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Spontaneous mutagenesis: the roles of DNA repair, replication, and recombination

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I. Introduction

Spontaneous mutations are mutations that arise by mechanisms that have yet to be identified. An early explanation for spontaneous mutagenesis was that it resulted from background radiation. However, Muller and Mott-Smith (1930) showed that only a very small fraction of spontaneous mutagenesis could result from the known levels of background radiation. Other studies (reviewed by von Borstel, 1969) have supported this evaluation. It is now generally accepted that intracellular mechanisms are the cause of spontaneous mutagenesis (reviewed by von Borstel, 1969; Cox, 1976; Loeb and Kunkel, 1982; Lawrence, 1982; Drake et al., 1983). In this review, we will use a genetic

approach to discuss the role of DNA replication, recombination and repair in spontaneous mutagenesis (see also Kondo et al., 1970; Kondo, 1973). While we will discuss the major hypotheses for spontaneous mutagenesis, our main objective is to emphasize an area that has been minimized in the earlier reviews, that is, the role of DNA damage and of DNA repair genes in spontaneous mutagenesis.

In earlier work on the involvement of error-prone DNA repair in spontaneous mutagenesis (Sargentini and Smith, 1981), the *uvrA*, *uvrB*, *uvrD*, *recA*, *recB*, *lexA*, and *umuC* mutations in *Escherichia coli* were studied, and it was shown that mutations that enhance error-prone repair also enhance spontaneous mutagenesis, and that mutations that reduce error-prone repair also reduce spontaneous mutagenesis. It was concluded, therefore, that much of spontaneous mutagenesis in *E. coli* is the result of error-prone repair. The questions that we wish to address here are the following: (1) What kinds of mutations are produced spontaneously, and what do these kinds of mutations suggest about the relative importance of various mechanisms for spontaneous mutagenesis? (2) If one surveys the literature on spontaneous mutagenesis in several species, can one demonstrate a major involvement of error-prone repair and of error-free repair in spontaneous mutagenesis? (3) From data for bacteria, can one predict mechanisms of spontaneous mutagenesis in higher organisms? We have attempted in this review not only to provide answers to these questions, but also to provide a conceptual basis for future work on the mechanisms for spontaneous mutagenesis.

II. Types of spontaneous mutations

A. Bacteria

What kinds of mutations occur spontaneously? In one of the few studies performed to quantitate the general classes of mutations that occur spontaneously, Hartman et al. (1971) classified 83 spontaneous histidine auxotrophs of *Salmonella typhimurium* and obtained the following distribution: 53% were caused by base substitution (either transitions or transversions), 11% were caused by frameshifts (i.e., insertions or deletions of one or a few base pairs), 23% were caused by deletions (i.e., deletions of more than a few base pairs), and 13% were apparently caused by insertions (i.e., insertions of large DNA elements) *. Since studies of this sort only detect mutations that inactivate a gene product (otherwise there would be no easy way to detect the mutants), one can presume that many missense mutations are overlooked in such studies because they have little or no effect on the measured phenotype (i.e., they are silent mutations). Thus, the listed proportion for base substitutions is most likely an underestimate, while those listed for the other classes of mutations are most likely overestimates. Also, these data of Hartman et al. (1971) are given only for the purpose of discussion, since the mutational spectrum observed at any given locus can certainly be different. For example, Farabaugh et al. (1978) showed that 67% of the spontaneous mutations detected by inactivation of the *lacI* gene were attributable to frameshift or small deletion mutations, and that these mutations all occurred at only one or two sites in the *lacI* gene. Similarly, Bukhari and Khatoon (1982) found that virtually all mutations selected for strong polarity in the *lac* gene were the result of the introduction of insertion sequences. Such "hotspots", if they are not the result of general phenomena, can severely affect one's perception of what is a general mutational spectrum. Since deletions and insertions were detectable in the aforementioned data of Hartman et al. (1971), but they comprised only about one-third of the mutagenesis, we favor the conclusion that, *in general*, base substitution is the most common form of spontaneous mutation in bacteria.

B. Fungi

Base substitutions also seem to be the most common type of spontaneous mutations in yeast. Whelan (cited in Lemontt, 1977) found that about 35% of spontaneous canavanine-resistant mutants of *Saccharomyces cerevisiae* arise by base substitu-

* The last category of mutations was originally classified as frameshifts that reverted spontaneously, but were not affected by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine or ICR191 compounds. In light of work by Malamy (1966) and others (reviewed in Starlinger and Saedler, 1972), we have interpreted this group of "frameshift mutants" to be insertion mutants.

tion. Sherman et al. (1974) characterized 41 spontaneous mutants defective in iso-1-cytochrome *c* and found 5 nonreverting mutants (probably insertion or small deletion mutants), 2 initiation mutants, and 12 nonsense mutants. The remaining 22 mutants were able to revert with mutagens such as ethyl methanesulfonate, and were thought not to be frameshift mutants. Thus, the latter can tentatively be labeled as missense mutants. Therefore, more than 80% of the 41 spontaneous *cyc1* mutants studied by Sherman et al. (1974) were most likely the result of base substitution.

One can conclude, in general, that base substitution is the most common type of spontaneous mutation in bacteria and fungi, This is fortunate since most of the data that were available for this review resulted from base-substitution assays. It is important to note that each kind of mutation (e.g., base substitution, frameshift, etc.) probably has a unique set of mechanisms for its induction (e.g., reviewed in Drake et al., 1983), and thus one needs to be aware of the molecular basis of the mutation assay before trying to apply its results to a given model for mutagenesis.

III. Replication errors

One difficulty in discussing the roles of replication, recombination, and repair in spontaneous mutagenesis, is that these three processes overlap each other. Thus, we will define what sort of material each section will include. This section on replication errors is meant to focus on the DNA replication that is part of the normal process of cell division. In this context, damage in the DNA template must not block DNA replication, i.e., it must be miscoding damage rather than noncoding damage. Popular relevant mechanisms for mutagenesis that will be discussed here include: (1) base tautomerization, (2) miscoding DNA damage, (3) polymerase errors, and (4) mutators, antimutators and mismatch repair.

A. Base tautomerization

From their model for the double-helical structure of DNA, Watson and Crick (1953) postulated that transition mutagenesis (A ↔ G, or C ↔ T) occurred by the production of base tautomers via proton migration. Similarly, Topal and Fresco (1976) used tautomerization and base rotation to explain transversion mutagenesis (A or G ↔ C or T). The essence of such models is that at the moment of replication a base in the DNA template develops an inappropriate coding property, which leads to the incorporation of an incorrect base in the nascent DNA. Theoretically, base tautomerization could explain most spontaneous base substitutions, however, such models are difficult to verify and seem inconsistent with the data for the genetic control of spontaneous mutagenesis, which will be discussed later.

B. Miscoding base damage

Spontaneously modified bases may code differently than their normal precursors. Deaminated 5-methylcytosine (i.e., thymine) codes for adenine and thus, will cause a GC → AT transition. Since there is a good correlation between the occurrence of 5-methylcytosine in the *lacI* gene and the occurrence of mutation hotspots (Duncan and Miller, 1980), this suggests that 5-methylcytosine deamination plays a role in spontaneous mutagenesis.

The deamination of cytosine, yielding uracil in DNA, can also cause GC → AT transitions. The role of deaminated cytosine in spontaneous mutagenesis is suggested by the fact that the *ung* mutant (deficient in the removal of uracil from DNA) shows enhanced spontaneous mutagenesis (Hayakawa and Sekiguchi, 1978; Duncan and Miller, 1980; Duncan and Weiss, 1982), however, one would like to know whether an increased intracellular concentration of uracil *N*-glycosylase in an ung^+ cell would result in a lower rate of spontaneous mutagenesis. Such a finding would provide more valid support for the role of cytosine deamination in spontaneous mutagenesis in wild-type cells.

Methylated guanine is another modified base that should occur naturally in DNA and would be expected to cause GC → AT transitions (Drake et al., 1983).

C. Polymerase errors

Loeb and Kunkel (1982) have reviewed abundant data showing that DNA polymerases occasionally incorporate incorrect bases. The polymerase error rate is affected by the base sequence

of the template, the nature of the misincorporated base, and the nature and source of the DNA polymerase (Loeb and Kunkel, 1982). The polymerase error rate is also affected by perturbations in the relative sizes of the pools of nucleoside triphosphates (Fersht, 1979; Kunkel et al., 1981, 1982; reviewed by Kunz, 1982), and of divalent cations such as Mg^{2+} and Mn^{2+} (Sirover and Loeb, 1976; Goodman et al., 1983; Hillebrand and Beattie, 1984).

The role of polymerase errors in spontaneous mutagenesis is most strongly supported by studies with bacteriophage T4 mutants. That is, antimutator derivatives of phage T4 have been isolated and shown to be mutant at the gene for DNA polymerase (gene 43; Drake and Allen, 1968; Drake et al., 1969). Thus, a mutation that makes the phage DNA polymerase more accurate reduces the level of spontaneous mutations.

While the base sequence of the template clearly has an effect on misincorporation, i.e., base-substitution errors (reviewed in Loeb and Kunkel, 1982; also see Patten et al., 1984), it seems also to be an important factor in small and large addition/deletion mutations. In a model for misalignment mutagenesis, Streisinger et al. (1966) described how the occurrence of short, redundant base sequences in DNA were correlated with the sites of frameshift mutations and of mutations involving large additions or deletions of DNA. In a related fashion, Ripley (1982) and Ripley and Glickman (1982) have correlated the occurrence of DNA palindromes with the occurrence of frameshift and deletion mutations that are not easily explained by the Streisinger model. Such models of misalignment mutagenesis, and data to support them, have recently been reviewed by Drake et al. (1983). These models seem valid because of the good correlation between their predictions and the occurrence of spontaneous addition/deletion mutations at certain chromosomal sites.

D. Mutators, antimutators and mismatch repair

The mutator and antimutator mutations to be discussed in this section on DNA replication errors were selected either because (i) they are known to affect the normal replication process, (ii) they do not sensitize cells to killing by DNA damage, or (iii) their effect on mutagenesis is independent of the *recA* gene, i.e., the gene that controls most mutagenesis after DNA damage induction (reviewed in Witkin, 1976). Mismatch repair is generally regarded as a postreplication proof-reading process (Wildenberg and Meselson, 1975), rather than a repair process for DNA damage.

