# GENE CONVERSION AND TRANSFER OF GENETIC INFORMATION WITHIN THE INVERTED REGION OF INVERSION HETEROZYGOTES[1]

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ABSTRACT

Prior studies of recombination which monitor exchange events in exceedingly short intervals (i.e., separable sites within a cistron) reveal that the basic event in recombination involves a non-reciprocal transfer of information, termed conversion. As a logical consequence of the model suggested by the work in Drosophila, the present investigation examined recombination between rosy mutant alleles (*ry*:3–52.0) in *Drosophila melanogaster* in a paracentric inversion ($In(3R)P_{18}$) heterozygote, which placed the rosy region approximately at the center of the inverted region. Comparison of the results of this study with experiments carried out in standard chromosome homozygotes reveals a dramatic suppression of classical crossovers between the rosy mutant alleles in the inversion heterozygote. However, conversions continue to occur for all rosy mutant alleles in all heterozygous combinations in the inversion heterozygote. Moreover, the order of magnitude of conversion frequencies seen in the inversion heterozygote does not change from that seen in the standard chromosome homozygote study. The significance of these observations with reference to the role of rearrangements as barriers of information transfer is discussed. Particular attention is directed to the elaborate inversion polymorphisms seen in natural populations, and to notions concerning their role in the evolution of adaptive gene complexes.

CLASSICALLY, transfer of genetic information from one chromosome to its homolog during meiosis in higher organisms is envisioned to occur by a reciprocal process, crossing over, which invokes the occurrence of breaks at identical sites on non-sister chromatids followed by an exchange of parts leading to the production of precisely reciprocal exchange products. Supported by a tremendous literature of linkage studies in many organisms, the dogma of crossing over has played a central role in transmission genetics as a major tool in mapping experiments, as well as in population genetics theory.

A critical test of the dogma of precise reciprocity of linked exchange would examine the resultant products of exchange events restricted to smaller and smaller genetic intervals. Just such experiments have been carried out in several fungi as well as in *Drosophila melanogaster*, and it is now clear that precise reciprocity of exchange is only an approximation of the facts. The Drosophila

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studies have been the subject of recent detailed review (CHOVNICK, BALLANTYNE and HOLM 1971). In addition to contradicting the notion of precise reciprocity, the results of this work point to a non-reciprocal transfer of genetic information as the primary event in linked exchange.

The present investigation stems as a logical consequence of the following features of the model of linked exchange which emerges from the Drosophila work: (1) Recombination arises as a consequence of the repair of single strand breaks which have taken place within a restricted region along the DNA double helices of synapsed non-sister chromatids. (2) As a result of the repair process, the segments of the two non-sister strands within the restricted region come to be identical in genetic composition. We call this process conversion. (3) Converted segment sizes vary and include lengths much greater than single genetic sites, doubtless involving hundreds of nucleotide pairs. (4) The conversion event may, but need not involve exchange with the immediate flanking segments of non-sister DNA strands, as monitored by flanking genetic markers. Indeed, for the smaller conversion segments, the probability of flanking marker exchange approaches zero.

In view of this model, and the data from which it arose, it is apparent that traditional linkage experiments, involving markers set a few crossover units apart and thus monitoring exchange intervals of the order of $10^5$ to $10^6$ nucleotide pairs in length, clearly miss an important category of information transfer. In the case of rearrangement heterozygotes where classical single crossover classes are not recovered, the model predicts that conversions would continue to occur in regions that were effectively paired for exchange. The present report describes the results of experiments that monitor the transfer of genetic information by conversion cance for breeding procedures that utilize such rearrangements as barriers to prevent information transfer as well as for notions concerning the significance of within the inverted region of inversion heterozygotes. The results bear signifisuch rearrangement barriers of exchange in natural populations.

