QUANTITATIVE IMPLICATIONS OF THE DNA-REPAIR MODEL OF GENE CONVERSION¹

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Received October 21, 1965

THE repair of mispaired bases in regions of hybrid DNA (deoxyribonucleic acid) as a possible cause of gene conversion (interallelic recombination) in fungi (HOLLIDAY 1962, 1964; WHITEHOUSE 1963; WHITEHOUSE and HASTINGS 1965) and of genetic recombination in bacteria (CLARK and MARGULES 1965) is of sufficient current interest to warrant a quantitative evaluation of the relationships to be expected. One mathematical treatment has already been published (WHITEHOUSE 1964; WHITEHOUSE and HASTINGS 1965). The treatment here proposed differs in two important respects from that already published. In the first place, the dissimilar pairs of noncomplementary bases at heterozygous sites in the two recombining chromatids (Figure 1) are not assumed to respond identically. Instead it is proposed that they may well differ in the frequencies in which repair occurs, and in the relative frequencies of the different kinds of repair. Secondly, no attempt is made to account for the observed correlation

FIGURE 1.—The exchange of base chains between two nonsister chromatids gives rise to two recombined chromatids. ●, bases from one parent; ○, bases from the other parent; -, as in ●-○ and A-B, normal hydrogen bonding between complementary bases; *, as in A*Y, deficient hydrogen bonding between noncomplementary bases. The mutant site has the complementary base pair X-Y at the level occupied by complementary base pair A-B in wild type. The two recombined chromatids have different pairs of non-complementary bases, A*Y and B*X, respectively.

¹ Supported by grant GM-06965 from the Public Health Service.

between gene conversion and reciprocal recombination between outside markers (MITCHELL 1955) nor for the observed asymmetries in frequencies of the recombinant types occurring (LISSOUBA 1961; MURRAY 1963; STADLER and TOWE 1963). All extensive data relating to these points result from selective procedures which limit recovery to a single type of conversion event, with no indication of its frequency relative to those of other types, whereas such relative frequencies are the basis of quantitative analyses of the kind to be discussed. In addition, causal relationships between interallelic recombination and recombination between outside markers depend on the mode of origin of regions of hybrid DNA, which is still unknown, but for which at least three different models have been proposed (WHITEHOUSE 1963; HOLLIDAY 1964; UHL 1965), each with its own implications relative to such relationships. These relationships are not considered pertinent to the present analysis inasmuch as the nature of the repair mechanism should be completely independent of the mode of origin of hybrid DNA.

Basic aspects of repair models: (1) A gene (cistron, polaron) is postulated to consist of a single DNA molecule—i.e., a single double helix. (2) The mutations to be considered are postulated to differ from wild type in a single base pair. For example, a complementary base pair A-B in the wild-type molecule is replaced by the complementary pair X-Y in the mutant. (3) Whereas in most instances the four chromatids taking part in meiosis comprise two pairs of sister chromatids, one pair derived from each parent, it occasionally happens that the base chains of two nonsisters become separated and reassociated to form hybrid DNA complexes, each consisting of one base chain from one participating chromatid and the complementary base chain from the other (Figure 1). (4) Except at the mutant site all base pairs in the hybrid DNA will be complementary. At the mutant site, however, the base pairs must be noncomplementary, and different noncomplementary pairs must be present at the heterozygous sites in the two chromatids with hybrid DNA—A*Y in one, B*X in the other, in the example illustrated (Figure 1). (5) If no repair occurs, segregation during the two meiotic divisions results in a tetrad of products comprised of one pure wild type, one mutant, and two which are still heterozygous at the mutant site. Completion of segregation in these instances occurs at the first postmeiotic mitosis, following one round of DNA replication during which each strand of each hybrid double helix has reproduced its exact complement. Among the eight products resulting, four will be wild type and four mutant—hence differing from normal segregation only in the division at which segregation has occurred. The division at which segregation has occurred is readily detected in linearly ordered 8-spored Ascomycetes, such as *Sordaria* (KITANI, OLIVE and EL-ANI 1962), and even in unordered 8-spored asci in genetically well-marked crosses. (6) Repair consists in the removal of one of the two noncomplementary bases at a heterozygous site, and its replacement by the base which is complementary to that remaining. (7) At the hybrid site in each recombined chromatid, repair results either in the restoration of a pure wild-type allele or a pure mutant allele, depending upon which base was replaced. In the example illustrated, wild type results when the Y of A*Y has been replaced by B and when the X of B*X has been replaced

