Genet. Res., Camb. (1970), **15**, *pp.* 55–64
With 3 text-figures
Printed in Great Britain

Gene conversion: observations on the DNA hybrid models

By ANDRZEJ PASZEWSKI

Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, ul. Rakowiecka 36, *Poland*

(*Received* 17 *July* 1969)

SUMMARY

Some features of gene conversion in fungi and their bearing on the hybrid DNA models are discussed. Available experimental data from tetrad analysis seem to give a more complex picture of polarity in intragenic recombination and of the relations between conversion and postmeiotic segregation, and between conversion and crossing-over, than predicted by the models.

A new hypothesis of the mechanism of gene conversion with special attention given to the aspect of asymmetry in this phenomenon is proposed as an alternative to the mechanism suggested by the DNA hybrid models.

Whitehouse (1963), Holliday (1964) and Hastings & Whitehouse (1964) proposed models of genetic recombination which postulated a common mechanism for both conversion and crossing-over. During the past few years evidence has been accumulated which gives support to many predictions of these models and is not compatible with the 'switch' model developed earlier by Freese (1957) and its later modifications. (1) It has been shown that meiotic DNA replication is semi-conservative (Taylor, 1965; Chiang, Kates & Sueoka, 1965). (2) Rossen & Westergaard (1966) found that the round of DNA replication in the fungus *Neottiella rutilans* occurs prior to the nuclear fusion in the crozier, which indicates that recombination takes place after the main synthesis of DNA. (3) It was found that conversion like crossing-over occurs in both chromatids of a chromosome at random (Paszewski, 1967). (4) Conversion has been shown often to be correlated with the exchange of flanking markers, this constituting an argument for the common mechanism of both types of recombination. (5) Esposito (1968) found that intergenic and intragenic (mainly non-reciprocal) recombinations in yeast were influenced in a similar way both by u.v. radiation and by X-rays. This suggests that conversion and crossing-over share an event in common. (6) A mechanism of the dark repair of damage in DNA caused by u.v. irradiation (Setlow & Carrier, 1964; Boyce & Howard-Flanders, 1964; and others) is a plausible explanation for the homozygotization of heterozygous sites postulated by the models.

There are, however, data which are not easily accounted for by these models and their later versions (Whitehouse, 1966, 1967; Emerson, 1966). According to the

models one should observe reciprocal conversions fairly often and this is not the case. The hypothesis of hybrid DNA formation as an intermediate in gene conversion, besides its many unproven assumptions, does not seem necessary for the interpretation of most of the data. It seems that the relation between conversion and postmeiotic segregation is much more complex than predicted by the models (hereafter the term conversion is used to describe recombinations resulting in 2:6 and 6:2 ratios and the term postmeiotic segregation for all other types of aberrant segregation). Furthermore, experimental data accumulated during recent years suggest that the concept of polarization in intragenic recombination and of a relation between conversion and crossing-over should be revised.

These questions are discussed below. Data from tetrad analysis will be predominantly considered here, as they give most information about the pattern of recombination and leave a minimum of 'degrees of freedom' for interpretation.

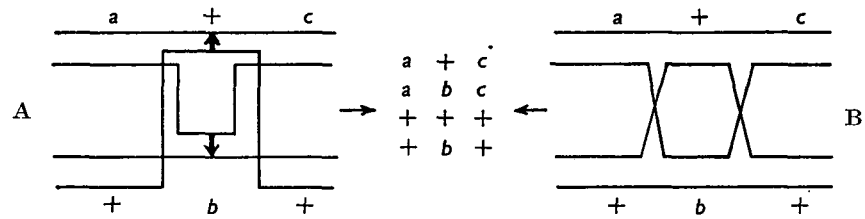

Fig. 1. Possible origins of a tetrad from a cross $a+c \times +b+$ with the central marker recombined. In scheme A it is shown that two conversions in opposite directions, possibly occurring independently, may involve all four chromatids (arrows link the pairs of chromatids which interreact and show the direction of conversion). The result is the same as for 'classical' two-strand double crossing-over which is represented by the scheme B.

