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Mismatch Repair in Heteroduplex DNA

(DNA repair/gene conversion/bacteriophage lambda)

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ABSTRACT **DNA with base pair mismatches was prepared by annealing mixtures of genetically marked DNA from bacteriophage λ. This heteroduplex DNA was used to transfect bacteria under conditions minimizing recombination. Genetic analysis of the progeny phages indicates that: (*i*) Mismatch repair occurs, usually giving rise to a DNA molecule with one chain with the genotype arising from repair and one parental chain. (*ii*) The frequency of repair of a given mismatch to wild type depends on the marker, ranging from 3 to 20%. (*iii*) Excision tracts may extend several hundred nucleotides but are usually shorter than about 2000 nucleotides. (*iv*) In Rec-mediated bacteriophage crosses, recombination of markers closer than about 10^3 nucleotide pairs frequently occurs by mismatch repair within heteroduplex DNA. (*v*) The average amount of heteroduplex DNA formed in a Rec-mediated recombination event is a few thousand nucleotide pairs.**

Current models for genetic recombination require the formation of DNA molecules with regions in which polynucleotide chains of different parentage are paired. If mutant sites are included in a heteroduplex region, base pair mismatches are formed. Mismatch repair would then account for gene conversion and certain other phenomena of recombination (1–4).

The infection of bacteria with artificially constructed heteroduplex DNA provides a system for detecting and characterizing mismatch repair. This approach has been used with heteroduplex DNA from bacteriophages λ, SPP1, and ϕX174 (5–8) and from *Diplococcus pneumoniae* (9). In each case the results were interpreted in terms of mismatch repair, although other explanations may also be given, including recombination following replication.

The experiments reported here were designed to detect mismatch repair in bacteriophage λ and, if present, to ascertain the frequency for different mutations and the extent of the segment excised. We have transfected *Escherichia coli* with λ heteroduplex DNA containing two or more mismatched base pairs at known positions on the λ chromosome. Conventional recombination was minimized by using *recA* bacteria and *int red* phages. The production of phages of recombinant genotype may then be ascribed to mismatch repair.

MATERIALS AND METHODS

Phages from which heteroduplexes were prepared have the deletions *b*2 and *bio*69. Helper phages carry the deletion *bio*256. The *bio* deletions remove the recombination genes *int* and *exo* and, together with *b*2, most or all of the site at which *int* acts. In a *recA* host, recombination between phages carrying these deletions is generally less than 10% of that found in wild-type crosses. Phages with *am* mutations listed in Table 1 plate on C600 and QR48 but not on W3102 or 152. Strains CA85 and 288 suppress Q*am*73 and P*am*80, respectively. The physical locations of the mutations used in heteroduplexes are shown in Fig. 1.

Phage stocks were prepared on C600 by the agar layer method, purified by differential centrifugation and equilibrium sedimentation in CsCl solution, and dialyzed at 4° against suspension medium (19). Purified stocks were diluted to 10^{12} per ml in 10 mM Tris·HCl/0.2 mM EDTA, pH 8.0 and extracted with water-saturated phenol adjusted to pH 8 with Tris. Phenol was removed by repeated dialysis against 10 mM Tris·HCl/10 mM NaCl/0.2 mM EDTA, pH 8.0.

Equal volumes of the two DNA solutions at 10^{11} phage equivalents per ml in 10 mM Tris·HCl/1 mM EDTA, pH 8.4, were combined and kept at 92.5° for 2.5 min and then quickly chilled. Saturated CsCl solution was added to a concentration of 0.3 M and the DNA was annealed at 57° for 15 min, whereupon about half of the initial infectivity was regained. Several transfections were also done with formamide-denatured and annealed DNA, as well as with alkaline-denatured and heat-annealed DNA, with the same results.