## MATERIALS AND METHODS

*The genetic system:* The rosy cistron in *Drosophila melanogaster* (*ry*:3–52.00) is a solitary unit concerned with the enzyme xanthine dehydrogenase (XDH), located within an intensely mapped short region of the right arm of chromosome 3 (salivary section 87D). Of the various genetic systems used in studies of genetic organization in Drosophila and other multi-cellular organisms, the rosy cistron stands as an example of the simplest type. Strong genetic and biochemical evidence argues that it is a structural gene for XDH (GRELL 1962; YEN and GLASSMAN 1965). Mutations restricted to the rosy cistron are homozygous viable, and fall into three groups: (1) a class of "wild type isoalleles" which produce electrophoretic variants of the enzyme (YEN and GLASSMAN 1965); (2) a "leaky" mutant which has very much reduced enzyme activity (Hubby 1961); (3) and a large group of mutants which are enzymatically inactive and exhibit a brownish mutant eye color phenotype resulting from a reduction in the red (drosopterin) pigments (CHOVNICK *et al.* 1964). Study of this last class of mutants failed to find any evidence of alleles complementation (SCHALET, KERNAGHAN and CHOVNICK 1964), and investigation of allele recombination has been restricted to this class of mutants.

Figure 1 presents a map of the centromere-proximal region of the right arm of chromosome 3 of *Drosophila melanogaster* indicating the location of rosy, the centromere, and other markers

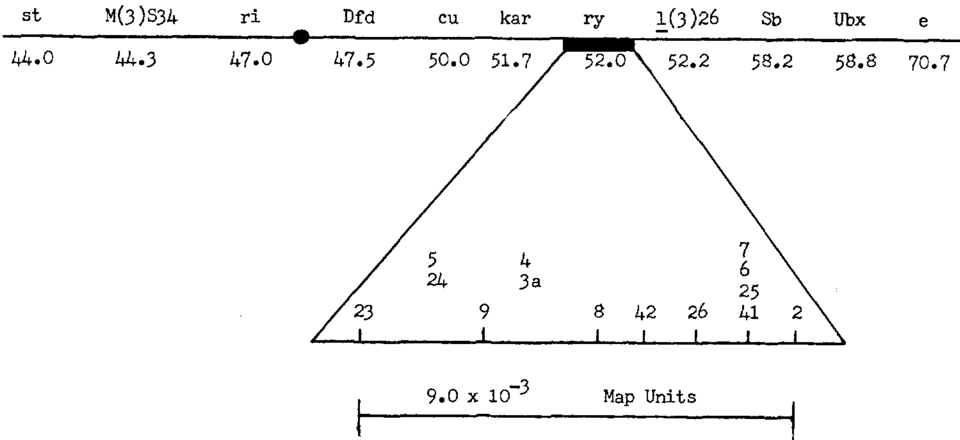


FIGURE 1.—A genetic map of the rosy region of chromosome 3. The map positions of various mutants used in this study are indicated, and the genetic fine structure of the rosy cistron is summarized.

used in the study (LINDSLEY and GRELL 1968). In addition, Figure 1 presents a summary map of separable sites within the rosy cistron obtained from prior mapping experiments (CHOVNICK 1966; CHOVNICK, BALLANTYNE and HOLM 1971).

*Selective system matings:* The experiments described in the present report involve crosses of rosy mutant heterozygous females, generated from preliminary crosses and mated as indicated in Figure 2. *In(3LR)DcxF*, *In(3LR),cu kar Ubx$^A$*, and *In(3LR)MKRS* are complex, multiple-break rearrangements which serve as effective balancers of the rosy region. *In(3R)P$_{18}$* was obtained from DR. E. B. LEWIS, and is discussed in a subsequent section. Other mutants noted in Figure 2 are described by LINDSLEY and GRELL (1968). Large scale crosses of rosy mutant heterozygotes involve matings of fifteen pairs of parents/half-pint milk bottle, on standard Drosophila medium, maintained at 23°–26°. Parents are transferred to fresh cultures at two-day intervals through three broods with a fourth brood of three days providing a total of nine days of egg laying. Experiments are run in numbered trays, each containing thirty numbered bottles. Brood transfer of parents is to numbered bottles and trays such as to permit identification of clusters of exceptional progeny, should they occur. Immediately after each transfer, 1.4 ml of