				At heterozygous site A*Y		
	Nature of repair	Base change	Frac-tion	To wild allele	To mutant allele	Failure
				A*Y to A-B	A*Y to X-Y	Remains A*Y
				pr	$p(1-r)$	$1-p$
At heterozygous site B*X	To wild allele	B*X to B-A	qs	$6+ : 2m$ $prqs$	$4+ : 4m$ $p(1-r)qs$	$5+ : 3m$ $(1-p)qs$
	To mutant allele	B*X to Y-X	$q(1-s)$	$4+ : 4m$ $prq(1-s)$	$2+ : 6m$ $p(1-r)q(1-s)$	$3+ : 5m$ $(1-p)q(1-s)$
	Failure	Remains B*X	$1-q$	$5+ : 3m$ $pr(1-q)$	$3+ : 5m$ $p(1-r)(1-q)$	$4+ : 4m^{**}$ $(1-p)(1-q)$

**With postmeiotic segregation in two spore-pairs.

FIGURE 2.—Products resulting from different repair alternatives at the heterozygous sites in two recombined chromatids expressed as the ratios of wild type (+) to mutant (m) among octads of ascospores; together with algebraic terms representing fractions of each repair alternative in each chromatid and of the expected fraction of resultant spore patterns produced from combinations of alternatives in the two chromatids.

p = fraction in which repair occurs at site A*Y, among which r = fraction repaired to wild type, $1-r$ = fraction repaired to mutant, $1-p$ = fraction in which no repair occurs at site A*Y;

q = fraction in which repair occurs at site B*X, among which s = fraction repaired to wild type, $1-s$ = fraction repaired to mutant, $1-q$ = fraction in which no repair occurs at site B*X.

by A. Replacement of A by X in A*Y and of B by Y in B*X each restores the mutant allele. (8) It is assumed that the alternative events (i.e., repair to wild, repair to mutant, and repair failure) may occur with different relative frequencies at heterozygous sites in the two recombined chromatids. The possible combinations of alternative events at the two heterozygous sites are summarized in Figure 2, in which the resulting spore-ratios (designated as wild type to mutant, +:m) from each combination are also shown. Each octad of spores has one wild-type pair and one mutant pair, derived respectively from the wild-type and mutant chromatids which did not recombine. Pairs of spores derived from each recombined chromatid may be both wild-type, both mutant, or one of each, depending on the nature of repair or its failure.

Algebraic formulation: The three alternative events possible at a heterozygous site can be treated as two pairs of alternatives. First, repair either occurs or fails to occur. The fraction in which repair occurs at site A*Y is taken as p (where p can have any value from zero to one), hence the fraction without repair is $1-p$. At site B*X, the repaired fraction is taken as q , the unrepaired fraction as $1-q$. Secondly, when repair has occurred there results either a wild-type allele or a mutant allele. At site A*Y, among the repaired fraction p , the fraction becoming wild type is taken as r , that becoming mutant is then $1-r$; and at site B*X, among the repaired fraction q , the fraction becoming wild type is taken as s , that becom-

TABLE 1

Expected fractions and observed numbers of asci with spore patterns resulting from hybrid DNA

Ratio	Postmeiotic segregation	Expected fraction	Observed fraction	Observed numbers		
				Sordaria†	Ascobolus‡	
6+:2m	None	$prqs$	a	98	257	22
2+:6m	None	$p(1-r)q(1-s)$	b	13	120	4
5+:3m	1 spore pair	$pr(1-q) + (1-p)qs$	c	108	58	89
3+:5m	1 spore pair	$p(1-r)(1-q) + (1-p)q(1-s)$	d	20	136	24
4+:4m	2 spore pairs	$(1-p)(1-q)$	e	15*	..	..
4+:4m	None	$prq(1-s) + p(1-r)qs$	None	..	..	..
Total regular segregation $\times 10^{-3}$:				130	7	3.5

* There were 9 observed in a sample of 150, which is equivalent to 15 in a sample of 254.

