*INTRACHROMOSOMAL EXCHANGE AT THE BAR LOCUS IN DROSOPHILA**

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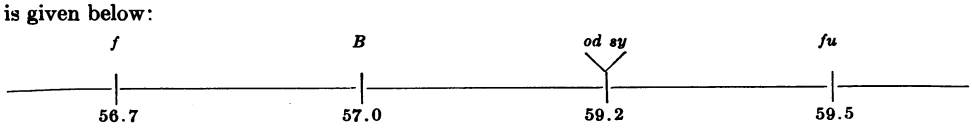
The A^b complexes in maize[1-3] are adjacent, serial duplications whose members have retained synaptic homology and carry the phenotypically distinctive alpha and beta alleles. Certain of the alpha isolations from these complexes are anomalous in that they occur as nonrecombinants for marker loci, and thus are not ascribable to conventional crossing over. Our analyses[4, 5] indicate that these alpha isolates are not the result of gene mutation of the adjacent beta element, or of multiple exchanges in short segments. Rather, they indicate that the nonrecombinant alpha occurrence involves a highly specified, physical loss of the adjacent beta member and that the homologue need not participate in the event.

The mechanism proposed[5, 6] to account for these losses of beta assumes that when pairing forces are initiated at meiosis, the adjacent members of the duplication may either (*a*) engage their counterparts in the homologue in regular or oblique synapsis, or (*b*) pair with each other intrachromosomally to form a double-loop configuration. In the latter case, an exchange between paired members would result in the loss or gain of one complete member of the duplication, depending on the strands involved. The consequences of this event in the case of A^b would be the occasional appearance of alpha strands that are nonrecombinant for markers among other alpha derivatives that result from crossing over in legitimately synapsed homologues and thus appear as recombinants.

The bar duplication in *Drosophila melanogaster* affords a critical test of intrachromosomal recombination. As identified cytologically,[7, 8] bar represents a tandem, serial repeat of the seven bands of the 16A subdivision of the X-chromosome, and Sturtevant's[9] analysis of unequal crossing over at the locus, in the light of this finding, can only mean that the 16A members of the duplication engage in oblique synapsis with counterparts in the homologue, and hence that the adjacent members are themselves synaptically equivalent.

As shown in Figure 1, which illustrates intrachromosomal association of the 16A members of bar, exchanges posed at the chromatid level and occurring within the double loop should lead to the removal or addition of one complete 16A member, no more, no less. At the phenotypic level these exceptions are expected to appear as strands that are nonrecombinant for outside markers. Moreover, analyses of salivary gland chromosomes of progeny of exceptional individuals should afford a precise determination of the extent of these changes at the cytological level.

Materials and Methoas.—In the experiments reported here, bar-locus changes from B to B^+ (bar to normal), B to BB (bar to double-bar), BB to B (double-bar to bar), and BB to B^+ (double-bar to normal), were sought among male, or where feasible, among male and female offspring of appropriately marked mothers. A map of a portion of the X-chromosome spanning the bar locus is given below:



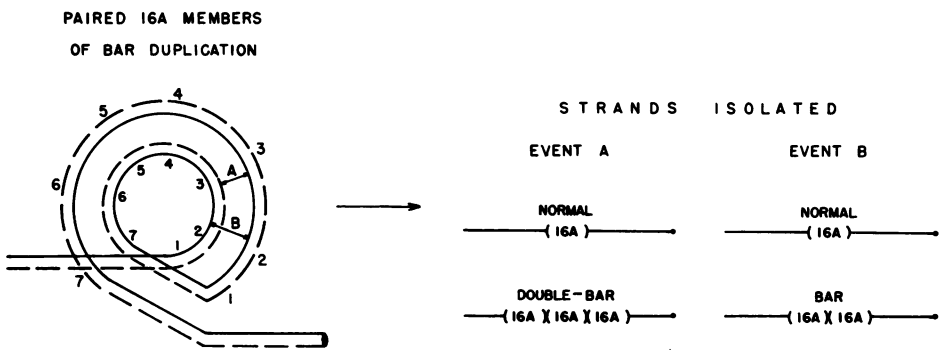


FIG. 1.—Diagrammatic representation of intrachromosomal exchange. At the left, adjacent 16A members of the bar duplication are shown paired with each other at meiosis to form the double loop. Exchanges within this double loop, posed at the chromatid level, lead to single-membered (wild-type) strands and triplication (double-bar) strands, as shown at the right. Since only a single chromosome is involved, exceptional strands are nonrecombinant for marker loci.