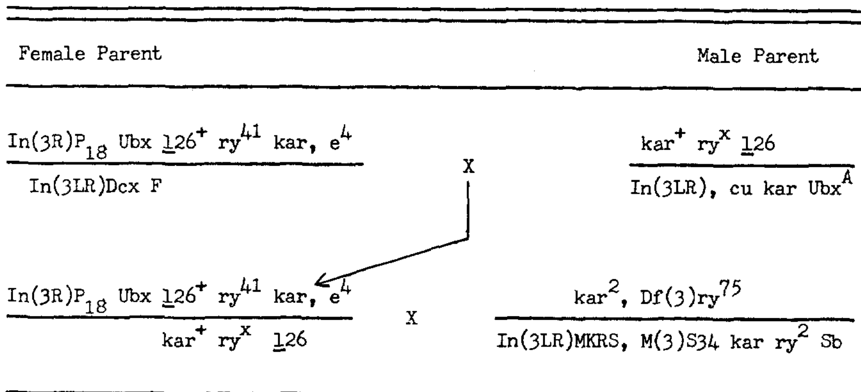


FIGURE 2.—Production of rosy mutant heterozygous females, and subsequent testcross on selective medium.

0.2% aqueous purine (Sigma Chemical Co.) is added to each developing culture which contains approximately 50 ml of standard medium. Prior experiments revealed that such supplementation effectively kills all mutant zygotes lacking XDH activity, without significantly influencing either hatchability or survival of zygotes possessing this activity (FINNERTY, BAILLIE and CHOVNICK 1970; FINNERTY, DUCK and CHOVNICK 1970). Estimation of the total number of zygotes sampled in each cross is accomplished, as in the earlier work, by omitting purine from a sample of the cultures in each experiment, and counting total progeny in those bottles. Such purine treatment leads to the production of cultures rich in larval growth, but only rare individuals complete development and emerge as adults. The surviving exceptions are ry+ in eye color phenotype, and occur as single individuals of either sex, distributed at random among the matings.

*Genetic tests of exceptional progeny:* Surviving progeny of the selective system crosses (Figure 2), invariably ry+ Sb or ry+ Sb+ in phenotype, are mated to flies of the genotype *In(3LR)MKRS, M(3)S34 kar* $ry^2$ *Sb/kar*$^2$, *Df(3)ry*$^{75}$. In addition to establishing a stock culture for each exceptional chromosome, the progeny of this cross permit confirmation of the genetic composition of the exceptional chromosome with respect to *kar*, *ry*, *Ubx* and *e* (phenotypic identification of the latter two markers is possible in heterozygotes).

The ry+ progeny of this cross fall into two classes: (A) ry+Sb flies carry the exceptional chromosome balanced over *In(3LR)MKRS* and (B) ry+Sb+ flies carry the exceptional chromosome over *kar*$^2$, *Df(3)ry*$^{75}$. Then each *ry+* exceptional chromosome is subjected to the following four tests: (1) Class A progeny are mated to *kar*$^2$*l26d/In(3LR)DcxF* flies. The absence of Sb+D+ among the progeny of this cross indicates the presence of the *l26* flanking marker on the *ry+* exceptional chromosome. (2) The presence or absence of the $e^4$ allele on the *ry+* exceptional chromosome, while noted from its heterozygous phenotype, is confirmed by crossing Class A progeny to a homozygous ebony stock and noting the body color of the Sb+ progeny. (3) Class B progeny are mated to *cu kar* $ry^{26}$ *l26 Sb/In(3LR),cu kar* $Ubx^A$ flies. The appearance of ry+Sb progeny confirms the presence of the *l26+* allele on the *ry+* exceptional chromosome, and several virgin females of this class subsequently are crossed to *cu kar* $ry^{23}$*/cu kar* $ry^{23}$ males to assay the extent of crossing over in the rosy region. (4) The presence or absence of the *Ubx* marker on the *ry+* exceptional chromosome is determined by its heterozygous phenotype. However, confirmation of this diagnosis is obtained by crossing Class A or B progeny to *cu kar, Df(3)ry*$^{36}$ *Sb Ubx/In(3LR)DcxF* flies. The appearance of ry+Sb Ubx, non-Dichaete flies confirms the absence of *Ubx* on the *ry+* exceptional chromosome. If such progeny appear, several virgin females subsequently are crossed to *cu kar* $ry^{23}$*/cu kar* $ry^{23}$ males to assay the extent of crossing over in the rosy region. It should be noted that testcrosses (3) and (4) provide females heterozygous for the *ry+* exceptional chromosome and a chromosome carrying a series of rosy region markers in standard chromosome order. The testcross of such females assays approximately 150 progeny/exceptional chromosome, sufficient for easy diagnosis of the *ry+* exceptional chromosome as either *In(3R)P*$_{18}$ or standard order (Table 1).