For transfection (20), *E. coli* strain QR48 was grown to saturation in tryptone broth and diluted 100-fold into 20 Mm KH_2PO_4, 15 mM $(NH_4)_2SO_4$, 1 mM $MgSO_4$, 10 μM $FeSO_4$, 0.1% yeast extract, 0.05% glycerol, adjusted to pH 7.0 with KOH. After aeration at 37° for 17 hr, the culture was diluted 6-fold into fresh medium, aerated 5 hr at 37°, and chilled. Further steps were done at 4° unless indicated. After centrifugation the cells were resuspended in 10 mM $MgSO_4$ at 2×10^9 per ml. Purified *imm*434 *b2 bio*256 helper phages were added at a multiplicity of 5 and adsorbed for 7 min at 37°. The culture was centrifuged, and the bacteria were gently resuspended at 2×10^9 per ml in 10 mM Tris·HCl, pH 8.0/10 mM $MgSO_4$/10 mM $CaCl_2$ at 4°. The efficiency of transfection increases, reaching 0.1% at 2.5 hr. DNA was diluted in Tris/NaCl/EDTA to 2×10^8 molecules per ml and kept at 55° for 5 min. The DNA was rapidly cooled, and 0.1 ml was incubated with 0.2 ml of helped cells for 40 min at 37°, giving about 0.05 λ equivalents of DNA per cell. For the assay of infective centers, an aliquot of the mixture was diluted in Tris/$MgSO_4$/$CaCl_2$ and 0.1 ml was plated with 0.25 ml of C600(*imm*434 *red*14 *mi*20) or QR48 and also 152(*imm*434 *red*14). The helper phages do not form plaques on these strains. For the production of lysates, the transfection mixture was diluted 10-fold into tryptone broth and aerated at 37° for 120 min. Chloroform was added to promote lysis, and the total phage titer and the titer of λam^+ were determined by plating on C600(*imm*434 *red*14 *mi*20) and 152(*imm*434 *red*14 *mi*20), respectively. More than 1000 am^+ plaques were counted in most assays.

RESULTS

Mismatch Repair Occurs with Characteristic Marker-Dependent Frequencies. Table 2 presents the frequency of

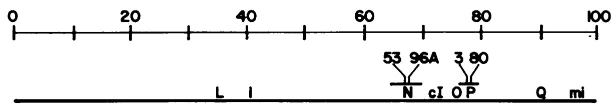

FIG. 1. Map showing physical location of mutations. The λ *b2 bio69* chromosome contains about 45,000 nucleotide pairs.

λ*am*⁺ in lysates from cells transfected with heteroduplex DNA mismatched for various pairs of *am* mutations. The values range from 0.2 to 9.9%. Since the transfection was done with a randomly annealed mixture of equal quantities of two types of DNA, the actual frequency of wild type from heteroduplex transfection is twice that tabulated.

As a control to show that recombination with the helper does not make an important contribution to the observed production of λ*am*⁺ from heteroduplexes, transfections were done with double *am* helpers. Heteroduplex transfections give the same wild-type frequency regardless of whether *am*⁺ or double *am* helper phages are used (Table 3).

As seen in Table 3, some wild type λ is produced when homoduplexes transfect cells with wild-type helper phages, but the frequency is low compared with the yield from heteroduplex transfections. Presumably these λ*am*⁺ arise by recombination with the helper since (see Table 3) the frequency of wild type from homoduplex transfections falls to the reversion level when double amber helper phages are used instead of *am*.⁺ When each of the 28 possible pairwise mixtures of homoduplexes was tested with wild-type helper, the frequency of λ*am*⁺ in no case exceeded 10% of the value produced in the corresponding heteroduplex transfection. This agrees with the results of the transfections using double *am* helpers in showing that recombination with the helper is at most only a minor pathway for the formation of wild-type λ from heteroduplexes.

TABLE 1. *Bacteria and phage strains*

Strain	Characteristics	Ref. or source
Bacteria		
C600	*su*II⁺	(10)
W3102	*su*	(11)
152	*su recA*	Nitrosoguanidine mutagenesis of W3102
QR48	*su*II⁺ *recA*	(12)
CA85	*su*I⁺	Jacob via Beckwith
288	*su*III⁺	Spontaneous in AC 594 (13)
Phages		
λ*b2*	Partial deletion of *att*	(14)
λ*bio69*	*int* through *exo* deleted	(15)
λ*bio256*	*int* through *c*III deleted	Signer
λ*red14*	*bet*	(12)
λ*mi20*	Minute plaque	Nitrous acid mutagenesis of λ
λ*cI857*	Temperature-sensitive clear plaque	(16)
λ*imm434*	Lambdoid phage with immunity 434	(17)
λL*am63*, λI*am2*, λN*am53*, λN*am96A*, λO*am8*, λP*am3*, λP*am80*, and λQ*am73*	Ambers suppressible by *su*II⁺	(18)