The main purpose of this section is simply to indicate the ubiquity and complexity of genes assumed to be involved in mutation avoidance, i.e., mutations in these genes produce mutator strains. The isolation and characterization of mutator mutants in such organisms as bacteriophage, bacteria, yeast, Drosophila, and maize (reviewed in Mohn and Würgler, 1972; E.C. Cox, 1976) have been valuable in understanding how spontaneous mutations can occur, but have been much less informative as to how spontaneous mutations do occur. Answers to the latter question come directly from the study and understanding of antimutator mutants. However, only a few antimutator mutants have been found. We will discuss mutators, antimutators, and strains deficient in mismatch repair according to the organisms in which they appear.

1. Bacteriophage. Mutations affecting the gene-43-coded DNA polymerase of phage T4 result in enhanced transition (Speyer et al., 1966) and transversion (Hall and Lehman, 1968) mutations. Antimutator phage T4 DNA polymerase mutants have also been described (Drake and Allen, 1968; Drake et al., 1969). Muzyczka et al. (1972) concluded that spontaneous mutagenesis in phage T4 is the result of the antagonistic interaction of the polymerase misfunction (to insert incorrect nucleotides) and the 3′-5′ exonuclease function (to remove incorrect nucleotides).

Other support for the involvement of replication errors in spontaneous mutagenesis comes from the mutator or antimutator phenotypes (depending on the reversion assay, i.e., type of transition or frameshift) of phage T4 gyrase (gene 32) and deoxycytidylate hydroxymethylase mutants (reviewed in Drake, 1973). However, the latter mutant also shows enhanced recombination (Bernstein, 1967).

2. Bacteria. Bacterial mutator and antimutator mutations are listed in Table 1, according to the criteria that these mutations affect spontaneous mutagenesis, but have no known effect on DNA repair or experimentally induced mutagenesis.

However, 3 mutants, *uvrD*, *dnaE*(*polC*), and *lig*, have defects in DNA repair (reviewed in Hamelin et al., 1976; van der Schueren et al., 1977; Youngs and Smith, 1977) and/or radiation mutagenesis (reviewed in Bridges, 1980; Sargentini and Smith, 1980), and they are listed in Table 1 because they show *recA-independent* mutator activity. This *recA*-independent phenotype has generally been considered as diagnostic for the involvement of replication errors in spontaneous mutagenesis (e.g., E.C. Cox, 1976). The spontaneous mutation rates of the other mutants listed in Table 1 are also *recA* independent, however, this was tested in only a few of the mutagenesis assays listed in Table 1.

The possible role in spontaneous mutagenesis of the *dnaE* mutants, which have altered DNA replication polymerases, is logically related to the fidelity of DNA replication. One might also consider that *dnaE* mutants, and more likely the *lig* mutant, may enhance spontaneous mutagenesis by blocking the replication fork or the resealing of DNA strand breaks, respectively. Both of these actions appear to result in the induction of the SOS phenomenon (reviewed in Witkin, 1976; Walker, 1984), which can lead to enhanced spontaneous mutagenesis, as evidenced by data for the *tif* (Witkin, 1974, 1975b; Mount, 1977) and *dnaB* (Witkin, 1975c) strains. If the SOS phenomenon is involved, one would expect to find a *recA*-dependent mutator effect with some of the mutagenesis assays that have yet to be tested for a *recA* involvement in these strains.

Besides DNA polymerase III (the *dnaE* gene product), another component of the DNA polymerase III holoenzyme also affects replication errors. The ϵ-subunit is now known to be determined by the mutator gene *mutD* (also known as *dnaQ*) (Erlich and Cox, 1980; Scheuerman et al., 1983; Horiuchi et al., 1978; Maruyama et al., 1983).

The availability of substrates for DNA synthesis may indirectly affect spontaneous mutagenesis. The *purB* (purine auxotrophy) mutant (Geiger and Speyer, 1977) would seem to exhibit its antimutator effect by increasing the fidelity of DNA replication via changes in the relative pool sizes of DNA precursors (reviewed in Kunz, 1982). DNA precursor pool sizes are also relevant to the regulation of the *mutD* (Erlich and Cox, 1980) and *tif* (Witkin, 1974) mutator effects, which suggest that altered deoxynucleoside triphosphate selection can be an important mechanism of spontaneous mutagenesis.

After an incorrect nucleotide has been incorporated into DNA, the cell still can use mismatch repair to correct the error. The *mutS*, *mutH*, *mutL*, and *uvrD* mutations (Table 1), and the *dam* mutation (Table 5) are known to affect mismatch repair (Nevers and Spatz, 1975; Glickman and Radman, 1980). These mutators are analogous to the phage T4 mutators described earlier in that, in both cases, reduced DNA fidelity is thought to result from a relative reduction in "proof-reading" function.

If the *mutD*, *mutH*, *mutL*, *mutS*, *uvrD*, and *dnaE* mutations all enhance spontaneous mutagenesis by decreasing the accuracy of DNA replication, then the *mutT* and *mutB* mutations must operate at a different level or pathway because, unlike the former mutators, they do not seem to generally enhance spontaneous frameshift mutagenesis (Table 1). The specificity of the *mutT* mutator for AT → CG transversions argues that this strain may be specifically deficient in the repair of altered thymine or adenine residues much like the *ung* mutant which yields GC → AT transitions due to unrepaired deaminated cytosine lesions (Duncan and Weiss, 1982). The *mutB* mutator has not yet been tested for a base-substitution specificity.

3. Fungi. Mutations in fungi that act as mutators are listed in Table 2, again according to the criteria that they have no known effect on DNA repair or experimentally induced mutagenesis. Compared with bacteria, much less is known about these mutators, but one can comment on their mutational specificy. The *gam2, gam4, mtm1, and mtm2* mutators all show a specificity for mitochondrial DNA relative to nuclear DNA even though the mutators are nuclear genes (Foury and Goffeau, 1979; Johnston and Johnson, 1983; Johnston, 1979). The *mtm3* mutator and the LB_6 antimutator affect both mitochondrial and nuclear DNA. The other 6 mutators listed in Table 2 have been tested only for their effects on nuclear DNA. Of these 6 mutators, only the *mut1* and *mut2* genes have thus far been shown to exhibit specific mutator effects, but this may reflect the greater

TABLE 1

MUTATOR AND ANTIMUTATOR MUTATIONS IN BACTERIA [a]

Mutant [a]	Mutagenesis assay [b]	Mutagenesis compared to wild type	References [c]
mutT	Str^r(ms), *trpA*(AT → CG), *arg*, λ*susP3*, λ*susN7*, Cap^r, Flu^r, T1^r, T3H^r, T4^r, T5^r, Amp^r, *argE3*	Enhanced	3,31,32
	lacZ(fs), *trpA540*(fs), T2^r	Normal	26
mutB	*hisG46*(ms), Nal^r, Rif^r(ms), *gal6*(ms)	Enhanced	20
	hisD3052(fs)	Normal	20
mutD	*trpA*(AT ↔ GC, AT ↔ CG, AT ↔ TA, GC ↔ CG), Str^r(ms), Nal^r, Rif^r(ms), Chl^r, *leuB6*, *his-4*(oc), *argE*(oc), Azi^r, *tfrA*, *trpA*(fs)	Enhanced	4,6,7,12,16,18
mutH	*hisG46*(ms), Nal^r, Rif^r(ms), *gal6*(ms), Str^r, *trpE65*(oc), Str^r, Azi^r, T1^r, T2^r, auxotrophy, *hisD3052*(fs), leu(fs), *argA*(fs), *his*(fs)*trp*(fs), *trpE9777*(fs), *ilv*(fs), *lacZ*(fs)	Enhanced	10,11,20,27
	trpA21	Reduced	27
mutL	Str^r(ms), Spc^r(fs), T1^r, T7^r, *trpA*(AT ↔ GC), T3^r, T2^r, T6^r, *hisG46*(ms), Nal^r, Rif^r(ms), *gal6*(ms), *lacZ*(fs), *trpA*(fs), *hisD3052*(fs), *trpE9777*(fs), *trpD*(de)	Enhanced	1,11,15,20,25–27
mutS	T1^r, T3^r, T7^r, Pen^r, Str^r(ms), Cys^r, Azi^r, Kan^r, T2^r, Van^r, *trpA*, *his*, *thr*, *leu*, *lys* (AT ↔ GC), *hisG46*(ms), Nal^r, Rif^r, *gal6*(ms), *lacZ*(fs), *trpA*(fs), *hisD3052*(fs), *trpE9777*(fs), *lacU118*(oc), *lacX90*(oc)	Enhanced	5,11,20,23,24,26,27
uvrD	Str^r(ms), T7^r, *leu-6*, *ilvD188*, T4^r, *trp*, T6^r, *trpA46*(ms), Val^r, *trp*(oc), *trpA* (AT ↔ GC), *his*, *hisG46*(ms), Nal^r, Rif^r(ms), *gal6*(ms), Spc^r, *lacZ*(fs), *trpA*(fs), *hisD3052*(fs), *trpE9777*(fs)	Enhanced	14,20–22,26–30
	Phage genes, *trpA* (AT → CG, GC → TA), *his-4*	Normal	14,21,30
dnaE9	*lacYA482*, Rif^r(ms)	Enhanced	13
dnaE486	*trpA*(TA ↔ AT, CG → GC, GC ↔ TA), Aza^r, *trpE9777*(fs), *trpA540*(fs)	Enhanced	9,27
	trpA540(fs), *trpA*(AT → GC), *trpA9813*(fs), *trpA21*(fs)	Normal	9,27
dnaE511	*trpA*(AT → TA, CG → GC, GC → TA), Aza^r, *trpE9777*(fs), *trpA21*(fs)	Enhanced	9,27
	trpA540(fs), *trpA*(AT → GC), *trpA9813*(fs)	Normal	9,27
dnaE672	*leu-6*, Val^r, Amp^r, Aza^r, Rif^r(ms)	Enhanced	19
lig(40°C)	*trpE9777*(fs), Val^r, Rif^r(ms), 5MT^r, λ*c*	Enhanced	2*,17,27
purB	Val^r, *metE*, *his*, *trp*	Reduced	8
	T7^r, Rif^r(ms)	Normal	8

[a] Data for both *Escherichia coli* and *Salmonella typhimurium* are presented. The *mutB* mutant has thus far only been found in *S. typhimurium*. Relevant alternate nomenclature for mutators, from Bachmann (1983) and references therein: *mutH* = *mutR*; *mutL* = *mut-25*; *uvrD* = *mutU*, *uvrE*, *recL*, and *uvr502*; *dnaE* = *polC*. *dnaQ* = *mutD* (Scheuermann et al., 1983; Maruyama et al., 1983). The mutants here were selected primarily because their rates of spontaneous mutagenesis were not affected by an additional *recA* mutation. However, this criterion of *recA* independence was not tested with all of the listed mutagenesis assays, and in the case of the *dnaE* alleles, only *dnaE9* was tested.

