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Genetics

Repair tracts in mismatched DNA heteroduplexes

(DNA repair/gene conversion/bacteriophage lambda)

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ABSTRACT **Heteroduplexes with mismatches at four sites were constructed from separated strands of λ DNA and used to transfect *Escherichia coli* under recombinationless conditions. The output phages from 967 single cells in one experiment and 1016 in another were analyzed to determine the pattern of mismatch repair. A wide range of repair frequencies was found among the mismatches studied. Repair involving two or more close sites in the same heteroduplex occurs much more often on the same strand than on opposite strands. Analysis of the pattern of repair suggests that repair tracts initiate at mismatches, propagate preferentially in the 5′→3′ direction, and extend an average distance of *ca* 3000 nucleotides.**

The repair of mismatched bases in DNA is thought to contribute to gene conversion and to be involved in certain other phenomena in genetic recombination (1–4). Mismatched bases in the heteroduplex regions formed during genetic recombination are postulated to provoke localized excision on one polynucleotide strand followed by repair synthesis using the intact strand as template. Although mismatch repair has not yet been demonstrated *in vitro*, evidence for its occurrence has been obtained from genetic studies of bacterial transformation and transfection with artificially constructed heteroduplex DNA (5–11).

Wildenberg and Meselson (10) found that when *Escherichia coli* is transfected with heteroduplex molecules of bacteriophage λ, different amber/wild-type mismatches are repaired to homozygous wild type at rates characteristic of the individual amber. Well-separated pairs of mismatches were repaired independently; however, there was an indication that sites less than about 2000 nucleotides apart are sometimes repaired in a single event.

The present experiments further characterize the process of mismatch repair. Separated DNA strands from two genetically marked strains of λ were annealed to form the two possible heteroduplexes. *E. coli* was transfected with each heteroduplex and the genotypes of the output phages from individual cells were determined. A wide range of repair frequencies is found among the six markers studied. Even for a given mismatch in a particular heteroduplex, the frequency of repair on one strand can differ considerably from that on the other. Repair involving two or more close sites in the same heteroduplex occurs much more often on the same strand than on opposite strands. The pattern of repair suggests that repair events initiate at mismatches and propagate preferentially in the 5′→3′ direction, extending an average distance of *ca* 3000 nucleotides.

MATERIALS AND METHODS

Bacteria and phage strains are listed in Table 1. Phage stocks were prepared on C600 and C600.3 as previously described (10). All phages used for DNA preparations have the deletions *b2* and *bio*69 and are therefore *att*$^-$ *int*$^-$ *red*$^-$. DNA strands were prepared and annealed as described earlier (22) except that the D_2O–H_2O gradient step was omitted. Transfection with each single strand preparation after self-annealing showed

Table 1. Bacteria and phages

Strain	Characteristics	Ref.
	E. coli K12	
C600	*su*II$^+$	12
W3102	*su*	13
152	*su recA*	10
QR48	*su*II$^+$ *recA*	14
CA85	*su*I$^+$	10
288	*su*III$^+$	10
C600.3	C600/λ (plates λ*h*)	15
	Lambda	
*imm*434	Immunity 434	16
*b*2	Partial deletion of *att*	17
*bio*69	*int* through *exo* deleted	18
*bio*256	*int* through cIII deleted	10
*mi*20 (*mi*)	Minute plaque	10
c1857 (*c*)	Clear plaque	19
h	Extended host range	20
*Nam*53 (N)	Amber suppressible by *su*I$^+$, *su*II$^+$, *su*III$^+$	21
*Oam*8 (O)	Amber suppressible by *su*I$^+$, *su*II$^+$	21
*Pam*80 (P)	Amber suppressible by *su*II$^+$, *su*III$^+$	21