Parental females, except as noted otherwise, were heterozygous for *f* (forked bristle) and either *fu* (fused vein) or *od* and *sy* (outstretched wing; small eye), the latter being designated hereafter as *odsy*. Females were mated singly with $f^+ B^+ odsy^+ fu^+$ males carrying autosomal markers as a check on contamination, as well as a sex-linked recessive marker to permit identification of patroclinous male offspring. Presumptive exceptional offspring were given appropriate progeny tests to (*a*) confirm legitimacy of the male parent, (*b*) verify exceptional status of the case, and (*c*) identify the exceptional strand as recombinant or nonrecombinant for the marker loci. Nonrecombinant exceptions were further analyzed to determine eye phenotype in heterozygotes with *B* and to determine viability of the exceptional strand relative to stock X-chromosomes. Each such exception was also tested to determine its effect on crossing over in the *f-odsy* or *f-fu* intervals. Finally, preparations of salivary gland chromosomes of progeny of exceptional individuals were studied to determine the cytological basis, if apparent, for the change. Parental stocks were also analyzed cytologically to verify their constitutions.

Results.—Table 1 gives a summary of exceptional male offspring from hemizygous mothers carrying a *f B fu*, intact X-chromosome, and a deficient (lethal) homologue designated $Df(1)B^{263-20}$. According to Sutton[10] this deficiency, obtained by Demerec[11] from an irradiated bar male, includes the *f* locus, all of the left 16A section, and probably all but band $16A_7$ of the right section. Among 69,980 progeny males scored, there were 11 $f\ B^+\ fu^+$ recombinant exceptions, and four $f\ B^+\ fu$ nonrecombinants. Analyses of three of the latter indicate that they are genetically normal and that in each case the change from *B* to B^+ was associated with loss of a single 16A section of the bar duplication. The fourth case was associated with greatly reduced viability.

TABLE 1

NONRECOMBINANT EXCEPTIONAL MALE OFFSPRING* FROM THE MATING: $f\ B\ fu/Df263\text{-}20\ ♀ \times f^+ B^+ fu^+\ ♂$†

	Analysis of Nonrecombinant Exception				
Nonrecombinant exception	Strand constitution	Viability	Phenotype of heterozygote with *B*	Recombination in *f-fu* region	Salivary chromosome analysis
D-8	$f\ B^+ fu$	normal	half-bar	normal	one 16A member
D-9	$f\ B^+ fu$	normal	half-bar	normal	one 16A member
D-10	$f\ B^+ fu$	normal	half-bar	normal	one 16A member
D-12	$f\ B^+ fu$	low (stock lost)	...	...	...

* *BB* exceptions not scored. In addition to the nonrecombinant exceptions, there were eleven B^+ recombinants, all $f\ B^+ fu^+$ in constitution. One other presumptive $f\ B^+ fu^+$ exception died without mating.
† Total males scored: 69,980.

Exceptional B^+ individuals were also sought among the offspring of *f B odsy/ClB* inversion heterozygotes (Table 2). The *ClB* inversion chromosome carries the bar duplication and the wild-type alleles of *f* and *odsy* in the inverted section, and is lethal in males. Both male and female progeny were searched for B^+ exceptions. As expected, there were no wild-type exceptions that were recombinant for the *f* and *odsy* markers. However, five nonrecombinant B^+ exceptions were obtained. One of these, I-5, involves the parental *Cl"B"* strand, but it has not been determined whether this exceptional ClB^+ strand carries one or more 16A members.

The other four B^+ exceptions carry the *f* and *odsy* markers of the noninverted parental strand. Two of these cases, I-3 and I-4, are cytologically and genetically aberrant. The remaining two nonrecombinant exceptions, I-1 and I-2, appear normal in all respects. Analyses of salivary chromosomes indicate that the phenotypic change from bar to normal in these cases is associated with loss of a single 16A member.

A search was made for exceptional double-bar individuals among a portion of the male offspring of the mating indicated in Table 2, but none was found.