TABLE 2

FUNGAL MUTANTS WITH ALTERED SPONTANEOUS MUTAGENESIS BUT NORMAL SENSITIVITY TO DNA DAMAGE

Mutant	Mutagenesis assay [a]	Spontaneous mutagenesis compared to wild type	References [b]
MUT6	*lys1-1*(oc)	Enhanced	5
MIC12	*can*^{r}	Enhanced	8
gam2	*rho*$^-$ (de), Ery^r, Oli^r, Diu^r,	Enhanced	2
	his, met2,	Normal	2
gam4	*rho*$^-$ (de), Ery^r, Oli^r, Diu^r	Enhanced	2
	his, met2, can^r	Normal	2
rem1	*can*^{r}, *trp5-2*(oc, l), *trp5-2* *ade2-1*(oc, SS)	Enhanced	3
mtm1	Ery^r, Spi^r, *rho*$^-$ (de)	Enhanced	6,7
	his1-7(oc), *lys2, his1*	Normal	6
mtm2	Ery^r, Spi^r, *rho*$^-$ (de)	Enhanced	6,7
	his1-7(oc), *lys2, his1*	Normal	6
mtm3	Ery^r, Spi^r, *his1-7*(ms), *can*^{r}	Enhanced	7
	rho$^-$ (de)	Normal	7
mut8	*lys1-1*(oc)	Enhanced	9
mut1	*lys1-1*(oc, SS), *his1-7*(ms), *arg4-17*(oc, SS)	Enhanced	4,5,9,10
	lys1-1(oc, l), *arg4-17*(oc, l)	Reduced	4,10
	hom3-10(fs)	Normal	4,10
mut2	*lys1-1*(oc, SS, l), *his1-7*(ms), *hom3-10*(fs)	Enhanced	4,10[†]
LB_6	Ery^r, Oli^r, Diu^r, *can*^{r}, *CHX*^{r}, *his*	Reduced	1

[a] Mutation assay nomenclature: oc, ochre nonsense mutation; de, deletion mutation; l, oc site; SS, oc supersuppressor; ms, missense mutation; fs, frameshift mutation. The *rho*$^-$, Ery^r, Oli^r, Diu^r, and Spi^r mutations all occur in mitochondrial DNA. All other mutations listed occur in nuclear DNA.

[b] Refer to footnote e, Table 3 for an explanation of notated references. References: 1, Bianchi and Foury, 1982; 2, Foury and Goffeau, 1979; 3, Golin and Esposito, 1977; 4, Gottlieb and von Borstel, 1976; 5, Hastings et al., 1976; 6, Johnston, 1979; 7, Johnston and Johnson, 1983; 8, Maloney and Fogel, 1980; 9, Nasim and Brychcy, 1979; 10, von Borstel et al., 1973.

number of mutation assays used to evaluate these two mutators (Table 2). One would like to know if these fungal mutations sensitize cells to DNA-damaging agents, and whether each mutation retains its mutator phenotype in a *rad6 rev3* strain of *S. cerevisiae*, since this strain seems totally deficient in UV radiation mutability (Lawrence and Christensen, 1976), and would be expected to be deficient in the mutagenesis caused by most chemicals (Prakash, 1974). Also, the *mut1* and LB_6

[b] Mutation assay nomenclature: ms, missense; fs, frameshift; de, deletion; oc, ochre nonsense mutation. Str^r, Spc^r and Rif^r mutants have been classified by us as missense mutants on the basis of studies of such mutants (e.g., Silengo et al., 1967; Austin et al., 1971).

[c] Refer to footnote e, Table 3 for an explanation of notated references. References: 1, Balbinder et al., 1983; 2, Condra and Pauling, 1982; 3, E.C. Cox, 1973; 4. E.C. Cox, 1976; 5, E.C. Cox et al., 1972; 6, Degnen and Cox, 1974; 7, Fowler et al., 1974; 8, Geiger and Speyer, 1977; 9, Hall and Brammer, 1973; 10, Hill, 1968; 11, Hoess and Herman, 1975; 12, Horiuchi et al., 1978; 13, Konrad, 1978; 14, Kushner et al., 1978; 15, Liberfarb and Bryson, 1970; 16, Maruyama et al., 1983; 17, Morse and Pauling, 1975; 18, Scheuermann et al., 1983; 19, Sevastopoulos and Glaser, 1977; 20, Shanabruch et al., 1981, 21, Siegel, 1973; 22, Siegel, 1981; 23, Siegel and Bryson, 1964; 24, Siegel and Bryson, 1967; 25, Siegel and Ivers, 1975; 26, Siegel and Kamel, 1974; 27, Siegel and Vaccaro, 1978; 28, Smirnov et al., 1972; 29, Smirnov et al., 1973a; 30, Smirnov et al., 1973b; 31, Treffers et al., 1954; 32, Yanofsky et al., 1966.

mutations should be given a higher priority for study, because at least in some instances they exhibit an antimutator phenotype (Table 2). Therefore, an understanding of the biological function of these two genes would be very helpful towards understanding spontaneous mutagenesis in yeast.

4. Higher eukaryotes. Mutator lines of Drosophila, which are not radiation sensitive, have been reported (reviewed in M.M. Green, 1973). Although the insertion of mobile elements seems to play a large role in spontaneous mutagenesis in Drosophila (Rubin et al., 1982; Modollel et al., 1983; Leigh Brown, 1983), this finding may reflect the fact that only gene-inactivating mutations are detected with the assays that have generally been used to study spontaneous mutagenesis in Drosophila.

Mutator lines of mammalian cells have been reported. Meuth et al. (1979) described 3 thymidine-auxotrophic lines of Chinese hamster ovary cells that exhibit enhanced spontaneous reversion to thymidine prototrophy, and enhanced spontaneous frequencies of 6-thioguanine and ouabain resistance. Weinberg et al. (1981) described 3 lines of murine T-lymphosarcoma cells that show altered deoxynucleoside triphosphate pools, and enhanced frequencies of spontaneous dexamethasone and 6-thioguanine resistance. Both groups of workers concluded that abnormal deoxycytidine triphosphate pools were responsible for the enhanced rates of spontaneous mutagenesis that they observed (reviewed in Meuth, 1984).

IV. Recombination errors

Perhaps the first evidence for a role of genetic recombination in spontaneous mutagenesis came from an analysis of the meiotic effect in *S. cerevisiae* (reviewed in von Borstel, 1969). That is, certain spontaneous addition/deletion-type reversions are much enhanced during meiosis relative to mitosis (Magni, 1963; Machida and Nakai, 1980). This fact can be correlated to the notion that spontaneous recombination is also enhanced during meiosis relative to mitosis (e.g., Maloney and Fogel, 1980). However, two points detract from the meiotic effect as a demonstration that recombination errors play a role in spontaneous mutagenesis. First, there are data that suggest that recombination events are not really more frequent during meiosis (see Lawrence, 1982). Second, even if the meiotic effect is a real example of recombination errors, such a mechanism can only explain a small portion of spontaneous mutagenesis, since base-substitution reversions and other addition/deletion-type reversions do not seem to be enhanced during meiosis (von Borstel et al., 1964; Whelan et al., 1979; Machida and Nakai, 1980; reviewed in Lawrence, 1982). One way to resolve this question is to compare the genetic control of recombination with that for spontaneous mutagenesis. This has been done intentionally in only a few studies, which will be discussed below. We have compared the available data on the genetic control of spontaneous recombination and of spontaneous mutagenesis in bacteria (Table 3) and fungi (Table 4), and conclude, in general, that recombination errors do not play a major role in spontaneous mutagenesis (see below).

A. Bacteria

Table 3 compares recombination ability and spontaneous mutagenesis in bacteria in order to see if some correlation exists. The data are arranged such that mutations that have similar effects on recombination ability and on spontaneous mutagenesis are generally grouped together, and they can be discussed in these groupings.

The *dam*, *mutH*, *mutL*, *mutS*, *uvrD* and probably *polAexl* mutants are all deficient in mismatch repair (Wildenberg and Meselson, 1975; Nevers and Spatz, 1975; Glickman and Radman, 1980) and show enhanced recombination and spontaneous mutagenesis (Table 3). It seems most likely that their mutator effects are the result of decreased proof-reading of replication errors, and that their hyper-recombination phenotype is not directly the cause of the mutator effect.

Three mutants (*recA*, *lexA* and the *recB recC* double mutant) show both reduced recombination and reduced spontaneous mutagenesis. Since the *recA* gene controls both transductional and conjugational recombination (Clark and Margulies, 1965; Howard-Flanders and Theriot, 1966) and a portion of spontaneous mutagenesis (Kondo et al., 1970; Sargentini and Smith, 1981), it has been suggested that much of spontaneous mutagenesis

TABLE 3

RECOMBINATION PROFICIENCY VERSUS SPONTANEOUS MUTABILITY IN BACTERIA [a]

Mutant [b]	Recombination proficiency [c]	Spontaneous mutagenesis		References [e]	
		Compared to wild type	Assay [d]	Recomb.	Spont. mutagenesis
dam	Enhanced	Enhanced	bs,fs	5,13,36,67	5,12,13,15,37–39,41
mutH	Enhanced	Enhanced	bs,fs	13	13,18,19,45,52
		Reduced	fs		52
mutL	Enhanced	Enhanced	bs,fs	13	13,19,34,45,50–52
mutS	Enhanced	Enhanced	bs,fs	13	8,13,19,45,48,49,51,52
		Normal	fs		52
polAex1	Enhanced	Enhanced	fs	31	52,59
polA1	Normal	Normal	fs	14	22
		Enhanced	bs,fs,de		7,22,24,30,33,44,59,66*
		Reduced	fs		52
uvrD	Enhanced	Enhanced	bs,fs	67	13,32,45–47,51,53–55
		Normal	bs,de		23,32
recA	Reduced	Reduced	bs,fs,de	6	1,17,25,30,33,43,60,63
		Normal	de,bs		3,10,23–25,56
lexA	Reduced	Reduced	bs	65,67	43,61§,63
recB	Reduced	Normal	bs,de	21	3,43,56
recC	Reduced	Normal	de	21	3
recB recC	Reduced	Reduced	bs	20	29†,63
recF	Normal	Enhanced	bs	20	29†,56,63
recB recF	Reduced	Normal	bs	20	29
umuC	Normal	Reduced	bs,de	43	27*,28§,43
tdi	Normal	Reduced	bs	58	58
uvrA, B	Normal	Normal	bs,fs,de	21,67§	23,24,29*,30,42
		Enhanced	bs,fs		2,40§,42,43,56*
		Reduced	fs,de		2,33
ssb	Reduced	Enhanced	bs	11	16§,35
muc$^+$	Reduced	Normal	bs,fs,de	64	9,33,42
		Enhanced	bs,fs		9,33,42,62,63
		Reduced	de		4*
mutR1	Reduced	Enhanced	bs	26	26

[a] Bacteria are *Escherichia coli* except in a few cases where data for the very similar bacterium, *Salmonella typhimurium*, are used, and in the case of *mutR1* data, which are for *Neisseria meningitidis*.