complementary strand contamination of *L* (light) strands to be less than 2.5% and of *H* (heavy) strands to be less than 0.1%, as measured by infectivity relative to that of the corresponding heteroduplex preparation. Transfection with a heat-denatured and annealed equal mixture of λ+c*Pmi* DNA and λN+++ DNA gave a wild frequency half the average frequency found for the two separate heteroduplexes, indicating that the strand separation procedure does not affect repair. As an additional control, a sample of +c*PmiL*/N+++*H* heteroduplex DNA was dialyzed overnight at room temperature against 0.1 M NaOH and reannealed, a treatment which was found to hydrolyze poly(U,G) completely but to have no effect on the frequency of wild type from transfection. It has been shown that in our system independent DNA preparations and different methods of annealing give essentially similar results (10). All transfections were performed in *recA*$^-$ cells (QR48) with *att*$^-$ *int*$^-$ *red*$^-$ helper phages (*imm*434*b*2*bio*256NP). Phage crosses showed greatly reduced recombination under these conditions. The transfection procedure has been described (10).

The heteroduplexes used were +c*Pmi*/N+++ and *h*NOP/++++ in experiments I and II, respectively. In experiment I transfected cells were plated on QR48 before lysis, giving rise to infective centers. Phages from individual infective centers were analyzed by picking, diluting, and plating on C600. At least 16 plaques were picked and scored by spot tests. Reversion of ambers was much too infrequent to interfere with scoring.

