Journal of Supramolecular Structure
and Cellular Biochemistry 16:91-103 (1981)
Mechanisms of Chemical Carcinogenesis 17-29

The Repair of DNA Damage: Recent Developments and New Insights

E.C. Friedberg, T. Bonura, J.D. Love, S. McMillan, E.H. Radany, and R.A. Schultz

Department of Pathology, Laboratory of Experimental Oncology, Stanford University, Stanford, California 94305

This brief review presents the salient features of new developments in the enzymatic repair of base damage to DNA. DNA glycosylases and apurinic/apyrimidinic (AP) endonucleases are reviewed and evidence is presented that in at least two prokaryote systems incision of UV-irradiated DNA occurs by the sequential action of these two classes of enzymes. In contradistinction, the *uvrA*, *uvrB*, and *uvrC* gene products of E coli appear to function as a multi-protein complex that catalyzes hydrolysis of phosphodiester bonds in damaged DNA directly. The inducible rapid repair of O^6-methylguanine in E coli is also reviewed.

Key words: DNA repair, DNA glycosylases, E coli, AP endonucleases, UV radiation, alkylation damage

The phrase "DNA repair" has come to be used in the literature in a rather unrestricted sense to describe a large variety of cellular responses to DNA damage and now includes terms such as excision repair, post-replication repair, inducible repair, error-free repair, error-prone repair, adaptive repair, etc [1,2]. In this review we specifically define DNA repair as the removal or reversal of any alterations in the chemical composition or correct nucleotide sequence of DNA (Table I). Both for the purposes of convenience, and in recognition of their major biological relevance, a consideration of such alterations is confined to the informationally relevant constituents of DNA, the nitrogenous bases.

In addition to the *repair* of base damage to DNA by enzyme-catalyzed reactions, at least some biological organisms are clearly able to *tolerate* the persistence of base damage in DNA template strands without the permanent arrest of DNA replication (Table I). Evidence indicates that in the widely studied prokaryote, E coli, both the repair and the tolerance of DNA damage sometimes require the induction of specific gene functions [1,2].

In this article we briefly review some recent developments and new insights in the repair of base damage to DNA. The emphasis on prokaryote systems is unavoidable; it is clear that bacteria, particularly E coli and its phages, continue to be the most suitable model systems for the study of DNA repair. However, wherever relevant, information on both lower and higher eukaryotes is included.

Received February 17, 1981; revised and accepted May 11, 1981.

TABLE I. Cellular Responses to DNA Damage

A. Repair of DNA damage
1. Reversal of base damage
a) Enzymatic photoreactivation of pyrimidine dimers
b) Demethylation of O^6-methylguanine
c) Purine insertion
2. Removal of base damage
a) Nucleotide excision
b) Base excision
B. Tolerance of DNA damage
1. Post-replicative recombination bypass
2. Trans-dimer synthesis

EXCISION REPAIR OF DNA

DNA Glycosylases

One of the most significant recent developments in the molecular biology of DNA repair is the discovery of a new class of enzymes that effect the excision of damaged or inappropriate bases from DNA as the free base [3–6]. These enzymes are collectively referred to as DNA glycosylases, since they catalyze the hydrolysis of the N-glycosylic bond linking the nitrogenous bases to the deoxyribose-phosphate backbone of DNA. The number of DNA glycosylases already discovered in E coli is quite remarkable [5–13]. So far seven distinct enzymes have been described (Table II), and it is not unlikely that others are yet to be discovered. Thus a significant fraction of the genetic information of E coli is devoted to coding for this class of DNA repair enzymes. This genetic diversity is apparently necessary, since, as indicated in Table II, each DNA glycosylase is highly specific for a particular type of base damage or replacement in DNA.

All DNA glycosylases share a number of physiochemical characteristics: 1) All are relatively small proteins (Mr $< 30{,}000$) with no evidence of subunit structure [5–13]; 2) none require any known cofactor for activity and are active in the presence of EDTA [5–13]. Some of the substrates listed in Table II may appear rather esoteric at first glance; however, the FaP-DNA glycosylase, urea-DNA glycosylase, and hydrated thymine-DNA glycosylase all recognize forms of base damage known to result from ionizing or UV radiation exposure to DNA. Indeed, the selective pressure for the evolution of most of the known DNA glycosylases of E coli is readily understood in terms of the long-standing prevalence of radiation-induced and spontaneous base damage (eg, deamination) to DNA. The selective pressure for the evolution of an enzyme that specifically recognizes 3-methyladenine in DNA can only be speculated on. Conceivably, at some early stage of evolution, 3-methyladenine in DNA was a component of some aspect of gene regulation. Alternatively, bacteria such as E coli may have been exposed to inappropriate methylation in the course of what is now recognized as normal modification of DNA by site-specific methylation. Finally, primitive organisms might have sustained DNA damage by exposure to naturally occurring alkylating agents produced as metabolic products by other organisms.