[b] Relevant alternate nomenclature from Bachmann (1983) and references therein: *mutH* = *mutR*; *mutL* = *mut-25*; *uvrD* = *mutU*, *uvrE* and *uvr502*; *lexA* = *exrA*. *muc*$^+$ is the mutator gene carried on plasmid R46 and its derivative pKM101 (Shanabruch and Walker, 1980).

[c] Recombination ability relative to a wild-type strain was measured by procedures that rely on *recA*-dependent recombination, e.g., a conjugation procedure.

[d] Mutation assay nomenclature: bs, base substitution; fs, frameshift; de, deletion.

[e] Occasionally, the referenced work made no conclusion regarding how the mutant strain compared with the wild-type strain for the phenomenon in question. When this occurred (*), we interpreted the data on the basis of whether the mean of the data for one strain was within 1 S.D. of the mean of the data for the strain being compared, i.e., within = Normal; without = Enhanced or Reduced. In some cases (§), a statistical evaluation was not possible and our evaluation is simply our interpretation of the published data. In some cases our statistical evaluation, described above, gave an interpretation (†) that differed from that of the referenced authors. References: 1, Albertini et al., 1982; 2, Ames, 1971; 3, Anderson, 1970; 4, Balbinder et al., 1983; 5, Bale et al., 1979; 6, Clark and Margulies, 1965; 7, Coukell and Yanofsky, 1970; 8, E.C. Cox et al., 1972; 9, Fowler et al., 1979; 10, Franklin, 1967; 11, Glassberg et al., 1979; 12, Glickman, 1979; 13, Glickman and Radman, 1980; 14, Glickman and Rutgers, 1979; 15, Glickman et al., 1978; 16, Greenberg et al., 1975; 17, Hartman et al., 1984; 18, Hill, 1968; 19, Hoess and Herman, 1975; 20, Horii and Clark, 1973; 21, Howard-Flanders and Boyce, 1966; 22, Imray and MacPhee, 1976; 23, Inselburg, 1967; 24, Ishii and Kondo, 1972; 25, Jones et al., 1982; 26, Jyssum, 1968; 27, Kato and Nakano, 1981; 28, Kato and Shinoura, 1977; 29, Kato et al., 1977; 30, Kondo et al., 1970; 31, Konrad and Lehman, 1974; 32, Kushner et al., 1978; 33, Levine et al., 1984; 34, Liberfarb and Bryson, 1970; 35, Lieberman and Witkin, 1983; 36, Marinus and Konrad, 1976; 37, Marinus and Morris, 1974; 38, Marinus and Morris, 1975; 39, Marinus et al., 1983; 40, McCann et al., 1975; 41, Mohn et al., 1980; 42, Mortelmans and Stocker, 1976; 43, Sargentini and Smith, 1981; 44, Savic and Romac, 1982; 45, Shanabruch et al., 1981; 46, Siegel, 1973; 47, Siegel, 1981; 48, Siegel and Bryson, 1964; 49, Siegel and Bryson, 1967; 50, Siegel and Ivers, 1975; 51, Siegel and Kamel, 1974; 52, Siegel and Vaccaro, 1978; 53, Smirnov et al., 1972; 54, Smirnov et al., 1973a; 55, Smirnov et al., 1973b; 56, Southworth and Bridges, 1984; 57, Spudich et al., 1970; 58, Stacey and Oliver, 1977; 59, Vaccaro and Siegel, 1975; 60, Vaccaro and Siegel, 1977; 61, Volkert et al., 1976; 62, Waleh and Stocker, 1979; 63, Walker, 1977; 64, Walker, 1978b; 65, Witkin, 1969b; 66, Witkin, 1975a; 67, Zieg et al., 1978.

is due to errors made during genetic recombination (Kondo et al., 1970), and a similar suggestion could have been made by considering such data for the *lexA* mutant and the *recB recC* double mutant. However, since the *recA* and *lexA* genes also control error-prone DNA repair (reviewed in Witkin, 1976; Walker, 1984), and the *recB* gene exerts a partial role (Sargentini and Smith, 1980), one can also conclude that a deficiency in error-prone repair is the basis for the antimutator alleles of the *recA* and *lexA* genes and of the antimutator effect seen in the *recB recC* double mutant. This conclusion is supported by the knowledge that the *recB recF* double mutant, which seems totally deficient in recombination, is normal for spontaneous mutagenesis (Kato et al., 1977). Similarly, the *umuC* mutation, which causes a major reduction in the spontaneous mutagenesis observed in a *uvrB* strain, has no effect on recombination ability in that strain (Sargentini and Smith, 1981).

Table 3 also lists several mutants showing an inverse correlation between their levels of recombination and spontaneous mutagenesis. Some mutations reduce spontaneous mutagenesis while showing normal or enhanced recombination (*mutH*, *polA1*, *umuC*, *tdi*, and *uvrA,B*), and some mutations show reduced recombination, but normal or enhanced spontaneous mutagenesis (*recB*, *recC*, the *recB recF* double mutant, *ssb*, *muc*$^+$, and *mutR1*). Some of these inverse correlations are for frameshift as well as for base-substitution mutation assays.

From these data we conclude that recombination events play little role in spontaneous mutagenesis in bacteria. This conclusion certainly seems valid from the base-substitution data presented in Table 3. The frameshift data in Table 3 are more difficult to interpret. One complication is that only a few strains were tested for spontaneous frameshift mutagenesis. Another complication is that a strain such as *polA1* may only show its frameshift-mutator phenotype in assays that rely on the reversion of plus-type frameshift mutations (Siegel and Vaccaro, 1978; Savic and Romac, 1982). Deletion data were available for only a few strains, notably *recA*, and even in this case the data were contradictory on the ability of a *recA* mutant to produce spontaneous deletions. It is most likely that these contradictions are based on the fact that each worker used a different assay for the detection of deletions. Probably both *recA*-dependent and *recA*-independent mechanisms exist for spontaneous deletion formation. While the former mechanism presumably results from a recombination error, possible explanations of the latter mechanism include the imprecise excision of insertion elements to form deletions, which occurs in bacteria in a *recA*-independent manner (reviewed in Kleckner, 1977), and the possibility of recombination events between nonhomologous DNA segments (Franklin, 1967).

B. Fungi

Table 4 compares recombination ability (spontaneous mitotic heteroallelic recombination in this case) and spontaneous mutagenesis in fungi to see if some correlation exists. Most of the listed strains show hyper-recombination ability, and in most cases they show enhanced spontaneous mutagenesis with at least one mutation assay. These data, like those for the meiotic effect, might superficially argue that hyper-recombination leads to enhanced spontaneous mutagenesis, however, this correlation is only suggestive in terms of the source of the normal level of spontaneous mutagenesis. As stated earlier, antimutator data suggest more direct conclusions regarding mechanisms of spontaneous mutagenesis than do mutator data. The 2 fungal mutations listed in Table 4 that reduce spontaneous recombination show increased spontaneous mutagenesis (*rad51* and *rad52*), while the 5 mutations that reduce spontaneous mutagenesis show normal or enhanced spontaneous recombination (*rad53, mms3, rad2, rad6*, and *rad18*). These results seem to argue that there may be an inverse correlation between spontaneous recombination and spontaneous mutagenesis, but since so many other fungal mutants show both enhanced levels of spontaneous recombination and mutagenesis, it seems more likely that these two phenomena are not intrinsically related. However, essentially all of these spontaneous mutagenesis data are derived from base-substitution assays and perhaps, as was suggested by the meiotic effect, frameshift assays might provide a valid correlation. In the case of spontaneous deletion formation, fungi do show a mechanism that is independent of spontaneous mitotic recombination. The Tyl and δ transposa-

TABLE 4

SPONTANEOUS RECOMBINATION VERSUS SPONTANEOUS MUTABILITY IN FUNGI

Mutant [a]	Recombination frequency [b]	Spontaneous mutagenesis		References [d]	
		Compared to wild type	Assay [c]	Recomb.	Spont. mut.
MIC1	Enhanced	Enhanced	*can*^{r}	11	11
MIC5	Enhanced	Enhanced	*can*^{r}	11	11
MIC8	Enhanced	Enhanced	*can*^{r}	11	11
MIC9	Enhanced	Enhanced	*can*^{r}	11	11
MIC12	Enhanced	Enhanced	*can*^{r}	11	11
MIC15	Enhanced	Enhanced	*can*^{r}	11	11
MIC19	Enhanced	Enhanced	*can*^{r}	11	11
rad3	Enhanced	Enhanced	bs	6,18†	2,6
rem1	Enhanced	Enhanced	bs	3	3
rad53	Normal	Normal	bs	17	19
		Reduced	bs		19
mms3	Normal	Reduced	bs	12	12§
MIC23	Enhanced	Normal	*can*^{r}	11	11
mms8	Enhanced	Normal	bs	13	13
rad1	Normal	Normal	bs,de	18	2,15
		Enhanced	bs		2†,8§,15
rad2	Normal	Normal	bs	7,18	2,19
		Reduced	bs		19
		Enhanced	bs		2†,20
rad4	Normal	Normal	bs	18	2
		Enhanced	bs		2†
rad5	Normal	Enhanced	Auxotrophy	9,18	9
rad6	Enhanced	Enhanced	bs,de	6,14	4,14
		Normal	bs		6,14
		Reduced	bs		14
rad18	Enhanced	Enhanced	bs	1,12.5	16,19
		Reduced	bs		16†,19*
rad51	Reduced	Enhanced	bs	17	4,16
rad52	Reduced	Enhanced	bs	10,17	19
rec-1	Enhanced	Enhanced	*ad*, *pan*	5	5

[a] All strains are *Saccharomyces cerevisiae* except *rec-1* which is *Ustilago maydis*. Genetic nomenclature: *rad1* = *uvs-9*, uvs_z; *rad2* = *uvs-8*; *rad3* = *uvs-4*; *rad4* = *uvs5*; *rad5* = *uvs-10*, *rev2-1*; *rad14* = *uvs-11* (Game and Cox, 1971); *rad52* = *xrs1-1*; *rad53* = *xrs2-1*, *xrs2-2* (Game and Mortimer, 1974). Data for spontaneous recombination in other mutants are available, but they are not presented since spontaneous mutagenesis data were not available. These mutants are the following: *mms9*, *mms13*, and *mms21* (S. Prakash and Prakash, 1977); r_i^s and *rad9* (Kowalski and Laskowski, 1975); *rad14* (Snow, 1968); *spo8* (Baker et al., 1976); *rec3* and *rec4* (Rodarte-Ramon, 1972; Rodarte-Ramon and Mortimer, 1972); *rad50, rad54, rad55, rad56, rad57* (Saeki et al., 1980); cdc9 (Fabre and Roman, 1979; Game et al., 1979) (*cdc9* is an allele of *mms8*, Montelone et al., 1981a); *rev1* (Lemontt, 1971b).