Table 2. Observed and calculated numbers of double and single yielders

Experiment I					Experiment II				
+cPmi L N+++ H			N+++ L +cPmi H		hNOP L ++++ H			++++ L hNOP H	
Obs.	Calc.	Genotypes	Obs.	Calc.	Obs.	Calc.	Genotypes	Obs.	Calc.
47	21.4	+cPmi / N+++	69	27.0	10	3.8	hNOP / ++++	22	4.1
1	3.2	+cP+ / N+++	5	3.5	36	28.2	hNO+ / ++++	2	5.5
2	2.7	+cPmi / N++mi	3	2.5	4	5.7	hNOP / +++P	5	11.7
32	34.4	+c+mi / N+++	4	10.6	0	2.7	hN+P / ++++	2	5.3
5	10.9	+cPmi / N+P+	10	22.5	0	1.3	hNOP / ++O+	2	9.9
4	9.7	++Pmi / N+++	3	9.0	1	0.7	h+OP / ++++	1	0.6
5	12.0	+cPmi / Nc++	7	21.4	0	1.3	hNOP / +N++	1	0.8
0	1.7	NcPmi / N+++	1	3.5	3	1.3	+NOP / ++++	1	0.8
0	0.6	+cPmi / ++++	0	5.4	1	0.9	hNOP / h+++	3	1.0
5	5.2	+c++ / N+++	0	1.4	21	19.0	hN++ / ++++	17	7.0
1	1.3	+cPmi / N+Pmi	0	2.1	5	1.8	hNOP / ++OP	51	29.1
0	0.8	N+Pmi / N+++	1	1.2	1	0.2	++OP / ++++	1	0.2
1	0.4	+cPmi / +c++	2	4.4	0	0.4	hNOP / hN++	0	0.2
14	15.7	+++mi / N+++	9	3.5	0	0.5	h++P / ++++	1	0.8
9	6.1	+cPmi / NcP+	22	17.7	0	0.4	hNOP / +NO+	0	1.8
0	1.5	++P+ / N+++	0	1.2	1	5.5	h+O+ / ++++	0	0.8
0	1.5	+cPmi / Nc+mi	0	2.1	2	1.8	hNOP / +N+P	0	2.0
1	2.9	Nc+mi / N+++	1	1.2	0	0.9	+N+P / ++++	0	1.2
0	0.4	+cPmi / ++P+	0	4.4	0	0.4	hNOP / h+O+	0	2.3
0	0.2	NcP+ / N+++	0	0.4	6	9.9	+NO+ / ++++	0	1.2
0	0.1	+cPmi / +++mi	0	0.4	1	1.5	hNOP / h++P	0	2.7
0	1.7	+cP+ / N+P+	1	2.9	4	9.3	hNO+ / ++O+	1	13.5
0	4.2	+c+mi / N++mi	1	1.0	0	3.8	hN+P / +++P	3	15.4
1	1.9	+cP+ / Nc++	1	2.9	7	9.0	hNO+ / +N++	0	1.0
0	1.1	++Pmi / N++mi	0	0.8	1	1.1	h+OP / +++P	0	2.0
0	0.1	+cP+ / ++++	0	0.6	6	7.0	hNO+ / h+++	1	1.2
0	0.2	NcPmi / N++mi	0	0.4	0	2.0	+NOP / +++P	0	2.5
17	19.5	+c+mi / Nc++	4	8.3	0	0.9	hN+P / +N++	0	1.0
3	5.0	++Pmi / N+P+	2	7.5	0	0.2	h+OP / ++O+	0	1.6
0	1.0	+c+mi / ++++	0	2.1	0	0.7	hN+P / h+++	0	1.2
0	1.0	NcPmi / N+P+	1	2.9	1	0.4	+NOP / ++O+	0	2.1
0	0.2	++Pmi / ++++	0	1.9	1	0.2	h+OP / h+++	1	0.2
0	1.0	NcPmi / Nc++	0	2.7	0	0.4	+NOP / +N++	0	0.2
5	2.5	++++ / N+++	5	0.4	9	3.7	h+++ / ++++	8	1.2
6	0.8	+cPmi / NcPmi	8	1.7	6	0.5	hNOP / +NOP	14	5.1
10	1.3	N++mi / N+++	7	0.4	0	0.2	+++P / ++++	1	0.2
2	0.2	+cPmi / +cP+	22	3.5	0	0.2	hNOP / hNO+	0	0.4
0	0.2	N+P+ / N+++	1	0.2	1	1.8	++O+ / ++++	0	0.2
0	0	+cPmi / +c+mi	0	0.4	2	0.4	hNOP / hN+P	1	0.4
0	0.4	Nc++ / N+++	0	0.2	15	6.6	+N++ / ++++	11	1.6
0	0	+cPmi / ++Pmi	0	0.4	3	0.5	hNOP / h+OP	15	6.6
5	2.9	+c++ / Nc++	1	1.0	6	6.0	hN++ / +N++	3	1.2
0	0.6	++Pmi / N+Pmi	1	0.6	0	0.4	h+OP / ++OP	4	4.7
0	0.2	+c++ / ++++	1	0.2	4	4.8	hN++ / h+++	4	1.6
0	0.2	NcPmi / N+Pmi	0	0.2	0	0.7	+NOP / ++OP	8	6.2
1	0.4	N+Pmi / N+P+	1	1.0	0	0.1	++OP / ++O+	0	0.4
1	0.6	+c+mi / +c++	3	1.7	0	0.2	hN+P / hN++	0	0.2
0	0.2	N+Pmi / N++mi	0	0.2	1	0.4	++OP / +++P	1	0.4
0	0.1	+cP+ / +c++	0	0.6	2	2.2	hNO+ / hN++	0	0.2
5	1.9	+++mi / N++mi	0	0.4	0	0.7	h++P / +++P	0	2.5
3	1.0	+cP+ / NcP+	1	2.3	4	2.9	hNO+ / +NO+	0	2.3
0	0.4	+++mi / ++++	0	0.6	0	0.2	h++P / h+++	0	0.2
0	0.6	NcPmi / NcP+	5	2.3	0	0.2	+NOP / +NO+	0	0.4
1	0.8	++P+ / N+P+	2	1.0	1	1.8	h+O+ / ++O+	0	2.1
3	2.5	+c+mi / Nc+mi	0	0.8	0	1.3	hN+P / +N+P	0	2.7
0	1.5	Nc+mi / Nc++	0	1.0	0	0.4	+N+P / +N++	0	0.2
0	0.2	++Pmi / ++P+	0	1.5	0	0.1	h+OP / h+O+	0	0.4
0	0	++P+ / ++++	0	0.2	1	1.3	h+O+ / h+++	0	0.2
0	0.2	NcPmi / Nc+mi	0	0.2	0	0.5	+NOP / +N+P	0	0.4
0	0.4	Nc+mi / N++mi	0	0.2	0	1.3	+N+P / +++P	0	3.3
0	0	+cP+ / ++P+	0	0.6	1	2.4	hNO+ / h+O+	0	3.1
0	0	++Pmi / +++mi	0	0.2	1	0.2	h+OP / h++P	0	0.4
0	0.2	NcP+ / Nc++	0	0.4	2	3.1	+NO+ / +N++	0	0.2
0	0.2	+c+mi / +++mi	0	0.2	0	0.9	hN+P / h++P	0	3.5
0	0.2	NcP+ / N+P+	0	0.4	2	3.3	+NO+ / ++O+	0	2.9
190		TOTAL	205		173		TOTAL	185	
67		+cPmi	88		60		hNOP	98	
100		N+++	86		115		++++	91	
3		+cP+	24		53		hNO+	4	
8		N++mi	7		6		+++P	8	
38		+c+mi	15		6		hN+P	3	
8		N+P+	10		12		++O+	0	
3		++Pmi	3		5		h+OP	17	
20		Nc++	12		34		+N++	13	
3		NcPmi	5		13		+NOP	20	
12		++++	3		22		h+++	12	
11		+c++	2		28		hN++	25	
1		N+Pmi	0		11		++OP	54	
13		+++mi	5		1		h++P	4	
5		NcP+	16		10		+NO+	3	
3		++P+	0		9		h+O+	2	
1		Nc+mi	2		1		+N+P	3	
296		TOTAL	278		386		TOTAL	357	