† Data of KITANI *et al.* (1962).

‡ Data of C. C. C. YU-SUN and S. EMERSON (unpublished).

ing mutant as $1-s$. The algebraic terms for alternative events at A^*Y and B^*X , and for the resultant combinations at the two sites, are included in Figure 2. A summary of the expected fractions of the resulting spore ratios is given in Table 1, together with examples of observed numbers of the identifiable spore patterns.

Inasmuch as not all products of repair are identifiable as such it is not possible to derive the parameters p , r , q and s , directly from the observed frequencies of different ascus patterns. It is possible, however, to obtain partial solutions based on the relative frequencies of different observable patterns. A number of relationships so derived are here listed:

From the proportion $\frac{a}{b} = \frac{prqs}{p(1-r)q(1-s)}$, one obtains

$$r = \frac{a(1-s)}{a + (b-a)s} \quad (1)$$

From the proportion $\frac{c}{d} = \frac{pr(1-q) + (1-p)qs}{p(1-r)(1-q) + (1-p)q(1-s)}$, one obtains

$$p = \frac{q[(c+d)s-c]}{q[(c+d)(r+s) - 2c] - (c+d)r+c} \quad (2)$$

From the proportion $\frac{c}{a} = \frac{pr(1-q) + (1-p)qs}{prqs}$, one obtains

$$p = \frac{aqs}{q(ar+as+crs) - ar} \quad (3)$$

From equations 2 and 3, one obtains

$$q = \frac{a(s-r)}{a(s-r) - crs + (c+d)rs^2} \quad (4a)$$

$$p = \frac{a(r-s)}{a(r-s) - crs + (c+d)r^2s} \quad (4b)$$

From the proportion $\frac{c+d}{e} = \frac{p(1-q) + (1-p)q}{(1-p)(1-q)}$, one obtains

$$p = \frac{c+d-q(c+d+e)}{c+d+e-q(c+d+2e)} \quad (5)$$

From equation 1 it can be seen that, for any observed ratio of a (frequency of 6+:2m) to b (frequency of 2+:6m), for any one value of the parameter s there is a single value for parameter r . This relationship is graphed in Figure 3, making use of data from the g locus of *Sordaria* (KITANI, *et al.* 1962) in which $a = 98$, $b = 13$, and from two loci of *Ascobolus* (C. C. C. YU-SUN and S. EMERSON, unpublished) in which $a = 22$, $b = 4$ ($w-6$), and $a = 257$, $b = 120$ ($w-62$).

From equations 4a and 4b, unique values for parameters p and q derive from each value of s (and corresponding value of r), as shown in the left half of Figures 4, 5 and 6, based on data from the same *Sordaria* and *Ascobolus* loci. In each example, invalid values (greater than unit or less than zero) result for either p or q as values for r and s approach equality. Disregarding statistical fluctuations, this would mean that relative rates of repair to wild-type and mutant alleles actually do differ at the heterozygous sites (A*Y and B*Y) in the two recombined chromatids. The statistical significance of these deviations from equality at the two sites will be treated later.

The expected fraction of each of the six ascus patterns that can result from instances of hybridity in the DNA of two chromatids is obtained by substituting valid corresponding values of parameters p , r , q and s in the formulae listed in Table 1. The results of such substitutions are graphed in the right halves of Figures 4, 5 and 6, for the three loci under consideration. Patterns with ratios 6+:2m, 2+:6m, 5+:3m and 3+:5m, on whose observed frequencies the calculations were based, maintain their observed relative frequencies throughout the range of valid corresponding parameter values (curves a, b, c and d, in the figures).