[b] The interpretation of recombination frequency is based on data for spontaneous mitotic recombination or gene conversion (spontaneous mitotic heteroallelic recombination).

[c] Assays: de, deletion mutation assay; bs, base-substitution mutation assay (either missense or nonsense reversion); the marker employed in the mutation assay (e.g., *can*^{r} and auxotrophy) was listed when the general type of mutation (e.g., de, bs, etc.) involved was not known.

[d] Refer to footnote e, Table 3 for an explanation of notated references. References: 1, Boram and Roman, 1976; 2, Brychcy and von Borstel, 1977; 3, Golin and Esposito, 1977; 4, Hastings et al., 1976; 5, Holliday et al., 1976; 6, Kern and Zimmermann, 1978; 7, Kowalski and Laskowski, 1975; 8, Lawrence and Christensen, 1982; 9, Lemontt, 1972; 10, Malone and Esposito, 1980; 11, Maloney and Fogel, 1980; 12, Martin et al., 1981; 12.5, Mayer and Goin, 1984; 13, Montelone et al., 1981a, 14, Montelone et al., 1981b; 15, Moustacchi, 1969; 16, Quah et al., 1980; 17, Saeki et al., 1980; 18, Snow, 1968; 19, von Borstel et al., 1971; 20, Zakharov et al., 1970.

ble sequences have been described in yeast (Cameron et al., 1979), and the δ sequence has been implicated in the formation of deletions at the *sup4* locus (Rothstein, 1979). The *DEL1* mutator gene enhances the deletion of adjacent genes by a mechanism thought to involve transposable elements, and this deletion formation occurs in a *rad52* strain, which is recombination deficient (Liebman and Downs, 1980).

V. Repair errors

Mutations that sensitize cells to DNA-damaging agents have generally been shown to do so by reducing cellular capacity for DNA repair. In this section, mutations that affect DNA repair will be evaluated for their effect on spontaneous and experimentally induced mutagenesis. The point is to see if the direct correlation noted for *lacZ53*(amber) reversion in *E. coli uvrB* cells (Sargentini and Smith, 1981) can be found in other organisms and with other mutation assays.

A. Mechanisms of DNA repair

In order to appreciate the discussion of DNA repair mutants that follows, it is helpful to have some concept of error-free and error-prone DNA repair. The *uvrA, uvrB,* and *uvrC* genes, which determine the UV "excinuclease" of *E. coli* and, presumably of the closely related bacterium *S. typhimurium*, are required for the incision and excision steps in the excision repair process for certain lesions (e.g., UV radiation-induced pyrimidine dimers) in DNA (Sancar and Rupp, 1983). In general, DNA excision repair is considered to be largely error-free relative to the other major dark-repair process, postreplication repair (Witkin, 1966). This conclusion stems from the fact that *uvrA*, *uvrB*, and *uvrC* strains show enhanced mutability compared to wild-type strains of *E. coli* when given the same dose of UV radiation (e.g., Witkin, 1966; M.H.L. Green et al., 1972).

The concept of error-prone repair resulted from the finding by Witkin (1967) that a *lexA*(*exrA*) strain was not only deficient in the ability to survive UV irradiation, but was also deficient in UV radiation mutagenesis. The *lexA* gene product is a repressor of the *recA* gene, a gene required for UV radiation mutagenesis, and the classical *lexA* mutant is one in which the repressor protein is not removed under conditions that would normally cause derepression (reviewed in Witkin, 1976; Walker, 1984).

B. Bacteriophage T4

Some phage T4 mutant strains show similar results when studied for spontaneous and experimentally induced mutagenesis. The *px* strain is similar to the *recA* strain of *E. coli* in that it shows increased sensitivity to UV radiation, but reduced UV radiation mutagenesis, spontaneous mutagenesis, and recombination (Drake, 1973). The *px* strain seems to be deficient at the X gene and at some unknown gene(s) (Conkling and Drake, 1984). The *hm* mutation causes both enhanced UV radiation and spontaneous mutagenesis (Drake, 1973). Unlike these mutations, which show a direct correlation between their effects on UV radiation-induced and spontaneous mutagenesis, the *v* mutation, which causes a deficiency in the pyrimidine dimer-specific endonuclease (Friedberg and King, 1971), does not seem to cause an enhanced rate of spontaneous mutagenesis (Drake, 1973). However, this mutation only causes a 2-fold enhancement of UV radiation mutagenesis (Meistrich and Drake, 1972).

C. Bacteria

Mutations that sensitize bacteria or fungi to DNA-damaging agents are compared for their effects on spontaneous and experimentally induced mutagenesis in Tables 5 and 6, respectively. The mutations listed in these tables have been grouped on the basis of showing similar effects on spontaneous and experimentally induced mutagenesis. Mutations that appear to have no effect on spontaneous mutagenesis (Normal) are grouped where more careful testing may eventually place them. With this consideration in mind for the bacterial data (Table 5), almost all of the mutants show a direct or potentially direct correlation between their ability for spontaneous and for experimentally induced mutagenesis. While the *S. typhimurium uvrB* mutant shows an inverse correlation for certain frameshift mutation assays, the other *uvrA* and *uvrB* strains, which are hypermutable by UV radiation, more often show enhanced

spontaneous mutagenesis (Ames, 1971; McCann et al., 1975; Mortelmans and Stocker, 1976; Sargentini and Smith, 1981), i.e., they are mutators (*uvrC* strains have not been tested). This enhancement of spontaneous mutagenesis was demonstrated in one study (Sargentini and Smith, 1981) using both *uvrA* and *uvrB* strains, and using a frameshift mutation assay and several base-substitution assays. Depending upon the assay used, the spontaneous mutation rate per bacterium per cell division ranged from 1.9- to 6.2-fold greater for *uvrA* and *uvrB* strains than for isogenic wild-type strains. Such data suggest that excisable, cryptic lesions exist in the DNA, and, if not excised, they induce mutations with increased probability.

Mutations that inhibit error-prone repair in UV-irradiated cells also inhibit the enhanced spontaneous mutagenesis seen in *uvrB* strains. Specifically, *uvrB* strains carrying *lexA*, *recA*, *umuC*, or the *uvrD* and *recB* mutations in combination, have spontaneous mutation rates about 10-fold lower than the *uvrB* control strains (Sargentini and Smith, 1981). Mutations at *recA* and *lexA* reduce the spontaneous mutation rate by about 2-fold in uvr^+ strains (Kondo, 1968; Kondo et al., 1970; Sargentini and Smith, 1981), suggesting that about half of the spontaneous base substitutions in a DNA repair-proficient strain are the result of error-prone repair. Other, less quantitated examples of mutations that reduce spontaneous mutagenesis by presumably reducing error-prone repair are: *uvrD3, tsl, umuA, umuB, umuC, tdi, polC,* NTG1, NTG2, *supX*, and, in combination, *recB* and *recC* (Table 5). The notion that error-prone repair acts on DNA damage, and is not merely affecting replication or recombination, is supported by two pieces of data. (1) Replication-error processes have generally been categorized by their *recA* independence (reviewed in E.C. Cox, 1976), yet, as noted above, about half of spontaneous mutagenesis is *recA*-dependent. (2) A recombination-error process seems to be ruled out for base-substitution data because the *umuC* antimutator is recombination-proficient (Sargentini and Smith, 1981), and the recombination-deficient *recB recF* strain shows normal spontaneous mutagenesis (Kato et al., 1977).

Error-prone repair in *E. coli* is not thought to be fully activated in normal cells, rather its full activation depends on DNA damage or a block to DNA replication (reviewed in Witkin, 1976; Walker, 1984). Once it has been activated, it enhances spontaneous mutagenesis as seen in the *tif* (Witkin, 1974; Mount, 1977) and *dnaB* (Witkin, 1975c) strains. Some mutants listed in Table 5 that clearly exhibit their mutator effects through the induction of error-prone repair include the *tif* (conditionally activated *recA* protein), muc^+ [analogues of the *umuDC* genes carried on the plasmid pKM101 (Elledge and Walker, 1983)] and R-Utrecht (muc^+) strains. Mutants listed in Table 5 whose mutator effects may result from an association of impaired DNA replication with the induction of error-prone repair may include the *polA* (DNA polymerase I), *lig* (polynucleotide ligase), *dnaB* (protein essential for DNA synthesis), *mutU* (*uvrD*) (helicase II), *gyrA* and *gyrB*(K-12) (subunits of topoisomerase II) strains. Hypermutability associated with enhanced error-prone repair can be explained either as nontargeted mutagenesis (Witkin and Wermundsen, 1979) or as mutagenesis targeted at DNA damage of unknown origin (Miller and Low, 1984). The induction of error-prone repair should not be expected to enhance spontaneous mutagenesis at all sites. This conclusion follows from work with the most studied system for genetically enhancing error-prone repair, muc^+. The presence of the muc^+ plasmid, pKM101, is known to enhance spontaneous mutagenesis only at certain sites (Mortelmans and Stocker, 1976; Fowler et al., 1979; Miller and Low, 1984).