Reciprocal conversions should be observed as a consequence of hybrid DNA formation at a mutant site in two recombining chromatids and corrections of mispairing in opposite directions. This should be the case especially when the mutants used show conversions equally often in both directions—that is, from mutant allele to the wild-type allele and vice versa. Actually such events occur very rarely. A few asci were found in series 75 of white-spored mutants of *Ascobolus immersus* (Rossignol, 1967), which might have resulted from two conversions in opposite directions. No such asci were found in the series *84W* in the same organism (Paszewski & Prażmo, 1969). Some recombinations observed by Fogel & Hurst (1967) can be interpreted as reciprocal conversion, but two-strand double crossing-over is equally possible in this case. It should be noted that in two conversions in opposite directions more than two chromatids may be involved; thus the events described as reciprocal conversion may in fact not be reciprocal in the same sense as in two-strand double crossing-over (Fig. 1). The rare occurrence of tetrads such as are shown in the figure in intragenic three-point crosses may be due either to the rare formation of hybrid DNA at a mutated site as assumed in DNA hybrid models or to the necessity of occurrence of two recombination 'cycles'

(scheme A represents such a possibility). The second interpretation should be considered as a possible explanation of reciprocal conversions as there is evidence that more than two chromatids may be involved in intragenic recombination. The situation represented by scheme B is not likely to occur if *a*, *b* and *c* are alleles but has to be taken into account when *a* or *c* is a flanking marker.

Whitehouse & Hastings (1965) assumed that hybrid DNA may occasionally form at a given site only in one chromatid, so that conversion could be only non-reciprocal in such cases. In view of the rare occurrence of reciprocal conversions such a situation was considered later (Whitehouse, 1967) to be regular rather than exceptional.

Simultaneous conversions at three sites in one direction were observed in several asci in *Ascobolus* (Rossignol, 1967; Paszewski & Prażmo, 1969) but no reciprocal conversion for any site was found in these asci. This would mean that the length of the hybrid DNA in the two chromatids involved must differ considerably. However, as we have pointed out previously (Paszewski & Prażmo, 1969), it would be very difficult to explain this difference if the primary events occurred symmetrically in both chromatids as is postulated in the models.

There are difficulties connected with the hypothesis of 'repair' of mismatched bases in the hybrid DNA. According to the models, whenever the site of a mutation lies within the hybrid DNA region mispairing of bases will result. Such heterozygosity, if not modified, leads directly to postmeiotic segregation. A repair mechanism which removes the mispairing restores either a normal or a mutated condition. If repair proceeds in the same direction in two chromatids, conversion is observed. The postulated mechanism of repair would be similar to that involved in excision of thymine dimers and filling of the gaps in single DNA strands with new bases. However, there is no chemical and structural analogy between thymine dimers and mismatched bases in hybrid DNA, mainly because the former involve only one strand of the double helix and the latter both strands.

Moreover, in the case of single-pair differences, especially if mutations are of the transition type, there is no obvious chemical and structural reason for the occurrence of 'stress' in the double helix leading to the excision of one or both of the mismatched bases. It would be easier to imagine greater disturbances in the DNA structure in hybrid DNA in the case of deletion mutants. However, there is nothing characteristic in their recombinational behaviour that could distinguish them from mutants having short deletions or possibly point mutations (Mousseau, 1967; Rossignol, 1967). It is interesting that the same was true in the case of multipoint crosses involving mutants in the rII locus of bacteriophage T_4 (Doermann & Parma, 1967).

The existence of mutants having an impaired system for dark repair of damage caused by u.v. irradiation and being also unable to recombine suggests that the same enzymes may be involved in some stages of both processes, but not necessarily in the excision of mismatched bases (Howard-Flanders, 1968; Tuveson, 1969).

Recombination in phages can proceed by the breakage and reunion mechanism

(Meselson & Weigle, 1961). The joining of broken DNA molecules occurs in two phases (Tomizawa, 1967). First, a heterozygous overlap by single-stranded ends is formed (Fig. 2, I) and the molecules are held together by hydrogen bonds within the overlap. Secondly, the gaps in the single strands are 'patched' and the ends are joined by covalent bonds (Fig. 2, II). Meselson (1967) suggested that the processes just described can account for both conversion and postmeiotic segregation. This hypothesis could only explain conversion associated with crossing-over, and yet reciprocal conversions should be often observed. However, in this hypothesis the excision processes remove terminal portions of the polynucleotide chains during the course of breakage and joining. Thus it is an *exonucleotic* and not *endonucleotic* excision as in the repair hypothesis of the models. If a mismatched base pair happens to lie in the region of the primary overlap (Fig. 2, I) it most probably remains in the heterozygous state, although there is a possibility that some kinds of heterozygosity are repaired (Hogness, Doerfler, Egan & Black, 1966).