Table 3 summarizes information on exceptional strands among the progeny of *f B odsy/f⁺ B odsy⁺* females mated with *f⁺B⁺ odsy⁺* males. These females were

TABLE 2

NONRECOMBINANT EXCEPTIONAL OFFSPRING* FROM THE MATING: *f B odsy/ClB* ♀ × *f⁺ B⁺ odsy⁺* ♂

Nonrecombinant exception	Analysis of Nonrecombinant Exception: Strand constitution	Viability	Phenotype of heterozygote with *B*	Crossing over in *f-odsy* interval	Salivary chromosome analysis
I-1 ♀	*f B⁺ odsy*	normal	half-bar	normal	one 16A member
I-2 ♂	*f B⁺ odsy*	normal	half-bar	normal	one 16A member
I-3 ♀	*f B⁺ odsy*	lethal	half-bar	reduced	deficiency
I-4 ♀	*f B⁺ od*†	reduced	bar	reduced	new inversion
I-5 ♀	*ClB:* *f⁺ B⁺ odsy⁺*	"lethal"	half-bar	none	*Cl "B"* inversion

* Total progeny: 42,892 ♀ ♀; 20,155 ♂ ♂; there were no crossover exceptions.
† Phenotype is *sy⁺*; since the proximal breakpoint is close to *odsy* locus, loss of recessive phenotype is probably due to position effect.

TABLE 3

NONRECOMBINANT EXCEPTIONAL OFFSPRING* FROM THE MATING: *f B odsy/f⁺ B odsy⁺* ♀ × *f⁺ B⁺ odsy⁺* ♂ (Progeny totals: 29,414 ♀ ♀; 27,229 ♂ ♂)†

Nonrecombinant exception	Analysis of Nonrecombinant Exception: Strand constitution	Viability	Phenotype of heterozygote with *B*	Crossing over in *f-odsy* interval	Salivary chromosome analysis
N-1 ♀	*f⁺ B⁺ odsy⁺*	lethal	bar	reduced	deficiency
N-13 ♀	*f B⁺ odsy*	normal	half-bar	normal	one 16A member
N-14 ♀	*f⁺ B⁺ odsy⁺*	normal	...	...	...
N-16A ♀	*f B⁺ odsy*	reduced	half-bar	reduced	one 16A member; no detectable aberration
N-16B ♀	*f⁺ B⁺ odsy⁺*	lethal	bar	reduced	deficiency
N-22 ♀	*f⁺ B⁺ odsy⁺*	normal	...	...	...
N-24 ♀	*f B⁺ odsy*	lethal	half-bar	reduced	deficiency
N-30 ♂	*f B⁺ odsy*	normal	half-bar	normal	one 16A member
N-31 ♂	*f⁺ B⁺ odsy⁺*	normal	half-bar	normal	one 16A member
NBB-2 ♂	*f⁺ BB odsy⁺*	normal	intermediate	normal	three 16A members
NBB-4 ♂	*f⁺ BB odsy⁺*	normal	intermediate	normal	three 16 A members
NBB-8 ♂	*f⁺ BB odsy⁺*	reduced	intermediate	reduced	long duplication

* In addition to the nonrecombinant exceptions, there were the following crossover exceptions: 18 *f B⁺ odsy⁺* 14 *f⁺ B⁺ odsy*, 3 *f BB odsy⁺*, and 3 *f⁺ BB odsy*. Two presumptive B^+ exceptions died without mating.
† Double-bar exceptions scored among sons only.

full siblings of the *ClB* hemizygous parents of Table 2. Over 56,000 offspring were searched for exceptions, both sons and daughters for changes from bar to normal phenotype, but sons only for changes from bar to double-bar. In addition to two cases that died without mating, there were 32 crossover B^+ exceptions and nine nonrecombinant B^+ exceptions. Two of the latter, N-14 and N-22, identified in female offspring, exhibited normal viability, but were discarded when it developed that they had the same strand constitution as the male parent, thus rendering their analysis difficult and uncertain. Four other nonrecombinant B^+ exceptions, namely, N-1, N-16A, N-16B, and N-24, were found to be aberrant. The other three B^+ nonrecombinant exceptions, N-13, N-30, and N-31, are genetically and cytologically normal. Like I-1, I-2, D-8, D-9, and D-10 of Tables 1 and 2, their change from bar to normal phenotype was associated with loss of a single 16A member of the bar duplication.

Nine changes from bar to double-bar were identified among male progeny in this experiment. Six of these were recombinant for the *f* and *odsy* markers. The other three (Table 3) represent nonrecombinant *BB* exceptions. NBB-8 exhibits striking genetic abnormalities and is found cytologically to consist of a tandem, serial duplication of a segment of the X-chromosome extending from 16A into 17E. However, NBB-2 and NBB-4 show normal genetic behavior, and salivary gland preparations confirm the presence of three 16A members (triplication) expected of double-bar. It may be recalled that the model for intrachromosomal exchange predicts the occurrence of triplication (double-bar) as well as normal (wild-type) strands from the duplication, without marker recombination.