Expected frequencies of the two ascus patterns with 4+:4m ratios, on the other hand, vary considerably with changing values of the parameters (curves e and f in Figures 4, 5 and 6). That in which segregation is completed during meiosis, being indistinguishable from the identical pattern resulting from normal segregation (i.e., when no hybrid DNA has been formed), can only be estimated after a single set of corresponding parameter values has been selected as the most probable. That in which postmeiotic segregation occurs during the development of two spore pairs can be identified in certain instances, namely, by analysis of a random sample of unselected asci in genetically well marked crosses (CASE and GILES 1964); by visual selection based on spore position in linearly ordered asci in crosses segregating at a single site for a visible ascospore character (KITANI *et al.* 1962); and by visual selection of unordered asci segregating for two phenotypically distinguishable ascospore mutants at single mutant sites in independent

FIGURE 3.—Relationships between r and s (the fractions resulting in wild type among those which are repaired at sites A*Y and B*X, respectively), expressed as percentages, calculated by equation 1 from data from *Sordaria* (upper curve), from the $w-6$ locus of *Ascobolus* (middle curve), and from the $w-62$ locus of *Ascobolus* (lower curve). Projections of values of r and s (here expressed as decimal fractions) onto the diagonal result in a common baseline for corresponding values of these two parameters, such as used in Figures 4, 5 and 6.

FIGURES 4, 5 (Sordaria), 5 (Ascobolus, $w-6$) and 6 (Ascobolus, $w-62$).—Values of p and q (fractions of repair at sites A*Y and B*X, respectively), expressed as percentages, corresponding to different corresponding values of r and s ; and expected frequencies of different spore patterns resulting from all valid corresponding values of p , q , r and s : (a) expected frequencies of 6+ : 2m; (b) of 2+ : 6m; (c) of 5+ : 3m; (d) of 3+ : 5m; (e) of 4+ : 4m with postmeiotic segregation in two spore pairs; (f) of 4+ : 4m with segregation completed during meiosis, and indistinguishable from spore patterns resulting from normal segregation. *Note:* Because there is no independent method of identifying sites A*Y and B*X, reversal of corresponding values for r and s results in the reversal of corresponding values for p and q , and the entire information is shown in graphs covering either half of the baseline representing corresponding values of r and s .

loci, followed by identification of spore pairs by the segregation of other marker genes (possible in *Ascobolus*, for example). The only extensive data so far available relating to this ascus pattern are from *Sordaria* (KITANI *et al.* 1962), and the published data are not strictly comparable to those for the other patterns—nine were reported in a total of 150 asci with “aberrant” segregation ratios whereas the total of 6+:2m, 2+:6m, 5+:3m and 3+:5m asci was 239, leading to the implication that there may have been 15 4+:4m asci with postmeiotic segregation in a total of 154 asci with recognizable conversion ratios, or slightly more than the number with 2+:6m ratios. The maximum expected number of such 4+:4m asci from calculations yielding the exact observed numbers of the other four observable ascus patterns is about eight (Table 2), which still results in an extremely good fit between observed and expected.

With adequate data on the relative frequency of aberrant patterns with 4+:4m ratios resulting from postmeiotic segregation it becomes possible to evaluate p in terms of q directly from equation 5, which is based on the frequencies of such 4+:4m ratios relative to the sum of frequencies of 5+:3m and 3+:5m ratios. The resulting relationships for different relative frequencies of $c+d$ and e are shown in the family of dotted curves in Figure 7. The curve represented by the broken line is based on the data from *Sordaria*, in which $c+d = 128$ and $e = 15$, $(c+d)/e \times 100 = 89.5$. The solid-line curves in Figure 7 show the relationships between p and q resulting from the *Sordaria* data when calculated from equations 4a and 4b. If observed frequencies of all five detectable spore patterns truly represented