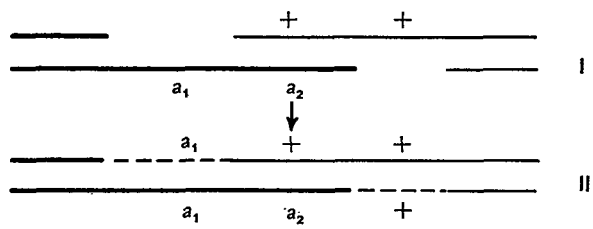

Fig. 2. Two stages in joining of DNA molecules derived from different parents. Repair synthesis of DNA (broken lines) restores the homozygous state at the two sites; the third site (a_2) remains heterozygous.

Postmeiotic segregation, in general, is a rather rare phenomenon and it is evident in cases where a number of alleles were taken for investigation that this segregation is mutant-specific (Stadler & Towe, 1963; Fields & Olive, 1967; Emerson & Yu-Sun, 1967; Gajewski, Paszewski, Dawidowicz & Dudzińska, 1968). In *Ascobolus immersus* (Rizet's strain) at least 86 mutants from six loci were utilized in intragenic recombination studies by tetrad analysis, and only four of them showed postmeiotic segregation. In the case of two of these mutants, which belong to series *46*, it was found that, relative to conversion, postmeiotic segregation was rarer in two-point crosses than in one-point (Gajewski *et al.* 1968). It would seem that the same is true in the case of a series of hyaline mutants of *Sordaria brevicollis* (Fields & Olive, 1967), although the frequencies of basic conversion, e.g. in crosses with the wild type, were only roughly estimated. These results cannot be explained if the only difference between conversion and postmeiotic segregation was due to repaired and non-repaired heterozygous DNA, respectively.

Kitani (1962) and Kitani, Olive & El-Ani (1962), studying conversion within the *g* locus in *Sordaria fimicola*, observed that postmeiotic segregation was much more strongly correlated with exchange of outside markers than was conversion.

All these facts suggest that conversion and postmeiotic segregation, while probably sharing some events in common, differ much more than is postulated by

the DNA hybrid models; and it seems doubtful whether the hypothesis of homozygotization is really necessary for the interpretation of recombination data. The mechanism suggested by Meselson (1967) seems to provide a better starting-point in the attempt to explain the origin of postmeiotic segregation.

An important feature of intragenic recombination is its polarity; i.e. alleles situated proximally to one end of a gene or its region convert in two-point crosses more frequently than those situated distally. It appears that, in most of the studies where many alleles were used, polarization was only tentative, in some loci it was not observed at all, or its pattern was very complicated. It is very difficult to make any generalization concerning this phenomenon when data from different loci are compared (Murray, 1963, 1969; Stadler & Towe, 1963; Case & Giles, 1964; Rossignol, 1964, 1967; Fields & Olive, 1967; Fincham, 1967, Fogel & Hurst, 1967; Mousseau, 1967; Paszewski & Prażmo, 1969).

Polarization may result from differences in the basic conversion frequencies of the mutants used (that is, conversions observed in one-point crosses), from the relative situations of the mutated sites or from both. Thus, a knowledge of the basic rates of conversion for the mutants studied seems necessary before making any useful interpretation of the polarization observed. The knowledge of these values will in many cases make the phenomenon of 'marker effect' less mysterious.

According to the models, polarization is a consequence of the occurrence of primary breakages in DNA in special sites (fixed opening points). It is very likely that a specific sequence of the bases in DNA plays an important role in this process as was suggested by Holliday (1967), although localization of sites having such a sequence within a gene is not clear. Whitehouse (1966) devised an 'operator' model in which the ends of genes are considered to be the points of first breakages of DNA. Besides some difficulties with this model discussed by Holliday (1967), a considerable amount of data in the papers cited above points to the possibility that primary breakages can occur just as readily in the central parts of genes. Thus, it seems that to consider the ends of a gene as the points of primary breakage is not justified on the basis of the available data.