The effect of the *ung* mutation (Table 5) is difficult to assess. The *ung* and *urg* (*B. subtilis* analog of *ung*) mutants do, in fact, show enhanced levels of spontaneous base substitution (Duncan and Weiss, 1982; Hayakawa and Sekiguchi, 1978), but such mutagenesis assays do not show any difference between *ung* and wild-type cells after sodium bisulfite treatment. Presumably, the uracil *N*-glycosylase in the wild-type cells is inactivated by the bisulfite treatment such that these cells are effectively Ung^- (Duncan and Weiss, 1982).

The *ssb* mutant provides the only data in Table 5 that clearly contradict the notion that the genetic control of spontaneous mutagenesis is the same as that for experimentally induced mutagenesis.

TABLE 5

SPONTANEOUS AND EXPERIMENTALLY INDUCED MUTATIONS IN DNA-DAMAGE-SENSITIVE BACTERIAL MUTANTS [a]

Mutant	Mutagenesis assay [b]	Mutation rate compared to wild type		
		Spontaneous [e]	Induced [f]	Reference [d]
Escherichia coli				
uvrA	*trpE65*(oc), *lacZ53*(am)	Enhanced	UV, enhanced	12,30,32*,35
	argF(am), *his-4*(oc), Lac$^-$, Str^r(ms)	Normal	UV, enhanced	16*,17,22*,32,40
uvrB	*lacZ53*(am), *trpE65*(oc), *trpE9777*(fs)	Enhanced	UV, enhanced	29,30,35
	ColB^r(de)	Normal	UV, enhanced	13
polA	*trpE65*(oc), ColB^r(de)	Enhanced	UV, enhanced	13,42*
	argF(am)	Enhanced	UV, normal [c]	17
lig	λ*c*	Enhanced	UV, enhanced	4*,23
recF	*his-4*(oc)	Enhanced	UV, enhanced	16†,32
muc$^+$	*argE3*(oc), *leuB19*(ms), *lacZ53*(am) *his-4*(oc), *his-4 argE3*(oc,S)	Enhanced	UV, enhanced	34,37,38
	trpE9777(fs)	Normal	UV, enhanced	8,9
tif	*trpE65*(oc), *his-4*(oc)	Enhanced	UV, enhanced	41
dnaB	*trpE65*(oc)	Enhanced	UV, enhanced	43
gyrA	Rif^r(ms)	Enhanced	UV, enhanced	5§
ung	λ*c*	Normal	SB, enhanced	7§
	trpA446(ms)	Enhanced	SB, normal	7
mutU	*ilvD188*, T6^r	Enhanced	UV, enhanced	31
uvrD3	*lacZ53*(am), *leuB19*(ms)	Reduced	UV, reduced	30,37§
gyrB(K-12)	Rif^r(ms)	Enhanced	UV, enhanced	5§
nalC, D	Rif^r(ms)	Normal	UV, enhanced	5§
gyrB(B/r)	Rif^r(ms), *trpE65*(oc)	Normal	UV, reduced	3
recA	*argF*(am), *lacZ53*(am), λ*c*	Reduced	UV, reduced	17,22*,30
	ColB^r(de), Lac$^-$	Normal	UV, reduced	13,22*
tsl	*his-4*(oc), Str^r(ms)	Reduced	UV, reduced	26§
lexA	*lacZ53*(am), *trpE65*(oc)	Reduced	UV, reduced	30,36§
rnmA	*trpE65*(oc)	Normal	UV, reduced	36§
umuA	ColB^r(de)	Reduced	UV, reduced	15§
umuB	ColB^r(de)	Reduced	UV, reduced	15§
umuC	*lacZ53*(am), *his-4*(oc) ColB^r(de)	Reduced	UV, reduced	14*,15§,30
tdi	*his*, *pro*	Reduced	UV, reduced	33
polC (42°C)	*trpE65*(oc)	Reduced	UV, reduced	2
NTG1,2	Azi^r	Reduced	MNNG, reduced	44
recB recC	*his-4*(oc)	Reduced	UV, reduced	16†
recB	*lacZ53*(am)	Normal	UV, normal	30
uvrD recB	*lacZ53*(am)	Reduced	UV, reduced	30
inm	Ara^r	Normal	UV, normal	28
		Normal	MNNG, reduced	28
dam	Val^r, *argE3*(oc), *lacZ608*(am), *his-4*(oc)	Enhanced	UV, normal	10,20
ssb	*trpE65*(oc), *argF*(am)	Enhanced	UV, reduced	11§,18
Salmonella typhimurium				
uvrB	*hisG46*(ms)	Enhanced	UV, enhanced	1,21§,24
	hisC207(fs), *hisC3076*(fs)	Normal	UV, enhanced	24
	hisC207(fs), *hisC3076*(fs)	Reduced	UV, enhanced	1,24
muc$^+$	15 *his*(oc, am, or UGA), *hisC3076*(fs, in *uvrB*)	Enhanced	UV, enhanced	24
	5 *his*(fs), P22*c*	Normal	UV, enhanced	24,39
R-Utrecht	*hisC527*(am)	Enhanced	UV, enhanced	19
	trpD1(ms)	Normal	UV, enhanced	19
supX	*leuD1*	Normal	UV, reduced	27

However, since the *ssb* protein is required for DNA replication (Meyer et al., 1979) and is involved in the fidelity of DNA synthesis (Kunkel et al., 1979), we would offer that the *ssb* mutation affects both replication and repair, and that whatever effect it has on the contribution of error-prone repair to spontaneous mutagenesis is overshadowed by its effect to reduce the fidelity of normal DNA replication.

D. Fungi

The effect of DNA repair mutations on spontaneous and experimentally induced mutagenesis in fungi is presented in Table 6, following the same criteria used for the bacterial data in Table 5 (see also Haynes and Kunz, 1981; Lawrence, 1982). Again, as for bacteria, many of these putative DNA repair mutations generally produce the same effect on spontaneous and on experimentally induced mutagenesis. The mutations in *S. cerevisiae* that prevent UV radiation-induced pyrimidine dimer excision are *rad1, rad2, rad3, rad4, rad7, rad10, rad14, rad16,* and *mms19* (reviewed in Wilcox and Prakash, 1981). The *uvs-2, uvs-3,* and *upr-1* mutants of *N. crassa* are similarly deficient (de Serres et al., 1980). Of these mutations, *rad1, rad3, mms19,* and *uvs-3* enhance both spontaneous and UV radiation mutagenesis (Table 6), and are thus reminiscent of the effect of the *uvrA* and *uvrB* mutations in *E. coli* (reviewed in Sargentini and Smith, 1981). The *rad2, rad14, uvs-2,* and *upr-1* mutations enhance UV radiation mutagenesis, but reduce or have no effect on spontaneous mutagenesis (Table 6). The remaining mutations affecting excision repair (*rad4, rad7, rad10,* and *rad16*) also enhance UV radiation mutagenesis (reviewed in L.

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[a] In fact, some mutants are included that are more resistant than a wild-type strain. The NTG1,2 and *inm* mutants are resistant to MNNG. Cells carrying plasmid R46 or its derivative pKM101 have the plasmid mutator gene, *muc*$^+$ (Shanabruch and Walker, 1980), and, like cells carrying the *N* group plasmids, exhibit UV radiation resistance.

[b] Abbreviations: ColB^r, Rif^r, Val^r, T6^r, Str^r, Azi^r, Ara^r, resistance to colicin B, rifampicin, valine, bacteriophage T6, streptomycin, azide, and L-arabinose, respectively. λ*c* and P22*c*, clear plaque mutants of bacteriophages λ and P22, respectively. oc, ochre nonsense mutation; am, amber nonsense mutation; fs, frameshift mutation; de, deletion; S, intergenic nonsense suppressor mutation; ms, missense mutation; UV, ultraviolet radiation; SB, sodium bisulfite; MNNG, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine.

[c] UV radiation mutagenesis may be enhanced if lower doses are tested (Witkin, 1975a).

[d] For an explanation of reference notations, refer to footnote e, Table 3. References: 1, Ames, 1971; 2, Bridges and Mottershead, 1978; 3, Bridges et al., 1983; 4, Condra and Pauling, 1982; 5, Crumplin, 1981; 6, Diver and MacPhee, 1981; 7, Duncan and Weiss, 1982; 8, Fowler et al., 1979; 9, Fowler et al., 1981; 10, Glickman et al., 1978, 11, Greenberg et al., 1975; 12, Hill, 1965; 13, Ishii and Kondo, 1972; 14, Kato and Nakano, 1981; 15, Kato and Shinoura, 1977; 16, Kato et al., 1977; 17, Kondo et al., 1970; 18, Lieberman and Witkin, 1983; 19, MacPhee, 1977; 20, Marinus and Morris, 1975; 21, McCann et al., 1975; 22, Miura and Tomizawa, 1968; 23, Morse and Pauling, 1975; 24, Mortelmans and Stocker, 1976; 25, Mount, 1977; 26, Mount and Kosel, 1975; 27, Overbye and Margolin, 1981; 28, Ruiz-Vazquez and Cerda-Olmedo, 1980; 29, Sargentini, 1979; 30, Sargentini and Smith, 1981; 31, Siegel, 1973; 32, Southworth and Bridges, 1984; 33, Stacey and Oliver, 1977; 34, Todd and Glickman, 1979; 35, This paper (data not shown); 36, Volkert et al., 1976; 37, Waleh and Stocker, 1979; 38, Walker, 1977; 39, Walker, 1978a; 40, Witkin, 1966; 41, Witkin, 1974; 42, Witkin, 1975a; 43, Witkin, 1975c; 44, Zamenhof et al., 1966.