TABLE 2. *Observed and predicted* percent of am⁺ phages in transfection lysates*

L63	I2	N53	N96A	O8	P3	P80	Q73	
	6.8 / *8.8*	4.3 / *4.1*	6.3 / *5.7*	4.2 / *4.3*	4.7 / *5.0*	9.4 / *7.0*	4.9 / *5.7*	L63
		6.5 / *5.7*	7.7 / *7.3*	5.0 / *5.9*	7.9 / *6.6*	9.9 / *8.6*	6.3 / *7.2*	I2
			0.2 / *2.6*	2.9 / *1.2*	2.9 / *2.0*	3.7 / *4.0*	1.8 / *2.6*	N53
				3.2 / *2.8*	4.5 / *3.5*	5.2 / *5.5*	4.5 / *4.2*	N96A
					0.9 / *2.1*	2.7 / *4.1*	4.2 / *2.7*	O8
						2.9 / *4.9*	3.9 / *3.5*	P3
							5.8 / *5.5*	P80
								Q73

* Predicted values are in *italics*.

We must further consider the possibility that even under *rec int red* conditions, a significant amount of conventional recombination may occur between λ molecules. However, such recombination would not explain the observation that the frequencies of wild type from heteroduplex transfections are unrelated to the distance apart of the *am* mutations on the λ chromosome. This is shown by attempting to order the mutations taken three at a time. For each of the 56 possible triplets of wild type frequencies involving three sites, the largest frequency should be associated with the outside pair. Instead we find that the frequencies of *am*⁺ disagree with the map order in 27 of the 56 cases. Finally, as will be seen, the segregation of unselected outside markers among λ*am*⁺ phages is inconsistent with conventional recombination in that parental outside marker combinations predominate and the two nonparental combinations occur equally often.

Having excluded conventional recombination and reversion, we consider mismatch repair as the source of λ*am*⁺ from heteroduplex transfections. We imagine that the product of the repair process is simply the initial heteroduplex which has undergone localized excision and resynthesis at one or more sites of mismatch. This is supported by analysis of unselected infective centers from the heteroduplex *c*I + Q*am73* +/+ P*am80* + *mi* picked from QR48. All mixed infective centers

TABLE 3. *Percent of am⁺ from transfections with homoduplexes and heteroduplexes using wild-type and double amber helpers*

DNA	Helper: P*am3* I*am2*	*am*⁺	L*am63* I*am2*
P*am3*/I*am2*	14.3	11.8	—
L*am63*/I*am2*	—	10.3	12.2
I*am2*	0.0003	1.5	<0.001
P*am3*	0.002	0.1	—
L*am63*	—	1.1	0.0014

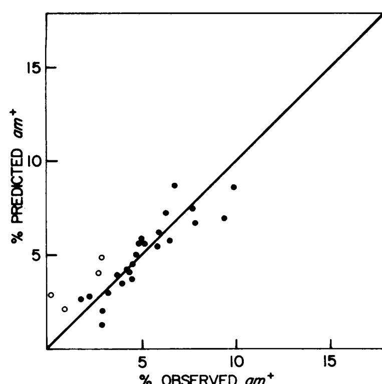

FIG. 2. Frequency of wild type from transfecting heteroduplexes. *Empty circles* correspond to the four most closely spaced pairs of mismatches.

contained only two phage types. In the 83 cases with repair at an *am* site, the wild or double amber phage usually possessed a parental outside marker combination and was accompanied by a phage type derived from the opposite parent.

The data of Table 2 allow us to calculate repair frequencies at individual mismatched sites. Assume that the two mismatched sites in a heteroduplex are repaired independently. Further assume that descendents of both polynucleotide chains of a transfecting DNA molecule usually emerge from the bacterium whether or not repair has occurred and that, on the average, both contribute equally to the lysate. If repair to wild and to amber are equally likely, the frequency of wild type in a lysate from transfection involving am_i and am_j is simply $^1/_4$ $(a_i + a_j - a_ia_j)$, where a_i is the frequency of repair to wild for the mismatch $am_i/+$. The factor $^1/_4$ arises because only half of the transfecting molecules are heteroduplexes and there are two polynucleotide chains in a duplex. For simplicity in computation, we disregard the product a_ia_j. This corresponds to setting the frequency of repair to amber equal to zero. Any particular a_k is then given by

$$\left(\frac{4}{N-2}\right)\left(\sum_{i \neq k} W_{ik} - \frac{\sum_i \sum_j W_{ij}}{N-1}\right)$$

with $i < j$ in the double summation. The W_{ij} are the observed frequencies of λam^+ in lysates, and N is the number of ambers studied. The single site repair frequencies calculated in this manner are given in Table 4. Since the DNA preparations each contain the two possible heteroduplexes, the single site