## RESULTS

*Preliminary crosses:* Table 1 summarizes the results of a series of crosses designed to examine recombination in the rosy region of several inversion heterozygotes as compared to standard order homozygotes. Clearly, the short paracentric inversion, *In(3R)P*$_{18}$, which includes the rosy region in salivary section 87C–E, exhibits the most dramatic suppression of classical exchange of the several inversions tested. Such result is entirely consistent with the larger sizes of the two pericentric inversions (LINDSLEY and GRELL 1968) which permit considerable exchange in the form of double crossovers. For this reason, *In(3R)P*$_{18}$ was chosen as the test inversion to examine the extent of non-reciprocal information transfer as monitored by rosy mutant allele conversion.

TABLE 1

*Crossing over in the rosy region of chromosome three in homozygous standard (Oregon-R) and heterozygotes for the indicated inversion chromosomes**

$\frac{cu^{I}\ kar^{II}\ ry^{III}\ Sb}{+\ \ +\ \ +\ \ +}$

| Chromosome tested | Classes | | | | | N |
|---|---|---|---|---|---|---|
| | Parental | I | II | III | I,III | |
| Oregon-R | 1851 | 44 | 11 | 133 | 2 | 2041 |
| *In(3LR)C-269* [78;98F] | 3118 | 14 | 2 | 25 | 1 | 3160 |
| *In(3LR)C-175* [65C;95E] | 5230 | 18 | 2 | 35 | 0 | 5285 |
| *In(3R)P$_{18}$* [81F;91F/92A] | 7794 | 1 | 0 | 0 | 0 | 7795 |

* Two-day-old females heterozygous for a standard chromosome carrying the markers *cu kar ry$^{41}$ l26 Sb* and a wild-type chromosome in standard or inverted order as indicated, were mated to *cu kar ry$^{41}$* homozygous males. Matings of five females to ten males were made in half-pint containers rebrooded on the third day for six days of egg laying to yield the above distribution of progeny.

Figure 3 illustrates the position of various genetic markers in the right arm of chromosome 3 relative to the cytological breakpoints of *In(3R)P$_{18}$* (E. B. LEWIS, personal communication, 1971). The salivary band localizations of the mutants *kar, ry* and *l26* are based upon cytological analysis of deficiencies by LEFEVRE (personal communication, 1970; 1971).

Insertion of rosy region recessive mutants into *In(3R)P$_{18}$ Ubx, e$^4$* was accomplished in a two-step procedure in which the markers were introduced first into the larger *In(3LR)C-269,* by picking a double crossover from the recombination experiment described in Table 1. Upon analysis, this double crossover carried the

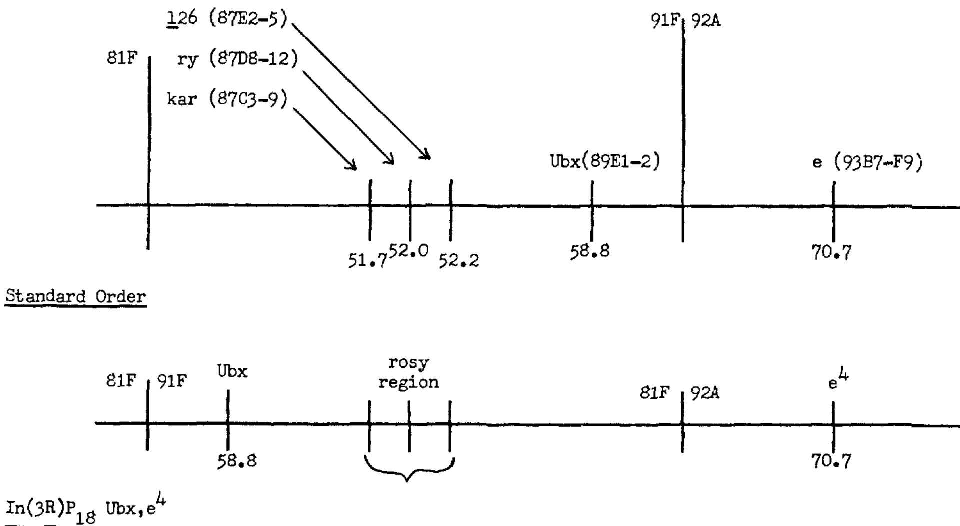


FIGURE 3.—A genetic map of the right arm of chromosome 3 relative to the cytological breakpoints of *In(3R)P$_{18}$*.