The specific sequences of bases should be regarded, in view of experimental data, as points of *preferential* breakage of DNA, rather than as *fixed* opening-points. Besides the distance of mutated sites from such points there are most probably other parameters which determine polarity, like mutant specificity and mutual relation of a *given* pair of mutants, to mention only two. As values of these parameters are variable, the pattern of polarity—that is, direction and degree—is better described by a *function* rather than by a 'model'. Values of the parameters are characteristic for every pair of alleles, although there may exist similarities in the patterns for different pairs of alleles, especially when one parameter—for instance, the distance from the point of preferential breakage—has a predominant bearing on the pattern.

It is very likely that enzymic degradation of DNA proceeds in opposite directions in the two strands of the double helix owing to their opposite polarization. Thus, if primary breakages within a gene occur predominantly in the same strand,

unidirectional polarization of recombination is to be expected. If primary breakages occur in both strands, a more complicated picture should be expected. Possibly mutants causing disturbances in the polarization pattern may create a new point of breakage, or cancel such a point, or change the strand which breaks.

Finally we should consider the relationship between conversion and crossing-over. There are numerous data showing a correlation between conversion and crossing-over; i.e. conversion within a gene is often associated with an exchange of outside markers. This correlation usually does not exceed 50% and is often much lower, which means that conversion may occur without crossing-over. Rizet & Rossignol (1966) carried out three-point intragenic crosses in *Ascobolus* and found that reciprocal exchange between outside sites was often associated with conversion at the middle site. In other words, they observed what is often called inexactly reciprocal crossing-over. These results strongly suggest that every crossing-over is associated with conversion over a shorter or longer length of a chromosome. This association is not detectable when conversion occurs in an unmarked region, and so with increasing distance between sites its manifestation becomes rare.

If this is true, it seems very likely that there is a sequence of events leading to gene conversion which is necessary but insufficient to accomplish crossing-over. In other words, the primary events in both types of recombination are identical. Non-reciprocality of conversion, discussed earlier, strongly suggests that these events are *asymmetrical* with respect to the two chromatids involved in the recombination. This is in contradiction with the DNA hybrid models, which assume a symmetry of these events, which probably are: breakages of polynucleotide strands, their partial degradation and their unwinding.

The data from experiments with *Ascobolus* clearly show that, with increasing distance of mutated sites within a gene, the relative frequency of crossing-over usually increases, that crossing-over may occur in more than one region of a gene and that sometimes its appearence or frequency depends on mutant specificity. On the other hand, recombination between complementing mutants from neighbouring loci can be both of the conversion and of the crossing-over type, and, as with non-complementing mutants, simultaneous conversions in two sites involved are frequent (Case & Giles, 1964; Paszewski, 1967). Thus, it does not look as if there exist different mechanisms for intragenic and intergenic recombination, and there is no need for postulating a special kind of intragenic crossing-over (Whitehouse, 1967).

CONCLUSIONS

On the basis of the available data it appears that two features of gene conversion and possibly crossing-over are relatively well established. They are that (1) a limiting amount of DNA must be synthesized, and (2) the process is asymmetrical with respect to the way the two chromatids are involved.

Conversion of deletion mutants to their wild-type alleles provides a direct proof for the first statement (Rossignol, 1967; Mousseau, 1967). Zimmermann (1968) showed that, when respiratorily deficient yeast cells are treated with mutagens

inducing lesions in DNA and kept for some time in buffer deprived of energy, the number of potential convertants increases. This can be shown by transferring the cells to the medium selective for convertants and containing glucose which can be utilized by the cells. These data suggest that degradation of DNA is a primary step to gene conversion and a limiting synthesis of DNA (which needs energy) is necessary to accomplish the process.