TABLE 4. *Calculated percent of repair to wild type of single mismatched sites*

	Not corrected	Corrected for simultaneous repair of close sites
L63	14.4	13.7
I2	20.7	20.1
N53	2.2	3.1
N96A	8.4	9.3
O8	2.7	3.8
P3	5.8	7.3
P80	13.7	15.3
Q73	8.2	7.6

TABLE 5. *Percent of am+ among infective centers and in lysates*

Mismatched sites	Infective centers	Lysates	Ratio*
L*am*63/I*am*2	18.3	10.7	1.7
L*am*63/N*am*96A	15.2	7.6	2.0
L*am*63/O*am*8	12.2	8.0	1.5
L*am*63/P*am*80	16.4	9.4	1.7
I*am*2/N*am*96A	10.8	9.4	1.2
I*am*2/O*am*8	12.7	10.2	1.3
I*am*2/P*am*80	16.8	9.4	1.8
N*am*96A/O*am*8	6.7	3.1	2.2
N*am*96A/P*am*80	12.5	7.4	1.7
O*am*8/P*am*80	8.6	3.6	2.4
			av. 1.7

* Due to occasional independent repair to wild at both mismatched sites, the expected ratio is slightly less than two and is given by: $2[1 - (a_ia_j/a_i + a_j)]$. This ratio averaged over the 10 pairs of mismatches is 1.9.

frequency is an average. The values span a considerable range, from 2.2% for N*am*53/+ to 20.7% for I*am*2/+. The predicted frequencies of wild type, calculated as $^1/_4(a_i + a_j)$, are presented in Table 2, and the relation between predicted and observed values is depicted in Fig. 2. The fit is reasonably good.

In addition to the additivity of single site repair frequencies that we observe, two additional and independent tests of our assumptions may be made. First, if descendents of both polynucleotide chains emerge from each transfected cell, most infective centers that yield λam^+ will also yield a parental type. Since these mixed infective centers will score as wild type on the selective indicator, the frequency of λam^+ among infective centers should be nearly twice the frequency of λam^+ in the corresponding lysate. Second, if the heteroduplex carries an additional mismatch with a repair frequency that is not too great, then the ratio of these two alleles among λam^+ should simply be equal to the ratio of the calculated repair frequencies of the amber mutations to which they are linked.

A set of five ambers was chosen to represent the range of single site repair frequencies. All 10 possible heteroduplex preparations were made from newly grown phage stocks. Table 5 presents the frequency of am^+ infective centers from each transfection and of λam^+ phages in each lysate. As predicted, they are related by a factor of approximately two. As one would expect from this, unselected infective centers containing λam^+ usually contained a parental type as well. The two sets of single site repair frequencies calculated from these data are in generally good agreement (Table 6), and in agreement with values obtained in the previous experiment (Table 4).

Of the ten heteroduplex preparations in Table 5, six were additionally mismatched at *c*I. Table 7 gives the clear/turbid ratio among wild-type infective centers, corrected for the preferential recovery of λc. In most cases this ratio is, as expected, close to the appropriate ratio of the calculated *am* single site repair frequencies. This confirms the occurrence of mismatch repair with characteristic site specific frequencies close to those independently calculated from wild-type frequencies.

Departures from Independent Repair Suggest Finite Excision Tracts. The additivity of repair frequencies that we observe

TABLE 6. *Calculated frequencies of repair to wild type of single mismatched sites*

	L63	I2	N96A	O8	P80
Infective centers*	18.9	16.7	8.1	4.9	13.9
Lysates (from this expt.)*	16.9	21.1	8.2	5.5	10.6
Lysates (from Table 4)	13.7	20.1	9.3	3.8	15.3

* The calculated single site repair frequencies from infective centers and lysates have been multiplied by 0.96 and 0.79, respectively, in order to normalize them to the corrected values of Table 4.

for well-separated mismatches implies that excision tracts are generally shorter than about 4000 nucleotides, the length of the shortest intervals showing good agreement between observed and predicted λam^+ frequencies. However, considerably less than the expected yield of λam^+ is found for the four closest pairs of mismatches (Fig. 2). The interval O*am*8-P*am*3 contains about 200 to 500 nucleotide pairs (21, 22), and the intervals N*am*53-N*am*96A, P*am*3-P*am*80, and O*am*8-P*am*80 are also shorter than about 10^3 nucleotide pairs. The finding of less than the expected yield of λam^+ from these heteroduplexes may be a reflection of simultaneous repair of closely spaced sites, due to excision tracts of finite length. If so, we estimate that such tracts may often extend a few hundred nucleotide pairs.