Genotypes obtained from those infective centers or single burst tubes yielding more than two genotypes or a forbidden pair of genotypes are included with the data for single yielders. Calculated numbers are obtained as explained in the *text*, assuming independent repair.

Table 3. Observed repair frequencies and computed repair initiation rates

Experiment I					Experiment II				
+cPmi L N+++ H			N+++ L +cPmi H		hNOP L ++++ H			++++ L hNOP H	
Frequency	Rate	Repair event	Frequency	Rate	Frequency	Rate	Repair event	Frequency	Rate
0.07	0.07	+ → N	0.10	0.04	0.22	0.21	h → +	0.15	0.04
0.03	0.00	N → +	0.15	0.18	0.16	0.14	+ → h	0.16	0.15
0.23	0.18	c → +	0.16	0.05	0.13	0.06	N → +	0.12	0.04
0.28	0.26	+ → c	0.37	0.31	0.21	0.16	+ → N	0.13	0.03
0.52	0.58	P → +	0.18	0.17	0.34	0.31	O → +	0.27	0.07
0.16	0.19	+ → P	0.37	0.14	0.17	0.15	+ → O	0.52	0.81
0.12	0.04	mi → +	0.11	0.11	0.75	1.38	P → +	0.26	0.53
0.10	0.11	+ → mi	0.08	0.04	0.15	0.24	+ → P	0.55	0.14

Repair frequencies were calculated assuming independent repair. Repair initiation rates were obtained from computer simulations (see *text*). The values given are 100× the likelihood that the mismatch will undergo the indicated repair event during an interval of 1/100 of the total repair period. The repair rate of an allele with flanking mismatches is computed for the pair for which the other mismatch lies in the 5′ direction on the strand carrying the allele.

In experiment II λ++++ overgrew λ*h*NOP in infective centers, making necessary a resort to liquid single burst analysis. The content of each single burst tube (*ca* 0.1 burst per tube) was plated on C600(*imm*434NOP) and all plaques were picked and tested, up to a maximum of 34. Whenever there were more than 34 plaques, representatives of each distinguishable type were tested. In experiment I, wild type, N, and P were identified by differential suppression on C600, CA85, and W3102. Plaque morphology was scored on C600. In experiment II, wild type, N, O, and P were identified by differential suppression on C600(*imm*434NOP) and 288(*imm*434NOP) and by complementation. Host range was scored on C600.3. All scoring procedures were validated by testing known genotypes.