There was one other case of a nonrecombinant change from bar to double-bar. This exception, RBB-1, has the strand constitution f^+ *BB* $odsy^+$ and occurred as an exceptional male among the progeny of a *f* B^+ *odsy*/f^+ *B* $odsy^+$ female. RBB-1 shows no genetic abnormalities and carries a triplication for the 16A region in its salivary gland X-chromosome. Since it occurred in routine recombination studies, the *f B odsy* male parent did not carry autosomal contamination markers. All things considered, it is extremely unlikely that RBB-1 is a contamination, but if so, it represents the only case in these studies in which a presumptive exception traces to illegitimate parentage.

Studies were undertaken to determine whether the double-bar triplication also yields nonrecombinant, exceptional derivatives. Table 4 summarizes pertinent information on exceptional offspring of appropriately marked females that were homozygous *BB*, or carried *BB* in one chromosome and either *B* or B^+ in the other. These matings produced 62 crossover exceptions and eight exceptions that were nonrecombinant for the markers. Among the latter are two cases of a change from double-bar to normal. One of these, since it was isolated in a female and had the same strand constitution as the father, was not analyzed further. For the other, NBB-1 Rev 19, genetic and cytological evidence indicates that the phenotypic change was associated with a loss of two 16A members of the triplication. In addition, there were five instances of a nonrecombinant change from double-bar to bar phenotype. Genetic and cytological analyses indicate that these strands are not aberrant and, since each carries two 16A members, that the exceptional event was associated with a loss of a single 16A member of the triplication. The case designated NBB-1 Rev 6 is anomalous and illustrates the importance of cytological

TABLE 4

NONRECOMBINANT EXCEPTIONAL OFFSPRING* FROM MARKED *BB/BB*, *BB/B*, AND *BB/B*$^+$ ♀♀† MATED WITH *f*$^+$ *B*$^+$ *odsy*$^+$♂♂

(Total strands tested: *BB* 22,606 in ♀♀, 27,903 in ♂♂; *B* 3,906 in ♂♂)

Female parent	Nonrecombinant exception	Analysis of Nonrecombinant Exception: Strand constitution	Viability and crossing over in *f-odsy* interval	Salivary chromosome analysis
f BB odsy/f$^+$ *BB odsy*$^+$	NBB-2 Rev 21 ♀	*f*$^+$ *B*$^+$ *odsy*$^+$	discarded	...
f BB odsy$^+$*/f*$^+$ *BB odsy*	NBB-1 Rev 2 ♂	*f*$^+$ *B odsy*	normal	two 16A members
	NBB-1 Rev 3 ♀	*f B odsy*$^+$	normal	two 16A members
	NBB-1 Rev 9 ♂	*f B odsy*$^+$	normal	two 16A members
	NBB-1 Rev 19 ♀	*f*$^+$ *B*$^+$ *odsy*	normal	one 16A member
f BB odsy/f$^+$ *B odsy*$^+$	SBB-1 Rev 1 ♂	*f B* odsy	normal	two 16A members
f$^+$ *BB odsy/f B odsy*$^+$	NBB-1 Rev 6 ♂	*f B*$^+$ odsy$^+$	normal	two 16A members (unchanged)
BB odsy/f$^+$ *B*$^+$ *odsy*$^+$	SBB-2 Rev 5 ♂	*f B odsy*	normal	two 16A members

* In addition to the 8 nonrecombinant exceptions treated in the table, there were 62 crossover exceptions distributed as follows: 10 *B*$^+$ and 31 *B* from *BB/BB* homozygotes; 4 *B*$^+$ from *BB/B* heterozygotes; and 22 *B* from *BB/B*$^+$ heterozygotes. Three presumptive exceptions died without mating.

† All offspring of *BB/BB* mothers were searched for *B* and *B*$^+$ exceptions; all offspring of *BB/B*$^+$ mothers were searched for *B* exceptions only; but only male offspring of *BB/B* females were searched for exceptions.

inquiry as an adjunct to genetic analysis in this type of investigation. The exceptional strand carries markers indicating that it came from the B-carrying chromosome of the *BB/B* parent. However, salivary gland preparations indicate that this strand, which exhibits normal genetic behavior and produces a normal eye phenotype, still carries the bar duplication.