markers *kar* $ry^{41}$ *l26* in *In(3LR)C-269*. Females of the genotype *In(3R)*$P_{18}$ *Ubx*, $e^4$ / *In(3LR)C-269 l26* $ry^{41}$ *kar* were crossed to *In(3LR)C-269 l26* $ry^{41}$ *kar* / *In(3LR) cu kar* $Ubx^A$ males and a double crossover chromosome carrying *In (3R)*$P_{18}$ *Ubx* $l26^+$ $ry^{41}$ *kar*, $e^4$ was recovered in a fly which carried *In (3LR)C-269 l26* $ry^{41}$ *kar* obtained from the male parent.

*Conversion experiments:* Following the breeding protocol of Figure 2, and the purine-selective-system treatment described above (MATERIALS AND METHODS), a series of large-scale matings were carried out which are summarized in Table 2. Each mating involves a test for recombination between $ry^{41}$ (the rightmost allele used in the present study) inserted into *In(3R)*$P_{18}$, and a clearly separable rosy mutant on a standard order chromosome. Additionally, each cross is heterozygous for the immediate flanking markers, *kar* and *l26*, and the inversion breakpoints may be considered as more distal markers. The four crosses are presented in Table 2 in order of increasing distance between the rosy mutant alleles as one proceeds down the table. From an estimated $5 \times 10^6$ zygotes sampled over the four experimental crosses, a total of 67 $ry^+$ chromosomes were recovered and completely analyzed. There were two $ry^+$ chromosomes recovered in flies that died prior to reproduction, and these arose in two different crosses. With one exception, the 67 $ry^+$ chromosomes of Table 2 fell into two classes: (1) forty-nine chromosomes carried *kar* $ry^+$ $l26^+$ *Ubx*, were *In(3R)*$P_{18}$, and consequently were classified as conversions of the $ry^{41}$ allele. (2) seventeen chromosomes were classified as $kar^+$ $ry^+$ *l26* $Ubx^+$ in a standard-order chromosome, and thus were classified as conversions of the $ry^x$ allele. The one exceptional chromosome arose in the cross involving $ry^{41}/ry^5$ heterozygous females and was *kar* $ry^+$ *l26* $Ubx^+$ in a standard-order chromosome. This chromosome is scored as a double crossover, one between the separable rosy mutant sites, and the second crossover occurring somewhere between the rosy region and either *Ubx* on one side, or the inversion breakpoint on the other side. It is listed in Table 2 as the only $ry^+$

TABLE 2

*Number and frequency of* ry+ *exceptional chromosomes recovered from crosses involving* In $P_{18}$ *heterozygous females of the indicated genotypes*

| Female parent | Total $ry^+$ progeny | Analysis of $ry^+$ chromosomes: Crossovers | Conv-$ry^{41}$ | Conv-$ry^x$ | Total progeny |
|---|---|---|---|---|---|
| *In* $P_{18}$ *Ubx* $l26^+$ $ry^{41}$ *kar*, $e^4$ / $kar^+$ $ry^{26}$ *l26* | 6<br>$8.6\times10^{-6}$ | 0 | 4<br>$5.7\times10^{-6}$ | 2<br>$2.9\times10^{-6}$ | $0.7\times10^6$ |
| *In* $P_{18}$ *Ubx* $l26^+$ $ry^{41}$ *kar*, $e^4$ / $kar^+$ $ry^{42}$ *l26* | 20<br>$15.4\times10^{-6}$ | 0 | 15<br>$11.5\times10^{-6}$ | 5<br>$3.9\times10^{-6}$ | $1.3\times10^6$ |
| *In* $P_{18}$ *Ubx* $l26^+$ $ry^{41}$ *kar*, $e^4$ / $kar^+$ $ry^8$ *l26* | 13<br>$14.4\times10^{-6}$ | 0 | 9<br>$10.0\times10^{-6}$ | 4<br>$4.4\times10^{-6}$ | $0.9\times10^6$ |
| *In* $P_{18}$ *Ubx* $l26^+$ $ry^{41}$ *kar*, $e^4$ / $kar^+$ $ry^5$ *l26* | 28<br>$13.3\times10^{-6}$ | 1<br>$0.48\times10^{-6}$ | 21<br>$10.0\times10^{-6}$ | 6<br>$2.8\times10^{-6}$ | $2.1\times10^6$ |
| Totals | 67 | 1 | 49 | 17 | $5.0\times10^6$ |