RESULTS AND DISCUSSION

With four markers there are 16 possible phage genotypes and 120 distinguishable pairs of genotypes. Only 65 pairs can be produced by mismatch repair alone, whereas the remaining 55 require conventional recombination. Approximately 60% of the infective centers and single bursts yielded phages of only a single genotype. In both experiments, these single yielders included all 16 possible genotypes. Approximately 40% of the infective centers and single bursts gave phages of two genotypes. These double yielders include nearly all of the 65 allowed pairs. The data are presented in Table 2.

Eight of the 967 infective centers of experiment I and 33 of the 1016 fertile single burst tubes of experiment II contained three or more phage genotypes. Only eight of the fertile single burst tubes contained a forbidden pair of phage genotypes, while no forbidden pairs were found in experiment I, confirming that conventional recombination is essentially absent. All of these exceptional cases may have resulted from the chance superposition of two transfected cells in an infective center or a single burst tube.

When only one genotype is obtained from a transfected cell, repair may have occurred at every mismatch. Alternatively, one strand may have failed to produce progeny phages or, if produced, they may not have been recovered. If such loss occurs after the opportunity for repair has passed and at random with respect to genotype, the frequencies of the various genotypes among single yielders will be equal to the corresponding frequencies among phage genotypes from double yielders. This hypothesis was evaluated by the χ^2 test for homogeneity. Considering both experiments together, there are 40 cases for which the number of expected occurrences is large enough (≥5) for reliable testing. In no case was χ^2 greater than 4.3 ($P > 0.03$), and in only three cases was it larger than 2.7 ($P > 0.1$). We conclude that single yielders arise simply from random strand loss and not from repair at every mismatch. Accordingly, it is incorrect to attribute the occurrence of pure bursts solely to mismatch repair (5, 6, 9, 11).

The overall frequency of repair at each mismatch may be defined as the number of double yielders in which a particular allele has been repaired divided by the total number of double yielders, excluding those repaired at all of the other sites. A wide range of repair frequencies is found, from a few percent to nearly 75% (Table 3). Also, for a given mismatch the frequency of repair on one strand can differ considerably from that on the other strand of the same heteroduplex.

If repair occurs independently at each mismatch, the frequency of each type of double yielder will be equal to the product of the appropriate frequencies of repair or no repair at each site. Table 2 presents the numbers of each type of double yielder calculated assuming independence. Although most of the individual numbers are too small for convenient statistical analysis, examination of the larger observed and calculated values indicates that the assumption of completely independent repair at each mismatch is not correct. The nature of the nonindependence is seen in the pattern of multiple repair involving the outside two markers of a set of three adjacent mismatches in the limited interval N–P (Fig. 1). Of the cases including repair of the outside two markers, by far the most common are

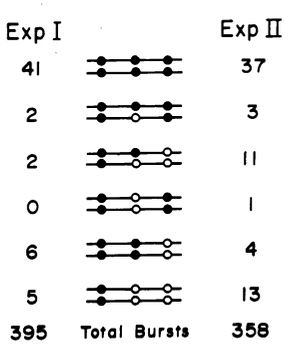

FIG. 1. Patterns of multiple repair among double yielders. The group of three adjacent markers represented in the figure is NcP for experiment I and NOP for experiment II. The data from both strands of both heteroduplexes are combined. ● and ○ represent the genotypes of the two parental DNA strands.

Table 4. Test for excision direction—Genotypes of phages from single and double yielders

Experiment I*					Experiment II†			
Single yielders		Double yielders			Single yielders		Double yielders	
A	B	A	B	Genotype	A	B	A	B
8	38	18	43	X00	16	71	14	86
9	10	12	21	XX0	7	12	8	11
49	17	65	19	00X	63	7	74	4
25	8	24	15	0XX	62	38	63	39

A denotes data for heteroduplex 000 L/XXX H. B denotes data for heteroduplex XXX L/000 H.