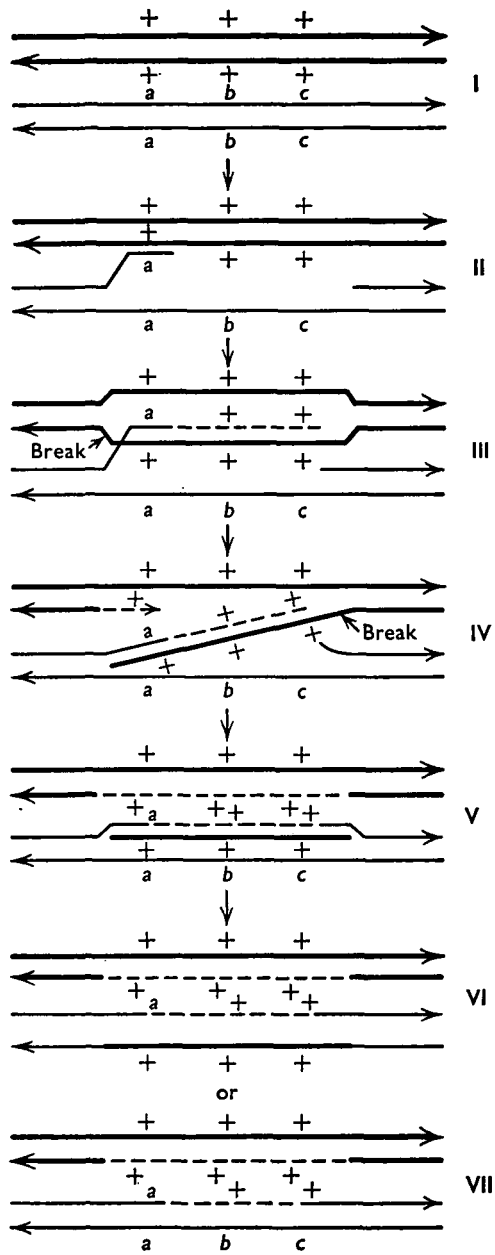

Fig. 3. Possible stages in gene conversion. Only two out of four chromatids are represented. See text for explanation.

https://doi.org/10.1017/S0016672300001373 Published online by Cambridge University Press

The second statement is based on the fact of the rarity of reciprocal conversions, both in cases when only conversion occurs and when it is associated with crossing-over.

It seems that many of the data concerning intragenic recombination could be more easily explained without postulating the formation of hybrid DNA at a mutant site as an intermediate, or at least limiting its participation in gene conversion to some cases. One can assume that recombination starts by breakage of a single strand in the DNA double helix, followed by its partial degradation and unwinding (Fig. 3, II). In consequence a strand with a free end is formed. This free end during chromosome conjugation triggers off an involvement of the homologous chromatid in recombinational processes, causing partial separation (possibly with immediate breakage) of its two strands. One of these strands serves as a template for the repair-type replication (Fig. 3, III) of the partly degraded strand. Then the template strand breaks (Fig. 3, IV) and a fraction of it is transferred to the first (recipient) chromatid, where a transitional three-strand structure is formed (Fig. 3, V). One of the two strands—that is, the 'borrowed' one or the old one (this alternative rather would be supported by experimental data)—must be degraded on the length of the triple structure, and then the ends of the polynucleotic strands are joined by a ligase-type enzyme. The gap in the donor chromosome is repaired by the normal repairing system (Fig. 3, VI). It is shown in the figure that on a certain length of a chromatid a hybrid DNA is formed, so it is possible to account for postmeiotic segregation at some sites. The configuration in Fig. 3 (IV) may be resolved in different ways than is shown, but they will not be discussed as the aim of this scheme is to show a line of argument rather than to provide a new model for recombination.

The scheme given above resembles in many aspects that proposed by Taylor (1967). The main difference is that Taylor assumes a delay in replication of a small portion of DNA, whereas here a degradation of DNA is preferred. Besides, Taylor assumes that meiotic DNA replication has some peculiarities. If in other fungi replication of DNA takes place before karyogamy as in *Neottiella*, Taylor's hypothesis is not easily applicable to explain gene conversion in these organisms.