crossover recovered in the study. Its flanking markers are entirely consistent with the known relative position of the two rosy mutants. The reader should note that in the analysis of the 67 exceptional chromosomes, the *Ubx* marker was never separated from $In(3R)P_{18}$. There was one recombinant between $e^4$ and the inversion, this arising in a chromosome which was *kar* $ry^+$ $l26^+$ *Ubx*, $In(3R)P_{18}$ and $e^+$.

Each row of Table 3 provides a comparison of the results of the present investigation with those data reported earlier for recombination tests involving the same rosy mutant alleles carried out in standard chromosome order homozygotes (Chovnick, Ballantyne and Holm 1971). The bottom row of Table 3 summarizes the total data for all comparisons in the table. As expected from classical notions of recombination in an inversion heterozygote, dramatic suppression of single crossovers between the rosy mutant alleles is seen. The only crossover scored in the inversion heterozygote data, in fact, is a double crossover as noted above. In contrast, conversions continue to occur for all rosy mutant alleles in all heterozygous combinations in the inversion heterozygote. While allele conversion frequencies from the $In(3R)P_{18}$ heterozygous females show a consistent pattern of reduction in comparison with the structural homozygote data, the order of magnitude of conversion frequencies does not change.

TABLE 3

*Comparison of* $ry^+$ *exceptional chromosomes recovered from crosses involving* In $P_{18}$ *heterozygotes females and standard chromosome homozygous females*

| Female parent | Total $ry^+$ progeny | Analysis of $ry^+$ chromosomes | | | Total progeny |
|---|---|---|---|---|---|
| | | Crossovers | Conv-$ry^{41}$ | Conv-$ry^x$ | |
| $In\ P_{18}$, $ry^{41}/ry^{26}$ | 6 | 0 | 4 | 2 | $0.7\times10^6$ |
| | $8.6\times10^{-6}$ | | $5.7\times10^{-6}$ | $2.9\times10^{-6}$ | |
| $ry^{41}/ry^{26}$ | 16 | 3 | 10 | 3 | $0.7\times10^6$ |
| | $22.9\times10^{-6}$ | $4.3\times10^{-6}$ | $14.3\times10^{-6}$ | $4.3\times10^{-6}$ | |
| $In\ P_{18}$, $ry^{41}/ry^{42}$ | 20 | 0 | 15 | 5 | $1.3\times10^6$ |
| | $15.4\times10^{-6}$ | | $11.5\times10^{-6}$ | $3.9\times10^{-6}$ | |
| $ry^{41}/ry^{42}$ | 30 | 5 | 18 | 7 | $1.3\times10^6$ |
| | $23.0\times10^{-6}$ | $3.8\times10^{-6}$ | $13.8\times10^{-6}$ | $5.4\times10^{-6}$ | |
| $In\ P_{18}$, $ry^{41}/ry^{8}$ | 13 | 0 | 9 | 4 | $0.9\times10^6$ |
| | $14.4\times10^{-6}$ | | $10.0\times10^{-6}$ | $4.4\times10^{-6}$ | |
| $ry^{41}/ry^{8}$ | 40 | 11 | 18 | 11 | $1.2\times10^6$ |
| | $33.3\times10^{-6}$ | $9.2\times10^{-6}$ | $14.9\times10^{-6}$ | $9.2\times10^{-6}$ | |
| $In\ P_{18}$, $ry^{41}/ry^{5}$ | 28 | 1 | 21 | 6 | $2.1\times10^6$ |
| | $13.3\times10^{-6}$ | $0.48\times10^{-6}$ | $10.0\times10^{-6}$ | $2.8\times10^{-6}$ | |
| $ry^{41}/ry^{5}$ | 52 | 21 | 20 | 11 | $1.3\times10^6$ |
| | $40.0\times10^{-6}$ | $16.2\times10^{-6}$ | $15.4\times10^{-6}$ | $8.4\times10^{-6}$ | |
| $In\ P_{18}$, $ry^{41}/ry^{x}$ | 67 | 1 | 49 | 17 | $5.0\times10^6$ |
| $ry^{41}/ry^{x}$ | 138 | 40 | 66 | 32 | $4.5\times10^6$ |