* In experiment I 000 = +cP and XXX = N++.

† In experiment II 000 = NOP and XXX = +++.

those involving all three mismatches on the same strand. Thus, multiple repair events tend to affect adjacent mismatches and tend to occur on the same strand. A simple explanation of such a pattern is that repair involves an excision process, which initiates at a mismatch and then proceeds for some distance along one strand.

To detect a possible directional preference for repair excision, we consider the situation in which three mismatches are present within an interval comparable to the average length of excision tracts. If excision starts at or very near a mismatch, directionality will influence the pattern of repair events differently in the two heteroduplexes. Let the marker arrangement in one heteroduplex be 000 on the L strand and XXX on the H; it will be the reverse in the other heteroduplex. With respect to the conventional genetic map, the 5′→3′ direction is rightward on L strands and leftward on H strands (23). Hence, if excision occurs in the 5′→3′ direction, the effect of excision tracts will be to favor an excess of the genotypes 0XX and 00X from the first heteroduplex relative to the second and the genotypes X00 and XX0 from the second heteroduplex relative to the first. These relationships are reversed for 3′→5′excision. Table 4 presents the data from experiments I and II for the *ca* 4000 base pair interval N–P. The excesses predicted by 5′→3′ excision are found in all four cases in experiment I and all four cases in experiment II among the phages from single as well as double yielders. For tracts long enough to reach beyond the marked interval, no combination of single site frequencies can obscure the direction of excision. For shorter tracts the direction can be obscured and spurious indications of direction can be generated by certain systematic and sufficiently great inequalities in the rate of initiation at particular mismatches. However, since the observed excesses are consistent in all cases, the data allow a provisional assignment of 5′→3′ directionality. Naturally, since the test can only detect an overall trend, it cannot exclude the occurrence of less extensive excision in the opposite direction.

We next attempt to determine, by computer simulation, the average excision tract length and the site-specific repair initiation rates. For simplicity, the computations were carried out for only two mismatched sites at a time. Separate computations were made for all six adjacent pairs of markers in experiments I and II. Considering both heteroduplexes, there are 18 possible outcomes of transfection for any pair of markers. The nonindependence of repair makes it impossible to write simple analytic equations for the probabilities of the various outcomes. Therefore, a numerical solution was obtained by an iterative procedure, under the following assumptions: (*i*) repair initiates

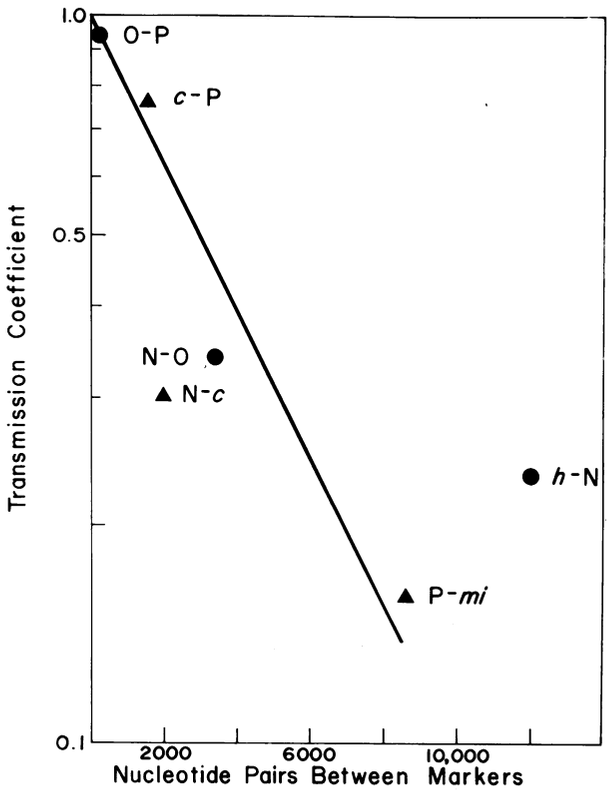

FIG. 2. Dependence of transmission coefficient on marker separation. The transmission coefficients computed assuming 5′ → 3′ excision as described in the *text* are: 0.94, 0.76, 0.34, 0.30, 0.16, and 0.24 for the intervals O–P, c–P, N–O, N–c, P–mi, and h–N, respectively. Triangles refer to marker pairs from experiment I and circles to pairs from experiment II. Marker separations are estimated from references (23, 26) and from restriction mapping data (27; and K. Backman, personal communication).