In order to estimate the influence simultaneous repair may have on the calculated single site repair frequencies, the latter were recalculated after setting the wild-type frequencies for the four shortest intervals equal to their expected values taken from Table 4. The recalculated single site frequencies, which presumably represent a closer approximation to the actual values, nevertheless exhibit the same pattern of site specificity (Table 4).

It will be recalled that when wild-type frequencies from heteroduplex transfections are used to determine the genetic map order of *am* sites taken three at a time, the correct order was obtained in half of the 56 possible cases. When only the 34 triplets that do not contain the four closest intervals are considered, the order obtained from heteroduplex transfections is correct in only $^1/_3$ of the cases, no more than a random association would yield. Thus, even the slight indication of linkage in the total set of data is removed by excluding the four closest pairs of mismatches, for which linkage may result from simultaneous repair.

Repair Tracts Are Usually Shorter Than about 2000 Nucleotides. In order further to define the length of repair tracts, heteroduplex DNA was prepared with mismatches at P*am*3 and P*am*80 and also at the flanking sites *c*I and *mi*, the former located no more than 2000 nucleotide pairs from P (21, 22). Since the frequency of phages nonparental for *c mi* in lysates from such heteroduplexes is low (Table 8), the segregation of these markers among am^+ phages provides a means for estimating the frequency of long repair tracts. If repair generally extends from P*am*3 to beyond *c*, selection for am^+ should greatly enhance the frequency of nonparental *c mi* combinations. In fact (Table 8), the proportion of recombinant *c mi* types among am^+, 26%, is not much higher than that in the unselected progeny of heteroduplexes (16%, taking account of homoduplexes). A similar conclusion follows from the preponderance (76%) of parental outside marker combinations found among am^+ phages in the lysate from the hetero-

TABLE 7. *Observed and calculated clear/turbid ratios among am^+ infective centers*

Mismatched sites	Observed	Calculated*
*c*I*am*2/N*am*96A	7.1	5.5
*c*L*am*63/N*am*96A	5.3	6.2
*c*O*am*8/N*am*96A	2.9	1.6
*c*O*am*8/P*am*80	0.72	0.94
*c*L*am*63/P*am*80	2.2	3.6
*c*I*am*2/P*am*80	2.9	3.2

* The ratio of single site repair frequencies from Table 6 is multiplied by 2.7 for normalization. The same excess of *c* over c^+ is found when lysates are plated on nonselective indicator. Good agreement was found between the clear/turbid ratios for λam^+ in lysates and the corresponding ratios given above for infective centers.

duplex *c*I + Q*am*73 +/+ P*am*80 + *mi*. Even those nonparental *c mi* types that do occur among am^+ phages (Table 8) cannot simply be accounted for by occasional long excisions extending through *c*I or *mi*. Instead, they appear to result from two separate (although perhaps somewhat clustered) repair events. This follows from the observation that among am^+, the two nonparental classes occur with equal frequencies, whereas long corrections would produce only one of them. Hence, without very special assumptions regarding the strand and directional specificity of repair and excision, it appears that repair tracts are usually shorter than 2000 nucleotide pairs.

FURTHER DISCUSSION

It is generally supposed that the main source of genetic exchange between very close mutations is mismatch repair within heteroduplex DNA (1–4). This hypothesis is consistent with the production of am^+ in the Rec-mediated phage cross P*am*3 × P*am*80 (Table 8). The wild-type phages exhibit nearly the same excess of parental outside marker combinations at *c*I and *mi* and the same equality of the two nonparental combinations as seen in the corresponding heteroduplex transfections. This pronounced departure from classical linkage relationships is a pattern of segregation expected for mismatch repair within heteroduplex DNA.

TABLE 8. *Distribution of c and mi from heteroduplexes mismatched at cI, Pam3, Pam80, and mi20 and from corresponding phage crosses*

	Heteroduplex transfections	Phage crosses
% Among unselected		
Parental	92	95
Nonparental	8	5
%* Among am^+		
Parental (1)†	18	34
Parental (2)	56	42
Nonparental (1)	12	14
Nonparental (2)	14	12

* Averaged over three of the four possible outside marker arrangements.