[e] Other data for the genetic control of spontaneous mutagenesis are available, but they are not presented here because there were no experimentally induced mutagenesis data to correlate with them. These data are for the following mutants and mutation assays: *lig: trpE9777*(fs) (Siegel and Vaccaro, 1978), Val^r, Rif^r(ms), and 5MT^r (Morse and Pauling, 1975); *recF*: Rif^r(ms) (Southworth and Bridges, 1984); *ung: trpA3, trpA11, trpA23, trpA58, trpA223*, (Duncan and Weiss, 1982), *lacI* (Duncan and Miller, 1980); *urg* (*Bacillus subtilis*): Rif^r (Hayakawa and Sekiguchi, 1978); *tag*: Rif^r(ms), Amp^r (Karran et al., 1980); *alkB*: Rif^r(ms) (Kataoka et al., 1983); *ada*: Rif^r(ms) (Jeggo, 1979); *dam: lacI, trpE9777*(fs) (Glickman, 1979), Rif^r(ms), Nal^r (Bale et al., 1979), *leu-6, proA2, lacY1*, Str^r(ms), Rif^r(ms) (Marinus and Morris, 1974); *mut-8: phoR,S, lacI*, Nal^r, *leu-6, his-4* (Hombrecher and Vielmetter, 1979); *mum*: *met* (Mohn, 1968); *mutR1* (*Neisseria meningitidis*): Str^r, *pro*, *arg*, *his*, *hom*, *gly*, and *cys* (Jyssum, 1968); *recA: lacZ(ICR36)*(fs) (Vaccaro and Siegel, 1977) *ton* (*trp*) (de) (Franklin, 1967), ColB^r(*trp*) (de) (Inselburg, 1967), T7^r (*pro*) (de), ColB^r (*trp*) (de) (Anderson, 1970), T1^r(*trp*) (de) (Spudich et al., 1970), *lacI*(de) (Albertini et al., 1982), Tc^r(de) (Jones et al., 1982), *hisG*(de) (Levine et al., 1984; Z. Hartman et al., 1984), *hisG*(ms) (Z. Harman et al., 1984); *recB*: ColB^r(*trp*) (de) (Anderson, 1970), T1^r (*trp*) (de) (Spudich et al., 1970); *spr: his-4* (Mount, 1977); *tif: his-4* (George et al., 1975); plasmids R205 and R144*drd3: trp* (Diver and MacPhee, 1981); *uvrB*, *polA*, *muc*$^+$: *hisG*(de) (Levine et al., 1984).

[f] Other data for the genetic control of experimentally induced mutagenesis are available, but they are not presented here because there were no corresponding data for spontaneous mutagenesis. These data are for the following mutants: *uvrC* (M.H.L. Green et al., 1972); *alkA* (Yamamoto and Sekiguchi, 1979); *alkB* (Kataoka et al., 1983); *ada* (Jeggo, 1979; Kataoka et al., 1983); *spr* (Mount, 1977); *uvrD* (Todd and Glickman, 1979); *gyrB* (Bridges et al., 1983); *recA*, *recC* (Witkin, 1969a).

TABLE 6

SPONTANEOUS AND RADIATION MUTAGENESIS IN RADIATION-SENSITIVE FUNGAL MUTANTS

Mutant [a]	Mutagenesis assay [b]	Mutagenesis compared to wild type		
		Spontaneous [c]	UV radiation [f]	Reference [d]
Saccharomyces cerevisiae				
rad1	*his1, leu2, ade1,*	Enhanced	Enhanced	16
	rho$^-$ (de)	Normal	Normal	16
rad2-17	*lys1-1* (oc: l and SS)	Normal	Enhanced	22,23
rad3	*trp5*	Enhanced	Enhanced	9
uvsρ5	*rho*$^-$ (de)	Enhanced	Enhanced	17
	his1(ms)	Normal	Normal	17
mms19	*lys2-1* (oc), *arg4-17*(oc)	Enhanced	Enhanced	20[§]
	trp2	Normal	Enhanced	20[§]
rad6-1	*trp5, cyc1-91*	Reduced	Reduced	9[§],10[§]
umu1	*can*^{r}	Reduced	Reduced	13[§]
umu5	*can*^{r}	Reduced	Reduced	13[§]
umu7	*can*^{r}	Reduced	Reduced	13[§]
pso1	*his1*(ms)	Reduced	Reduced	1
mms3	*arg4-17*(oc)	Reduced	Reduced	15[§]
rev3-1	*arg4-17*(oc: l)	Reduced	Reduced	11,21
	arg4-17(oc: SS)	Normal	Reduced	11,21[†]
umu2	*can*^{r}	Normal	Reduced	13[§]
umu3	*can*^{r}	Normal	Reduced	13[§]
umu4	*can*^{r}	Normal	Reduced	13[§]
cdc7-1	*arg4-17*(oc), *lys1-1*(oc), *ilv1-92*(ms), *lys2, ura1 adeX, tyr1*	Normal	Reduced	19
pso2	*his1*(ms)	Normal	Reduced	1
pso3	*his1*(ms)	Normal	Reduced	1
gam3	*rho*$^-$ (de)	Normal	Normal [e]	5
gam1	*rho*$^-$ (de)	Enhanced	Normal [e]	5
gam5	*rho*$^-$ (de)	Enhanced	Normal [e]	5
rad5	*ade*	Enhanced	Normal	12
	Auxotrophy	Enhanced	Reduced	12
ant1	*lys1-1*(oc: SS), *his1-7*(ms)	Reduced	Normal	21
spo7	lys2-1(oc: SS)	Reduced	Normal	4
	lys2-1(oc: l)	Normal	Normal	4
MIC1	*can*^{r}	Enhanced	Reduced	14
rad14	*arg4-17*(oc), *his5-2*(oc)	Reduced	Enhanced	20[§]
Neurospora crassa				
uvs-3	*ad-3A, ad-3B*	Enhanced	Enhanced	3,7
upr-1	*ad-3A, ad-3B*	Normal	Enhanced	3,7
uvs-2	*ad-3A, ad-3B*	Normal	Enhanced	3,7
mus8	*mtr*	Reduced	Reduced	8
uvs-1	*ad-3A, ad-3B*	Normal	Reduced	2,3
uvs-4	*ad-3A, ad-3B*	Normal	Reduced	2,3
uvs-5	*ad-3A, ad-3B*	Normal	Reduced	2,3
uvs-6	*ad-3A, ad-3B*	Normal	Normal	3,7
mus7	*mtr*	Normal	Normal	8
mus10	*mtr*	Normal	Normal	8
nuh-4	*mtr*	Enhanced	Reduced	8
mus9	*mtr, cyh*	Enhanced	Reduced	8
mus11	*mtr, cyh*	Enhanced	Reduced	8
Ustilago maydis				
rec-1	*ad1-1*	Enhanced	Reduced	6
Schizosaccharomyces pombe				
rad3	*ade7*	Reduced	Reduced	18[§]

Prakash and Prakash, 1979), but have not been tested with the same assay for spontaneous mutagenesis.

Of the mutations already mentioned, most cause similar effects on both experimentally induced and spontaneous mutagenesis. Only a few mutations listed in Table 6 (*rad5, MIC1, nuh-4, mus9, mus11,* and *rec-1*) have opposite effects on experimentally induced and spontaneous mutagenesis when measured with the same mutation assay. Hastings et al. (1976) originally noted this incongruity for the *rad6* and *rad51* mutations. While these mutations blocked most forms of experimentally induced mutagenesis, they enhanced spontaneous mutagenesis (although measured with other mutation assays than were used to monitor induced mutagenesis). The lesion-channeling concept was offered (Hastings et al., 1976) to explain this incongruity. That is, if multiple pathways of error-prone repair exist, and one pathway is blocked by a mutation, spontaneous mutations can be enhanced if the lesions that are normally repaired via the blocked pathway are able to be "channeled" into another error-prone pathway (presumably this pathway is more error-prone than the blocked pathway). Some support for this concept came from studying the *ant1 rev3* double mutant, which shows a greater deficiency in spontaneous mutagenesis (90%) then either single mutant (Quah et al., 1980). Unfortunately, while the *ant1* mutation made cells UV radiation sensitive, it had no effect on UV radiation mutagenesis (data not shown in Quah et al., 1980). If such data are forthcoming, then they would suggest that 90% of spontaneous base-substitution mutagenesis in *S. cerevisiae* is the result of error-prone DNA repair. If the channeling con-

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[a] Alternate genetic nomenclature: *rad2* = uvs_1, *rad2-17* = *uvs9-3*, *rad5* = *rev2-1*, *rad1* = uvs_z (Game and Cox, 1971).

[b] Abbreviations: de, deletion; oc, ochre; l, locus reversion; SS, supersuppressor; ms, missense.

[c] Gamma mutagenesis data.

[d] Refer to footnote e, Table 3 for an explanation of notated references. References: 1, Cassier et al., 1980; 2, de Serres, 1971; 3, de Serres et al., 1980; 4, Esposito et al., 1975; 5, Foury and Goffeau, 1979; 6, Holliday et al., 1976; 7, Inoue et al., 1981; 8, Käfer, 1981; 9, Kern and Zimmermann, 1978; 10, Lawrence and Christensen, 1982; 11, Lemontt, 1971a; 12, Lemontt, 1972; 13, Lemontt, 1977; 14, Maloney and Fogel, 1980; 15, Martin et al., 1981; 16, Moustacchi, 1969; 17, Moustacchi et al., 1976; 18, Nasim and Hannan, 1977; 19, Njagi and Kilbey, 1982; 20, L. Prakash and Prakash, 1979; 21, Quah et al., 1980; 22, Resnick, 1969; 23, von Borstel et al., 1971.