at a mismatch, (*ii*) excision goes in the 5′→3′ direction, (*iii*) initiation at any given site does not occur while excision initiated at another site is still in progress, and (*iv*) initiation rates at the various sites of mismatch remain constant. If the total time in which repair can occur is partitioned into intervals sufficiently small that the probability of having two events in one interval is much less than the probability of having one event, simple iterative equations can be written to predict the frequencies of all 18 outcomes. Altogether there are nine variables, the eight site-specific initiation rates and a transmission coefficient defined as the fraction of events that extend at least a distance equal to that separating the two markers. In general, the proportion of any given genotype (e.g., OPL/++H, O+L/++H, etc.) present at the ith interval is written as the sum of two terms: (*i*) the proportion present at the (i-1)th interval times the probability that the genotype undergoes no repair, (*ii*) the proportion produced from the other types present at the (i-1)th interval. The sets of 18 equations were solved in 100 steps with a Digital PDP 11 computer. Rosenbrock's method of rotating coordinates (24, 25) was used to find the set of variables which, for each set of 18 equations, minimizes the sum of the squares of the differences between computed and observed frequencies of the different outcomes.

An estimate of excision tract length is provided by a semilogarithmic plot of the calculated transmission coefficient against marker separation (Fig. 2). A constant probability of termination per unit distance would give rise to a straight line with slope inversely proportional to the mean tract length. The deviation of the h–N point from the line shown in the figure

may well be due to the infrequency of repair at these sites and to the inherent inaccuracy of the computation when the marker separation greatly exceeds the mean tract length. We have no explanation for the deviation of the N–*c* point. However, it should be mentioned that the fit of the computed frequencies of double yielders with the observed frequencies is worse for this pair than for any other. The slope of the line fitted to the other four points and the origin corresponds to an average excision tract length of about 3000 nucleotides. This is somewhat larger than the estimate of Wildenberg and Meselson (10) and is much longer than the 5′→3′ tracts found to predominate in the normal excision repair of UV dimers (28).

The repair initiation rates obtained by computer analysis are presented in Table 3. Although there are distinct differences and the two measures of repair are not strictly comparable, the computed rates tend to parallel the repair frequencies calculated on the basis of independence (Table 3) and show a similar wide range of values and similar asymmetry on the two strands at a given mismatch. There are eight rates at N and P for which the values computed separately from experiments I and II may be compared. Although the agreement is not close, there is a clearly significant correlation between the values from the two experiments. It is conceivable that the actual initiation rates for all mismatches we have studied are the same and that the large apparent differences are the result of excision tracts extending from hidden mismatches due to sequence differences accumulated during the separate descent of the parental phage strains. However, this seems most unlikely, since such hidden mismatches would have to be specially distributed and either very numerous or of a special class having much higher initiation rates than the mismatches we have studied.

The biological role of mismatch repair remains a matter for speculation. Depending on the parameters of heteroduplex formation during genetic recombination and on the pattern of repair excision, mismatch repair may make a major contribution to the overall recombination frequency of very close markers. However, in view of uncertainty regarding the biological role of recombination (29), other possible functions of mismatch repair should be considered. For example, mismatch repair may act to correct mutations that arise as replication errors. If so, it may be that mismatch repair acts in a directed manner in conjunction with sister chromatid exchange or that it occurs with particularly high efficiency on newly synthesized DNA strands, possibly because of their undermethylation or because of a special relation to the replication complex.

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