† Parental (1) = *c mi* combination entering with P*am*3; Parental (2) = *c mi* combination entering with P*am*80; Nonparental (1) = "single exchange class"; Nonparental (2) = "triple exchange class".

We find the same pattern of outside marker segregation among am^+ from heteroduplex transfection with the much more widely separated mutations P*am*80 and Q*am*73. That is, parental configurations predominate, totaling 76% and the two nonparental configurations are roughly equal. However, in Rec-mediated bacteriophage crosses of these mutations, the results conform instead to the expectations for conventional recombination. Parental combinations among am^+ are in the minority, totaling 25%, and the nonparental "single exchange" class greatly exceeds the "triple exchange" class. This rules out repair within long heteroduplexes as the main route to am^+ for these well separated mutations.

In fact, most of the am^+ phages from the P*am*80 × Q*am*73 cross are unlikely to have arisen by mismatch repair whatever length distribution is postulated for heteroduplex DNA. Since the single exchange configuration predominates in this cross, as it does whenever mutations more than approximately a thousand base pairs apart are used, any such repair mechanism would require that excision tracts usually extend from a mutant site to the adjacent outside marker. However, we believe excision tracts this long to be rare in heteroduplex transfections. We therefore conclude that most wild-type phages from Rec-mediated crosses between well separated mutations do not arise by mismatch repair.

Our measurements of single site repair frequencies allow us to estimate the amount of heteroduplex DNA formed in the course of recombination in phage λ. We ask what average proportion of the genome of a phage emerging from a cross has been included at any time along its line of descent in heteroduplex DNA. Assume that the probability of wild-type formation from transfecting heteroduplexes is the same as in heteroduplex DNA formed during recombination. Then the desired proportion equals the ratio of the wild-type frequency arising by repair in a cross to the wild-type frequency from transfection with the corresponding heteroduplex. Since nearly all wild-type phages from the cross P*am*3 × P*am*80 appear to arise by repair, and the wild-type frequencies are 0.06 and 0.001 from pure heteroduplex transfection and the bacteriophage cross, respectively, we estimate that an average of 1.7% of the λ genome is included in heteroduplex DNA. Another estimate is obtained from the marker pair P*am*80, Q*am*73. The maximum frequency of am^+ arising by repair in the bacteriophage cross may be estimated as 0.3% or one-quarter of the total am^+ frequency, this being the fraction with parental outside marker configurations. Since the am^+ frequency from pure heteroduplex transfection is 11.6%, we obtain 3% as an upper limit on the proportion of the genome included in heteroduplex DNA.

Given the amount of the λ genome included in heteroduplex DNA along the average line of descent, we may estimate the average amount of heteroduplex DNA per genetic exchange. The recombination frequency between markers at opposite ends of λ is approximately 0.13 in Rec-mediated bacteriophage crosses performed under our conditions. Current models for genetic recombination postulate two possible outcomes for each exchange event, giving either recombined ("crossover") or parental ("noncrossover") outside marker combinations. The parental outcome will not contribute to recombination between very distant markers. If recombinant outcomes are no more frequent than parental ones, the average number of exchange events per lineage is at least 0.26. From this, we estimate that the amount of heteroduplex DNA formed per exchange event is less than 0.017/0.26 or approximately 7%, corresponding to about 3000 nucleotide pairs. This is not what one would expect according to the model of Russo (23), in which nearly all recombination occurs by mismatch repair in very long heteroduplexes. Lastly it may be noted that the excess of parental outside marker combinations among λam^+ from the cross of P*am*3 by P*am*80 may be interpreted to mean that noncrossover exchange events occur somewhat more frequently than crossover ones.

Mismatch repair within regions of heteroduplex DNA can provide an explanation of the clustering of genetic exchanges within short intervals manifested as "localized negative interference" (6, 24) as well as the various patterns of aberrent segregation in eukaryotes termed gene conversion (1–4). It is of interest that conversion occurs with site specific frequencies that are often in the range we find for mismatch repair. It may be asked whether the mismatch itself provokes the repair we observe or if, instead, excision and resynthesis occur at the same site even without mismatches. Our finding that repair frequencies are marker specific and that there are considerable differences even between closely spaced sites is more compatible with provoked repair. Provoked repair with finite excision tracts can also account for map expansion and other marker effects in conversion (1, 3). As to the utility of mismatch repair, it may be noted that it provides a mechanism for recombination of very closely spaced mutations, enhancing the production of otherwise rare possibly advantageous genotypes and perhaps also facilitating the loss of deleterious mutations (25).

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