TABLE 2

Closeness of fit to observed data of numbers expected on two interpretations: identity (equation 8) and nonidentity (equations 4a and 4b) of rates of repair alternatives in the two recombined chromatids

Sordaria data*							Ascobolus data†		
Spore pattern	Observed	Equations 4a and 4b					Observed	Equations 4a and 4b	
		Actual values		Approximation		Equation 8		Equations 4a and 4b	
		$p=.935$	$p=.9$	$p=q=.73$	$p=.847$			Equation 8	
		$q=.694$	$q=.65$		$q=.997$				
		$r=.909$	$r=.9$		$r=.84$				
$s=.43$	$s=.5$	$r=s=.767$	$s=.29$	$r=s=.885$					
6+:2m	98	98.0	100.9	94.5	101.7	98.4	257	257.2	230.4
2+:6m	13	13.0	13.4	10.5	9.4	9.1	120	119.9	146.9
5+:3m	108	108.8	111.2	113.5	98.1	94.9	58	58.0	107.7
3+:5m	20	20.0	20.6	23.0	29.8	28.8	136	135.9	86.0
$\chi^2(3 \text{ df})$		0	..	..	5.7	..	..	<.0003	55
P		1.0	..	..	.13	..	..	>.999	<.001
4+:4m	15	..	7.9	12.5	..	22.9			
$\chi^2(4 \text{ df})$		..	6.5	1.9	..	8.9			
P		..	.16	.74	..	.06			

* From KITANI *et al.* (1962).

† Preliminary data of DR. CLARE C. C. YU-SUN and S. EMERSON.

N.B. Where two columns of expected numbers appear, one excludes and one includes the numbers of 4+:4m patterns showing postmeiotic segregation.

FIGURE 7.—Relationships between p and q (fractions of repair at sites A*Y and B*X, respectively), expressed in percentages. The family of dotted curves is based on formula 5 for various values of $(c+d)/e \times 100$, in which c is the observed number of 5+:3m asci, d that of 3+:5m, and e that of 4+:4m involving post-meiotic segregation in two spore pairs. The broken line curve is based on the *Sordaria* data (see Table 1). The solid line curves show the expected relationships between p and q when the *Sordaria* data are introduced into formulae 4a and 4b.

FIGURES 8 and 9.—Relationships between p and q based on formulae 4a and 4b and the $w-6$ (Figure 9) and $w-62$ (Figure 8) data from *Ascobolus*. *Ascobolus* data are not yet available for calculations based on formula 5.

the actual frequencies occurring in a large sample, curves for p in terms of q derived by the two methods (i.e., from equation 5 and from equations 4a and 4b) should intersect, thus limiting the range of possible values for the four parameters, p , q , r and s , very considerably. This has not been accomplished for the *Sordaria* data. For the two *Ascobolus* loci it is still impossible to make use of formula 5, but based on formulae 4a and 4b (Figures 8, 9) it may be predicted that the frequencies 4+:4m asci should differ at the two loci.

The special case of identical frequencies at both hybrid sites: If, as has been assumed (WHITEHOUSE 1964), repair to wild type, repair to mutant, and repair failure, each occurs at a rate which is identical at both A*Y and B*X heterozygous sites, the following simplifications can be made in the formulae (Table 1) for expected fractions of different spore patterns: for 6+:2m, $a = p^2r^2$; for 2+:6m, $b = p^2(1-r)^2$; for 5+:3m, $c = 2p(1-p)r$; for 3+:5m, $d = 2p(1-p)(1-r)$; and for 4+:4m with postmeiotic segregation, $e = (1-p)^2$.