The mechanism suggested here for gene conversion differs from the DNA hybrid models mainly in that the repairing mechanism with 'single-strand copy-choice' leads directly to gene conversion without formation of DNA heterozygous at the mutant site, and it postulates an asymmetry in the primary recombinational events and unequal role played by two chromatids involved in this type of recombination. It seems worth noting that the recombinations observed by Doermann & Parma (1967) in multi-point crosses involving different rII mutants of phage T_4 very much resemble gene conversion in fungi. Although the authors interpreted them as double crossovers, they questioned the hypothesis that hybrid DNA is an intermediate in the formation of these crossovers. Although there is evidence that recombination in phages can proceed by a breakage and reunion mechanism, the existence of another mechanism, perhaps similar to that involved in gene conversion, is possible.

I wish to thank Professor W. Gajewski and Dr A. Putrament for valuable discussion and critical reading of the manuscript.

After ending this text I encountered a recently published model for gene conversion by F. Stahl (*Genetics* **61** (Suppl. 1), part 2, 1–13, 1969). This new, very interesting model and the hypothesis given here differ but they share two features, namely, they assume asymmetry in recombination and non-repairing of mismatched bases.

REFERENCES

Boyce, R. P. & Howard-Flanders, P. (1964). Genetic control of DNA breakdown and repair in *E. coli* K-12 treated with mitomycin C or ultraviolet light. *Z. VererbLehre* **95**, 345–350.

Case, M. E. & Giles, N. H. (1964). Allelic recombination in *Neurospora*: tetrad analysis of a three-point cross within the *pan-2* locus. *Genetics* **49**, 529–540.

Chiang, K. S., Kates, J. R. & Sueoka, N. (1965). Meiotic DNA replication mechanism in *Chlamydomonas reinhardi*. *Genetics* **52**, 434–435.

Doermann, A. H. & Parma, D. H. (1967). Recombination in bacteriophage T_4. *J. Cell Physiol.* **70** (Suppl. 1), 147–164.

Emerson, S. (1966). Quantitative implications of the DNA-repair model of gene conversion. *Genetics* **53**, 475–485.

Emerson, S. & Yu-Sun, C. C. C. (1967). Gene conversion in the Pasadena strain of *Ascobolus immersus*. *Genetics* **55**, 39–47.

Esposito, R. E. (1968). Genetic recombination in synchronized cultures of *Saccharomyces cerevisiae*. *Genetics* **59**, 191–210.

Fields, W. G. & Olive, L. S. (1967). The genetics of *Sordaria brevicollis*. III. Gene conversion involving a series of hyaline ascospore color mutants. *Genetics* **57**, 483–493.

Fincham, J. R. S. (1967). Recombination within the *am* gene of *Neurospora crassa*. *Genet. Res., Camb.* **9**, 49–62.

Fogel, S. & Hurst, D. D. (1967). Meiotic gene conversion in yeast tetrads and the theory of recombination. *Genetics* **57**, 455–481.

Freese, E. (1957). The correlation effect for a histidine locus of *Neurospora crassa*. *Genetics* **42**, 671–684.

Gajewski, W., Paszewski, A., Dawidowicz, A. & Dudzińska, B. (1968). Postmeiotic segregation in locus '46' of *Ascobolus immersus*. *Genet. Res., Camb.* **11**, 311–317.

Hastings, P. J. & Whitehouse, H. L. K. (1964). A polaron model of genetic recombination by the formation of hybrid deoxyribonucleic acid. *Nature, Lond.* **201**, 1052–1054.

Hogness, D. S., Doerfler, W., Egan, J. B. & Black, L. W. (1966). The position and orientation of genes in λ and λdg DNA. *Cold Spring Harb. Symp. quant. Biol.* **31**, 129–138.

Holliday, R. (1964). A mechanism for gene conversion in fungi. *Genet. Res., Camb.* **5**, 282–304.

Holliday, R. (1967). In *International Conference on Replication and Recombination of Genetic Material, Canberra.*

Howard-Flanders, P. (1968). DNA repair. *A. Rev. Biochem.* **37**, 175–200.

Kitani, Y. (1962). Three kinds of transreplication in *Sordaria fimicola*. *Jap. J. Genet.* **37**, 131–146.

Kitani, Y., Olive, L. S. & El-Ani, A. S. (1962). Genetics of *Sordaria fimicola*. V. Aberrant segregation at the *g* locus. *Am. J. Bot.* **49**, 697–706.