[e] Other data for the genetic control of spontaneous mutagenesis are available, but they are not presented here because there were no corresponding experimentally induced mutagenesis data to correlate with them. These data are for the following mutants and mutation assays: *rad1-1: lys1-1*(oc) and *his1-7*(ms) (Brychcy and von Borstel, 1977); *rad2: ser*^{r} (Zakharov et al., 1970); *rad2-16: lys1-1*(oc) (von Borstel et al., 1971); *rad2-2: lys1-1*(oc) and *his1-7*(ms) (Brychcy and von Borstel, 1977), *rad3-12: lys1-1*(oc) and *his1-7*(ms) (Brychcy and von Borstel, 1977); *rad3: ilv1-92* (Kern and Zimmermann, 1978); *rad4-3: lys1-1*(oc) and *his1-7*(ms) (Brychcy and von Borstel, 1977); *rad6-1: his1-1, his1-315, trp5-48, trp5-2, lys1-1*(oc), and *ilv1-92* (Montelone et al., 1981b; Hastings et al., 1976; Kern and Zimmermann, 1978); *rad6-3: his1-1, his1-315, trp5-48, and trp5-2* (Montelone et al., 1981b); *rad18: lys1-1*(oc), *ura4-11*(fs) (von Borstel et al., 1971); *rad18-3: lys1-1*(oc), and *his1-7*(ms) (Quah et al., 1980); *rad51-1: lys1-1*(oc), and *his-7*(ms) (Hastings et al., 1976; Quah et al., 1980); *rad52-1: lys1-1*(oc), *ura4-11*(fs), and *thr3-10*(fs) (von Borstel et al., 1971); *rad53: lys1-1*(oc) (von Borstel et al., 1971); *rev3-1: lys1-1*(oc) and *his1-7*(ms) (Quah et al., 1980); *xrs3-1: lys1-1*(oc) (von Borstel et al., 1971); *rna3-3: can*^{r} (Johnston and Thomas, 1982); *dbf6: can*^{r} (Johnston and Thomas, 1982); *dbf2: can*^{r} (Johnston and Thomas, 1982); *rna6: lys2* (Johnston and Thomas, 1982); *mmg1: rho*$^-$; *mmg2: rho*$^-$; *mmg3: rho*$^-$; *mmg4: rho*$^-$ *(Devin and Koltovaya, 1981); mms8: ade2-1*(oc), *lys2-1*(oc), *lys2-2, trp5-c, trp5-r, tyr1-1, tyr1-2; ura3-1, ura3-313* (Montelone et al., 1981a); *mus*(SC15): *mtr*; *mus*(SC10): *mtr*; *mus*(SC25): *mtr*; *mus*(SC29): *mtr*: *mus*(SC3): *mtr*; *mus*(SC13): *mtr* (DeLange and Mishra, 1982); *MIC5, MIC8, MIC9, MIC15, MIC19: can*^{r} (Maloney and Fogel, 1980); *gam1*: Ery^r, Oli^r, *his, met2; gam3:* Oli^r; *gam5*: Ery^r (Foury and Goffeau, 1979); *xrs-3: lys1-1*(oc); *xrs-1: lys1-1*(oc), *ura4-11*(fs), *thr3-10*(fs); *xrs-2: lys1-1*(oc), *rho*$^-$ (von Borstel et al., 1971); *mut3: lys1-1*(oc); *mut4: lys1-1*(oc); *mut5: lys1-1*(oc); *mut9: lys1-1*(oc); *mut10: lys1-1*(oc) (Hastings et al., 1976); *mut7: lys1-1*(oc) (Nasim and Brychcy, 1979); LB_1, LB_2, LB_3, LB_4, LB_5, LB_7, LB_8, LB_9, LB_{10}: Ery^r, Oli^r, Diu^r, *can*^{r}, *CX*^{r}, *his, met* (Bianchi and Foury, 1982); *cdc8, cdc21: rho*$^-$, *lys2, ura1, his7, tyr1, cyh2, R1B* (Newlon et al., 1979); *spo7: ade2-1*(oc) (Esposito et al., 1975); *rev3: his1-7*(ms), *lys1-1*(oc) (Quah et al., 1980); uvs_2: ser^r (Zakharov et al., 1970).

[f] Other data for the genetic control of experimentally induced mutagenesis are available but they are not presented here because there were no corresponding data for spontaneous mutagenesis. These data are for the following mutants: *rad7, rad8, rad13, rad15, rad16, rad17, rad18, rad22, rad50,* and *rad52* (Lawrence and Christensen, 1976); *rad18* (Lawrence et al., 1974); *rad50, rad51, rad52, rad53, rad54, rad55, rad56*, and *rad57* (McKee and Lawrence, 1979); *rad50* (B.S. Cox and Parry, 1968); r_1^s (Averbeck et al., 1970; Eckardt et al., 1975); *rev1* (Lemontt, 1971a, 1972; Lawrence and Chistensen, 1976, 1978, 1979); *rev3* (Lemontt, 1971a, 1972; Lawrence and Christensen, 1976, 1979; McKee and Lawrence, 1979).

cept could be validated, it would help to explain the other fungal mutations (in Table 6) that clearly show opposite effects on spontaneous and experimentally induced mutagenesis. Otherwise, it seems more reasonable to offer the same explanation as was used in a similar situation for the *ssb* mutation (Table 5). That is, such mutations, while they may reduce error-prone repair might also reduce the fidelity of DNA replication. If so, then the reduction of DNA fidelity would overshadow the effect of such a mutation on reducing spontaneous mutagenesis resulting from error-prone repair (see also Lawrence, 1982).

E. Mammalian cells

Few data on spontaneous mutagenesis are available for DNA-damage-sensitive lines of mammalian cells. Liu et al. (1982a, 1983) described a line of Chinese hamster ovary cells that has a mutant form of DNA polymerase α. These cells exhibit enhanced UV radiation sensitivity and mutagenesis and enhanced rates of spontaneous mutagenesis, with several forward mutation assays. These cells are not thought to be deficient in excision repair, but only preliminary results are available (Liu et al., 1982b).

One prediction from the conclusion that *uvrA* and *uvrB* strains of *E. coli* are mutators was that cells from individuals with xeroderma pigmentosum (XP) should show a higher rate of spontaneous mutagenesis (Sargentini and Smith, 1981) because such cells are deficient in nucleotide excision repair (reviewed in Friedberg et al., 1979). It was also predicted, because of the correlations between mutagenesis and carcinogenesis (e.g., McCann et al., 1975), that individuals with XP would show a higher rate of spontaneous carcinogenesis. While the spontaneous mutation rate data for XP cells are not yet available, it is of interest to note that XP individuals have recently been shown to be prone to certain forms of cancer that would not be predicted from their sensitivity to light (Kraemer et al., 1984).

F. Spontaneous DNA damage

What could be the source of the "spontaneous" mutagenic DNA damage postulated to explain the enhanced spontaneous mutagenesis in excision-deficient strains of bacteria and fungi? One source includes factors present in any mutation assay procedure. The growth rate of the cells, the aeration rate of the culture, the pH and the temperature of the culture medium all have effects on spontaneous mutagenesis (Savva, 1982; for other physiological effects, see Clarke and Shankel, 1975). The near-UV radiation component of ambient light is known to be mutagenic, either directly (Webb, 1977) or indirectly through its effects on growth media (Webb and Lorenz, 1972). Oxygen apparently induces DNA damage (Morimyo, 1982) and is mutagenic (discussed in Hartman et al., 1984), it causes chromosomal aberrations in Fanconi's anemia cells (Joenje et al., 1981), and has been implicated in spontaneous carcinogenesis (Totter, 1980). Ames (1983) has listed numerous mutagens that are present in a wide variety of foods, and these mutagens may also be present in culture media.

The normal metabolism of DNA can result in mutations. Convincing evidence has been presented that base-substitution hotspots result from the spontaneous deamination of 5-methylcytosine residues to yield thymine residues, thus causing GC $\rightarrow$ AT transitions (Coulondre et al., 1978; Wang et al., 1982). Spontaneous depurination (Greer and Zamenhof, 1962; Lindahl and Nyberg, 1972) and targeted DNA *N*-glycosylase action (reviewed in Lindahl, 1982) should induce mutations because of the preferential insertion of purines (especially adenine) opposite apurinic or apyrimidinic sites (Sagher and Strauss, 1983). That is, apurinic or apyrimidinic sites should preferentially induce transversion or transition mutations, respectively, if they are encountered by a replication fork. The bypass of such lesions requires protein synthesis, i.e., it is an inducible process, and it is associated with mutagenesis, i.e., the bypass process is error-prone (Schaaper et al., 1982, 1983).

Mutagenic damage in DNA may also result from the metabolism of non-DNA cellular components. The oxidation of cellular fatty acids could be an important source of "spontaneous" mutagens (reviewed by Ames, 1983). Growth in the presence of phenylalanine, but not other common amino acids, produces excisable, DNA damage that produces mutations in *E. coli* via error-prone repair (Sargentini and Smith, 1983). Similarly, cysteine (as well as glutathione) is mutagenic in the

Ames tester strains if mammalian subcellular preparations are included in the assay (Glatt et al., 1983). As a more general example, a model system exists, using horseradish peroxidase and aromatic pyruvates, for an enzymatic reaction that requires oxygen to produce excited-state molecules (i.e., "UV-like") that can damage DNA (Cilento, 1980).

There is also evidence with mammalian cells for the metabolic production of chemical species that damage DNA. Fibroblasts from patients with Bloom's syndrome produce a clastogenic factor that causes chromosomal aberrations in normal human blood lymphocytes, while fibroblasts from normal individuals had no such effect (Emerit and Cerutti, 1981). Bloom's syndrome cells also show enhanced frequencies of spontaneous chromosomal aberrations and sister-chromatid exchanges (Chaganti et al., 1974), and enhanced spontaneous mutagenesis (Warren et al., 1981). Such metabolic damage to DNA has also been postulated to explain the characteristics of some other autosomal recessive diseases that are deficient in DNA repair (Lytle et al., 1983).

In addition, since it appears that DNA can be damaged by normal metabolic reactions such that the damage is recognized by error-prone repair systems (see above), it seems reasonable that damage could also be produced that causes coding errors during replication. For example, although *recA* strains are nonmutable by X- or UV radiation, they are mutable by certain chemicals (e.g., ethyl methanesulfonate and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine) that produce damage that is presumed to cause miscoding errors during replication (Kondo et al., 1970). Therefore, normal metabolic damage to DNA may also contribute to spontaneous mutagenesis by causing errors in DNA replication.

VI. Summary and conclusions

There appears to be no dearth of mechanisms to explain spontaneous mutagenesis. In the case of base substitutions, data for bacteriophage T4 and especially for *E. coli* and *S. cerevisiae* suggest important roles in spontaneous mutagenesis for the error-prone repair of DNA damage (to produce mutations) and for error-free repair of DNA damage (to avoid mutagenesis). Data from the very limited number of studies on the subject suggest that about 50% of the spontaneous base substitutions in *E. coli*, and perhaps 90% in *S. cerevisiae* are due to error-prone DNA repair. On the other hand, spontaneous frameshifts and deletions seem to result from mechanisms involving recombination and replication. Spontaneous insertions have been shown to be important in the strongly polar inactivation of certain loci, but it is less important at other loci. Perhaps with continued study, the term "spontaneous mutagenesis" will be replaced by more specific terms such as 5-methylcytosine deamination mutagenesis, fatty acid oxidation mutagenesis, phenylalanine mutagenesis, and imprecise-recombination mutagenesis.

While most studies have concentrated on mutator mutations, the most conclusive data for the actual source of spontaneous mutations have come from the study of antimutator mutations. Further study in this area, perhaps along with an understanding of chemical antimutagens, should be invaluable in clarifying the bases of spontaneous mutagenesis.

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