From the proportion $\frac{c}{d} = \frac{2p(1-p)r}{2p(1-p)(1-r)}$, one obtains

$$r = \frac{c}{c+d} \quad (6)$$

From the proportion $\frac{a}{b} = \frac{p^2 r^2}{p^2 (1-r)^2}$ one obtains

$$r = \frac{\sqrt{a}}{\sqrt{a} + \sqrt{b}} \quad (7)$$

From the proportion $\frac{a+b}{c+d} = \frac{p^2 r^2 + p^2 (1-r)^2}{2p(1-p)r + 2p(1-p)(1-r)}$, one obtains

$$p = \frac{2(a+b)}{2(a+b) + (c+d)(1-2r+2r^2)} \quad (8)$$

If identical rates occur in both recombined chromatids for each of the repair alternatives, then approximately identical values for r should be obtained from equations 6 and 7. When different values result, a probable value of r may be selected as that one giving the closest fit to the observed $a:b$ and $c:d$ ratios. The *Sordaria* data (Table 1) produce r values of .732 by equation 6, .844 by equation 7, and a probable value of .767. Data for the *w-62* locus of *Ascobolus* produce r values of .594 by equation 6, .299 by equation 7, and a probable value of .556. By substituting such probable values for r into equation 8, a probable value for p may be selected as that giving the smallest χ^2 when calculated spore-pattern frequencies are compared with observed. A p value of .73 was thus found for *Sordaria*, and of .885 for the *w-62* locus of *Ascobolus*.

Deviations from those observed of the calculated frequencies based on alternative interpretations are summarized in Table 2. Perfect agreement between calculated and observed is expected for the four ascus patterns upon which calculations were based (provided calculations are carried to sufficient decimal places) when based on the interpretation that dissimilar repair rates may exist in the two recombined chromatids, and the same relative proportions between these patterns should hold when the fifth ascus pattern (4+:4m with postmeiotic segregation) is included. Excellent fits to both *Sordaria* and *Ascobolus* data are obtained by this interpretation. The interpretation that identical repair rates occur in both recombined chromatids gives only a fair fit to the *Sordaria* data, and does not account for the *Ascobolus* data considered here.

DISCUSSION

The quantitative treatment developed above is directly applicable to studies of heterozygosity at only a single mutant site. When there is segregation at two or more mutant sites in a single cistron, additional factors become important. (1) What is the extent of hybrid regions of DNA: do they include entire cistrons or only parts thereof; if parts, do they vary in extent, and are some regions more likely to be involved than others? (2) When two heterozygous mutant sites occur

in a common region of hybrid DNA, is the type of repair occurring at one independent of that occurring at the other?

Some published observations suggest that there is considerable variation within one cistron, both in extent of DNA hybridity and in the interdependence of type of repair occurring at two included mutant sites. For example, CASE and GILES (1964), by complete tetrad analysis in a cross heterozygous at three mutant sites of the *pan-2* locus of *Neurospora*, observed 13 asci in which interallelic recombination had occurred. One terminal site was involved in 12 asci, the other in five, and the middle site was never involved unless one or both terminal sites were also involved. On the DNA-repair interpretation, regions of hybrid DNA must have included a single mutant site in eight asci, two adjacent sites in one ascus, and all three sites in four asci, with one terminal site included in 12 of the 13 asci. In all but one of the instances in which more than one mutant site was involved, repair involved replacement of bases in the same base-chain of the double helix at all sites repaired. In the exceptional instance, replacement was in a common chain at two adjacent sites but in the complementary chain at the third site. Although meager, these data suggest that regions of hybrid DNA are variable in length, but are usually initiated at one end of the cistron. They also suggest that in the excision of bases a string of some length is removed from one strand of the double helix, resulting in a loss of independence in repair type between closely linked mutant sites. Other sources, for example studies with *Ascobolus* (LISSOUBA, MOUSSEAU, RIZET and ROSSIGNOL 1962), and with *Neurospora* (MURRAY 1963; STADLER and TOWE 1963), support the same inferences.

I am greatly indebted to DR. CLARE C. C. YU-SUN for permission to include some of her unpublished data.

SUMMARY

On the basis that ascus patterns characteristic of gene conversion result from repair of mispaired bases in regions of hybrid DNA in two recombined chromatids, a quantitative treatment is developed in which different repair rates are permitted in the two complementarily hybrid chromatids. The method employed is not directly applicable to examples in which there exists more than a single heterozygous mutant site within a cistron.

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