## DISCUSSION

Prior recombination studies which monitored information transfer in small genetic intervals involving parts of a single cistron provide inescapable evidence that the basic event is non-reciprocal. These experiments, involving both the maroon-like cistron (SMITH, FINNERTY and CHOVNICK 1970) and the rosy cistron (CHOVNICK, BALLANTYNE, BAILLIE and HOLM 1970; BALLANTYNE and CHOVNICK 1971), comprise the basis for the revised model of linked exchange (CHOVNICK, BALLANTYNE and HOLM 1971) which suggested the present investigation (see Introduction).

The present results, demonstrating that conversion takes place in rearrangement heterozygotes, undiminished in order of magnitude, should be considered in concert with two additional facts: (1) The data from multisite crosses, which provide opportunity to observe simultaneous multiple conversion events, suggest that multiple conversions occur in Drosophila, as in fungi, as if the constraint of classical interference does not exist (BALLANTYNE and CHOVNICK 1971). (2) Each conversion event involves transfer of genetic information of the order of $10^2$ nucleotide pairs in fungal systems. Experiments presently in progress are designed to provide an independent estimate of the size range of conversion segments in Drosophila. However, the existing data in Drosophila are entirely consistent with such an estimate (CHOVNICK, BALLANTYNE and HOLM 1971). Taken together, these observations indicate a dimension to information transfer between homologous chromosomes that heretofore has not been fully appreciated.

The demonstration that conversion events take place in rearrangement heterozygotes, undiminished in order of magnitude, additionally raises problems for breeding procedures that utilize such rearrangements to prevent information transfer. Moreover, these results serve to qualify notions concerning the significance of rearrangement barriers of exchange in natural populations. Consider, for example, the extensive inversion polymorphisms found in natural populations of Drosophilidae and other Diptera (DOBZHANSKY 1970). Conventional interpretation of the significance of these chromosomal polymorphisms argues that with suppression of recombination in structural heterozygotes, natural selection superimposed upon independent mutational events will lead, eventually, to the formation of adaptive gene complexes associated with each inversion type. Thus in the presence of a barrier to prevent exchange between two homologous chromosomes, spontaneous site mutations occurring with a frequency of $10^{-8}$ will provide the source material for natural selection to produce the different gene complexes. However, serious conceptual difficulties are raised by the fact of conversion operating to reduce genetic variability between such chromosomes at a frequency several orders of magnitude greater than mutation.

However, a considerable body of circumstantial evidence does exist in support of the notion of adaptive gene complexes in association with inversion polymorphism, and an effort to reconcile these observations with the implications of the present investigation is warranted. Clearly, effective pairing between homologs is a precondition for conversion. The present data were recovered from an experimental system which placed the rosy region approximately in the center of the inversion. One might argue that the central region is most likely to exhibit

effective pairing, but that such pairing diminishes as one moves in both directions towards the inversion breakpoints. Finally, it might be argued that geometrical constraints preclude pairing of homologous regions on both sides of each breakpoint, and that adaptive gene complexes might well develop in just these regions. It is instructive to note that the effect upon conversion frequency of heterozygosity for a small deletion adjacent to the rosy region has been investigated (CHOVNICK, BALLANTYNE and HOLM 1971). In this case, heterozygosity for *Df(3)kar*$^{31}$, which is missing salivary bands 87C3 through 87C9, reduces by one-half the conversion frequency of the left end of the rosy cistron (salivary band 87D10), but not the right end of the cistron. If this observation is taken as an estimate of the reduction in pairing in a region some ten cistrons from a breakpoint, we may infer that the influence of a breakpoint as an effective barrier of information transfer is restricted to the immediately adjacent few cistrons.

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