of sporulation-defective mutants in *Schizosaccharomyces pombe*, some of which interfere with meiosis but do not affect mitosis. Similarly, among some 40 conditional sporulation-defective mutants reported by SIMONET and ZICKLER (1972) in Podospora, five to eight loci affecting meiosis but not mitosis were identified. In these cases, as in Drosophila, a variety of meiotic anomalies are distinguished. ESPOSITO *et al.* (1970, 1972) have found several conditional mutants affecting meiosis in Saccharomyces; some of these have effects at stages earlier than would be detectable by the methods utilized in Drosophila. HARTWELL, CULOTTI and REID (1970) have collected a large number of conditional mutations that interrupt the yeast cell cycle. Some of these most probably will be defects in processes shared by mitosis and meiosis—processes that have not yet been amenable to study in Drosophila. To these examples of systematic mutant collections may be added the many fortuitous discoveries of meiotic mutants that have been reported in a variety of species, especially in higher plants. Unfortunately, because of space limitations, they cannot be enumerated here; for reviews see, for example, RILEY (1966) and TAYLOR (1967).

A third approach, currently under investigation by B. S. BAKER and by E. LIFSCHYTZ (personal communication), is the collection of conditional mutations affecting mitosis in Drosophila. The idea here is to examine the genetic control of those meiotic events shared in common with mitosis. This should be possible if the mitotic divisions are allowed to occur under permissive conditions (thereby achieving viable individuals) and the meiotic divisions examined under restrictive conditions. Indeed, as a possible example, WRIGHT (1973) reports a cold sensitive sex-linked zygotic lethal that may also be a meiotic mutant.

Finally, it seems likely that mutations affecting the fidelity of meiosis that are different from the types already collected could be obtained by using selective criteria other than anomalies in recombination and segregation. Thus, for example, mutations affecting the meiotic stability of abnormal chromosomes such as rings might provide new insights into the genetic control of replication and recombination. It is, in fact, known that the meiotic mutant, *c(3)G*, results in a reduced transmission of ring-*X* chromosomes (SANDLER 1965). Additional examples of criteria that might be applied are the behavior of anaphase bridges, the disjunction of asymmetric dyads and the anaphase separation of wholly heterochromatic elements.

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