Three of the double-bar to bar revertants of Table 4 were crossed to produce marked heterozygotes with a stock *B* allele, and 21,800 of their offspring were searched for exceptions. In addition to 14 crossover *B*$^+$, and five crossover *BB* exceptions, three noncrossover exceptions were found. One of these, designated FBB Rev 1 Case 2, produces a normal eye phenotype and, since it carries a *f*$^+$ *B*$^+$ *odsy*$^+$ strand, evidently originated from the stock *f*$^+$ *B odsy*$^+$ strand of the mother. This derivative is genetically normal and carries one 16A member. Of the other two, one was identified as a mutation from bar to infrabar, not unlike that obtained as a patroclinous male by Sturtevant.[9] From cytological studies it is apparent that, like the original infrabar, it retains the two 16A members of the bar duplication from which it came. The other exception, designated C-lethal, occurred among the offspring of a *f B odsy*$^+$*/f*$^+$ *B odsy* mother and was identified as having wild-type effect. On the basis of its *f B*$^+$ *odsy* strand constitution it appears to be a crossover. However, it is lethal in males and reduces, but does not eliminate, crossing over in the *f-odsy* segment. The C-lethal exception, it turns out, is deficient for a segment of the X-chromosome extending from 15F into 16E, including the *f* locus and both 16A members of bar, but not the *odsy* locus. Evidently, this aberration occurred in the *f*$^+$ *B odsy* parental chromosome and, since the *f*$^+$ allele was included in the deficient segment, it appeared as a recombinant.

One other exception deserves mention here. It occurred as a single wild-type patroclinous male among the progeny (*ca.* 16,000) of a homozygous *f B odsy*, attached-X female mated with a *g* (garnet) *f B fu* male, in experiments designed to determine whether intrachromosomal recombination occurs in males. It carries the *g*, *f*, and *fu* markers, has normal viability, and gives normal crossing over in the *f-fu* interval. However, in heterozygotes with *B* this derivative gives a typical bar phenotype, and cytological analysis indicates that it retains both 16A members. Apparently it represents another case of mutation.

Discussion.—It is interesting to note that Sturtevant,[9] in his classical work on bar, recorded a single case of nonrecombinant reversion from B to B^+, though he considered its status as a valid case doubtful. Also, Braver,[12] in an experiment testing the effect of a nearby inversion on unequal crossing over at the bar locus, obtained (personal communication) a nonrecombinant wild-type revertant from a homozygous bar parent.

In the studies reported here, 29 bar-locus exceptions that were nonrecombinant for marker loci were given detailed genetic and cytological analyses. Of these, eight are associated with aberrations, and three others represent mutations unaccompanied by cytological changes. The remaining 18 cases are of the type expected from intrachromosomal recombination; they exhibit normal genetic behavior, and in each case cytological analysis indicates a gain or loss of 16A members corresponding to the changed phenotype. These include nine changes from B to B^+ (loss of one member), three from B to BB (gain of one member), five from BB to B (loss of one member), and one from BB to B^+ (loss of two members). The frequency of the nonrecombinant B to B^+ event (based on 9 cases among 215,376 gametes) appears to be about 1 per 24,000, whereas crossover exceptions of the same type, occurring at the rate of 1 per 1700 gametes (based on 46/78,433), are about 14 times as frequent.

Although the exceptional, nonrecombinant derivatives reported here are expected on the model of intrachromosomal exchange illustrated in Figure 1, the alternative that these exceptions may result from multiple (double) exchanges within the marked segment must be considered. This scheme requires a primary exchange between obliquely synapsed 16A members of the duplication to account for the exceptional bar phenotype, as well as a coincidental exchange involving the same strand and occurring within the marked segment on one or the other side of the bar locus, to produce an apparent noncrossover exception.

If exchange events here are governed exclusively by a mechanism of restrictive chromosomal interference, such double exchanges are not expected since *f* and *odsy* define a segment of only 2.5 map units, which is well beyond the threshold for complete interference. Even assuming that interference is absent, the nonrecombinant exceptions are too frequent, relative to the crossovers, to be explained as doubles, since only 2.5 per cent of strands involved in a primary event at the bar locus are expected to encounter a coincidental exchange between the markers.

In view of the suggestion by Pritchard[13] that multiple exchanges in Aspergillus may take place in localized regions of pairing, and of evidence in Drosophila[14] that is held to support this idea, it is appropriate to consider whether such a mechanism might account for the nonrecombinant bar exceptions. While some exceptions of this type may have such an origin, the evidence and considerations presented below suggest that most, if not all, of them arise intrachromosomally.