Meselson, M. (1967). The molecular basis of genetic recombination. In *Heritage from Mendel* (ed. R. A. Brink), pp. 81–104. University of Wisconsin.

Meselson, M. & Weigle, J. (1961). Chromosome breakage accompanying genetic recombination in bacteriophage. *Proc. Natn. Acad. Sci., U.S.A.* **47**, 857–868.

Mousseau, J. (1967). Analyse de la structure fine d'un gène chez *Ascobolus immersus*. Contribution a l'étude de la recombinaison méiotique. Ph.D. thesis, University of Paris.

Murray, N. E. (1963). Polarized recombination and fine structure within the *me-2* gene of *Neurospora crassa*. *Genetics* **48**, 1163–1183.

Murray, N. E. (1969). Reversal of polarized recombination of alleles in *Neurospora* as a function of their position. *Genetics* **61**, 67–77.

PASZEWSKI, A. (1967). A study on simultaneous conversions in linked genes in *Ascobolus immersus*. *Genet. Res., Camb.* **10**, 121–126.

PASZEWSKI, A. & PRAŻMO, W. (1969). The bearing of mutant and cross specificity on the pattern of intragenic recombination. *Genet. Res. Camb.* (in the Press).

RIZET, G. & ROSSIGNOL, J. L. (1966). Sur la dimension probable des éxchanges réciproques au sein d'un locus complexe d'*Ascobolus immersus*. *C. r. hebd. Séanc. Acad. Sci., Paris* **262**, 1250–1253.

ROSSEN, J. M. & WESTERGAARD, M. (1966). Studies on the mechanism of crossing-over. II. Meiosis and the time of meiotic chromosome replication in ascomycete *Neottiella rutilans* Fr. Dennis. *C. r. Trav. Lab. Carlsberg* **35**, 233–260.

ROSSIGNOL, J. L. (1964). Phénomènes de recombinaison intragénique et unité fonctionnelle d'un locus chez l'*Ascobolus immersus*. Thesis, University of Paris.

ROSSIGNOL, J. L. (1967). Contribution à l'étude des phénomènes de recombinaison intragénique. Ph.D. Thesis, University of Paris.

SETLOW, R. & CARRIER, W. (1964). The disappearance of thymine dimers from DNA: an error-correcting mechanism. *Proc. Natn. Acad. Sci., U.S.A.* **51**, 226–231.

STADLER, D. R. & TOWE, A. M. (1963). Recombination of allelic cysteine mutants in *Neurospora*. *Genetics* **48**, 1323–1344.

TAYLOR, J. H. (1965). Distribution of tritium-labeled DNA among chromosomes during meiosis. I. Spermatogenesis in the grasshopper. *J. Cell Biol.* **25**, 57–67.

TAYLOR, J. H. (1967). Patterns and mechanisms of genetic recombination. In *Molecular Genetics*, vol. 2 (ed. J. H. Taylor), pp. 95–135. New York, London: Academic Press.

TOMIZAWA, J. (1967). Molecular mechanism of genetic recombination in bacteriophage: joint molecules and their conversion to recombinant molecules. *J. Cell Biol.* **70** (Suppl. 1), 201–214.

TUVESON, R. W. (1969). An evaluation of the relationship between ultraviolet sensitivity and crossing-over in bacteria and fungi. *Am. Nat.* **130**, 23–30.

WHITEHOUSE, H. L. K. (1963). A theory of crossing-over by means of hybrid deoxyribonucleic acid. *Nature, Lond.* **199**, 1034–1040.

WHITEHOUSE, H. L. K. (1966). An operator model of crossing-over. *Nature, Lond.* **211**, 708–713.

WHITEHOUSE, H. L. K. (1967). Secondary crossing-over. *Nature, Lond*, **215**, 1352–1359.

WHITEHOUSE, H. L. K. & HASTINGS, P. J. (1965). The analysis of genetic recombination on the polaron hybrid DNA model. *Genet. Res., Camb.* **6**, 27–92.

ZIMMERMANN, F. K. (1968). The effect of liquid holding on chemical-induced lethality and mitotic gene conversion in *Saccharomyces cerevisiae*. *Molec. Gen. Genetics* **103**, 11–20.