Since, on the multiple-exchange hypothesis, the exceptional derivative is dependent on an intrabar primary exchange, an aberration that reduces the frequency of crossover exceptions should occasion a corresponding reduction in the frequency of nonrecombinant (double-exchange) exceptions. Thus, it may be calculated that the deficient homologue of the $B/Df263\text{-}20$ hemizygote results in a sixfold reduction in B^+ crossover exceptions as compared with the B/B parent. But the frequency of nonrecombinant B^+ exceptions among the progeny of the $B/Df263\text{-}20$

hemizygote (3/69,980) is not correspondingly reduced; in fact it approximates that for nonrecombinant exceptions from the nondeficient B/B source (6/145,396).

Another test of the multiple-exchange hypothesis is provided by the B/B^+ heterozygote, for example $f^+ B^+ fu^+/f B fu$. Here $f^+ B fu^+$ strands may conceivably arise as double crossovers but are not expected from intrachromosomal exchange. Among 13,192 gametes from marked B^+/B and B^+/BB heterozygotes, Sturtevant[9] identified six exceptional and 342 nonexceptional single crossovers within the marked segment, but the critical type expected from double exchange was not represented among the progeny. We found no such double crossovers among 25,000 offspring of marked B^+/B heterozygotes, and conclude therefore that multiple exchanges within the *f-fu* segment are rare or nonexistent.

Finally, on the multiple-exchange hypothesis it is anticipated that B/Df hemizygotes, in which one homologue is deficient for all 16A chromatin, and in which therefore the opportunity for interhomologue exchange in the bar region is removed, would yield no nonrecombinant exceptional offspring. To this end we have employed the deficiency designated C-lethal which arose spontaneously in our experiments and which, as already noted, is deficient for a segment extending from 15F into 16E and including the *f* locus, both 16A members, but not *odsy*. Several exceptional individuals have been identified among the offspring of f^+B *odsy*$^+/Df$C-lethal *odsy* hemizygotes, among them two nonrecombinant B^+ revertants designated C-1 and C-2. Both show normal genetic behavior, and cytological analysis of these cases reveals that the change from B to B^+ in each was associated with loss of a single 16A member of the bar duplication. These findings indicate that nonrecombinant exceptions may occur by a mechanism that does not require participation of the homologue; in short, they support the model for intrachromosomal exchange illustrated in Figure 1.

If this mechanism has general significance, it must be taken into account in interpreting instances of anomalous recombination or segregation, such as aberrant tetrads and the so-called conversion phenomena. In fact, the senior author, in a study[15] employing the NBB-8 duplication, has shown that apparent multiple exchanges within a segment of less than three map units are entirely accountable in terms of single exchanges within the serial duplication. It is conceivable that many of the mutants employed in recombination experiments, especially the induced ones, owe their mutant phenotypes to position effects associated with duplications. If so, reversion would accompany removal of the position effect through loss of a duplication member, as either an intrachromosomal or an interhomologue event.

Reddish-alpha, in *Drosophila virilis*, investigated by Demerec,[16, 17] is a case in point. The behavior of this mutable allele of *y* (yellow) was anomalous in that reversions to wild type were, more often than anticipated, associated with crossing over between *y* and the closely linked *sc* (scute) locus. We think it likely that reddish was a serial duplication in which one of the breaks occurred near the y^+ allele, giving a position-effect reddish phenotype. Reversions to wild type are thus interpretable as losses of one member of the duplication occurring either through intrachromosomal exchange (nonrecombinant) or through legitimate exchanges between homologues (crossover), much as alpha is isolated from the alpha:beta complex in maize.

Intrachromosomal exchange may be significant for the evolution of genetic

systems. We note that the mechanism calls for gain, as well as loss, of duplication members, and that several instances of nonrecombinant changes from bar to double-bar were identified in this study. It may be suggested that intrachromosomal exchange provides a model for the highly specified addition of genetic material, and that it may be of special significance for organisms in which interhomologue events may not be available for such additions to the genome. It is particularly inviting to consider that adjacent, functional units governing related processes may have such an origin.

Summary.—Genetic and cytological analyses of 29 bar locus exceptions that were nonrecombinant for marker loci reveal that 18 of these changes were associated with discrete loss or gain of 16A members of the salivary chromosome. In addition two such exceptions were identified among progeny of hemizygotes carrying an X-chromosome homologue deficient for 16A chromatin. From this and other evidence it appears that these nonrecombinant exceptions are not the result of multiple exchanges (negative interference). Rather, they support the model for intrachromosomal exchange.

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