TABLE II. DNA Glycosylases of E coli

Enzyme	Substrate	Products	Reference
Ura-DNA glycosylase	DNA containing deoxyuridine	uracil + depyrimidinated DNA	[7]
Hx-DNA glycosylase	DNA containing deoxyinosine	hypoxanthine + depurinated DNA	[8]
3-MA-DNA glycosylase	DNA containing 3-methyldeoxyadenosine	3-methyladenine + depurinated DNA	[9]
FaPy-DNA glycosylase	DNA containing formamidopyrimidine moieties	2,6-diamino-4-hydroxy-5-N-methyl-formamidopyrimidine + depurinated DNA	[10]
5,6-HT-DNA glycosylase	DNA containing 5,6-hydrated thymine moieties	5,6-dihydroxydihydrothymine and 5,6-dihydrothymine + depyrimidinated DNA	[11]
Urea-DNA glycosylase	DNA containing urea moieties	urea + depyrimidinated DNA	[12]
7MG-DNA glycosylase	DNA containing 7-methyldeoxyguanosine	7-methylguanine + depurinated DNA	[13]

Apurinic/Apyrimidine (AP) Endonucleases

The products of the reaction of DNA glycosylases with DNA are free bases and apurinic or apyrimidinic (AP) sites in the DNA. Evidence suggests that a primary mechanism for the repair of AP sites is their excision from DNA by the classical excision/resynthesis/ligation model long proposed for the repair of many forms of DNA damage (Fig. 1) [1–4]. In the case of AP sites the specific incision of the DNA required to initiate the excision/resynthesis events is effected by a unique class of enzymes called AP endonucleases [4,5,14].

AP endonucleases were first described in E coli in the early 1970s [15,16], but it wasn't until the discovery of the DNA glycosylases that their importance in DNA repair was fully realized. Again E coli has served as a primary system of investigation and to date five distinct enzymes with AP endonuclease activity have been isolated from this organism (Table III) (see [1–5,14] for recent reviews). Why this redundancy? An obvious approach to this question would be to examine the phenotype of mutants defective in each of the AP endonucleases listed in Table III; however, thus far mutants defective in exonuclease III are the only ones that have been isolated [17–19]. On the other hand, recent detailed biochemical characterization of AP endonucleases of E coli in vitro suggests that their redundancy may reflect varying substrate specificities. Thus, for example, endonuclease III has been reported to have an associated DNA glycosylase activity [11,20] that catalyzes the excision of 5,6, dihydroxydihydrothymine and 5,6, dihydrothymine from DNA. In addition, whereas endonucleases III and IV and the AP endonuclease function of exonuclease III are specific for sites of base loss in duplex DNA, endonuclease VII of E coli is specific for sites of base loss in single stranded regions of DNA [4, Bonura T, Schultz R, Friedberg EC, manuscript submitted]. Warner et al [21] have provided evidence suggesting different directional specificity of endonuclease activity. Thus endonuclease IV and exonuclease III are 5′ acting en-

TABLE III. AP Endonuclease of Escherichia coli [4,5,14]

Enzyme	Principal features
1. AP endonuclease function of exonuclease III (endonuclease II of E coli endonuclease VI of E coli)	Quantitatively the major AP endonuclease. Is one of several catalytic functions of exonuclease III. Does not require cofactors. Active only on duplex AP DNA. Hydrolyzes phosphodiester bond 5′ to AP site.
2. Endonuclease IV	Accounts for most residual AP endonuclease action on duplex DNA in exonuclease III-defective mutants. No associated catalytic activities. Is a 3′ endonuclease.
3. Endonuclease III	An AP endonuclease that has associated DNA glycosylase that removes 5,6 saturated thymine monoadducts from DNA. Active only on duplex AP DNA. Is a 3′ AP endonuclease.
4. Endonuclease V	Not yet well characterized, but seems to attack DNA with multiple forms of damage, including AP sites. Requires MG^{++}.
5. Endonuclease VII	An AP endonuclease specific for sites of base loss in single stranded DNA. No cofactor requirement.

zymes (ie, they catalyze incision of phosphodiester bonds so as to leave the deoxyribose-phosphate moiety on the 3′ terminus at the site of incision), whereas endonuclease III is a 3′ acting enzyme. Finally, although it is generally assumed that AP endonucleases do not discriminate between sites of purine and pyrimidine loss in duplex DNA, this distinction could well provide a further basis for varying substrate specificity. Thus it might be very informative to measure the Km of each AP endonuclease of E coli for duplex DNA containing exclusively apurinic or apyrimidinic sites.

The Role of DNA Glycosylase and AP Endonuclease Activities in Pyrimidine Dimer Excision

It has been recognized for many years that a unique enzyme activity must catalyze the incision of UV-irradiated DNA at sites of pyrimidine dimers in order to effect their excision. A search for such enzymes resulted in the isolation of so-called "UV endonucleases" from M luteus [22–24] and phage T4-

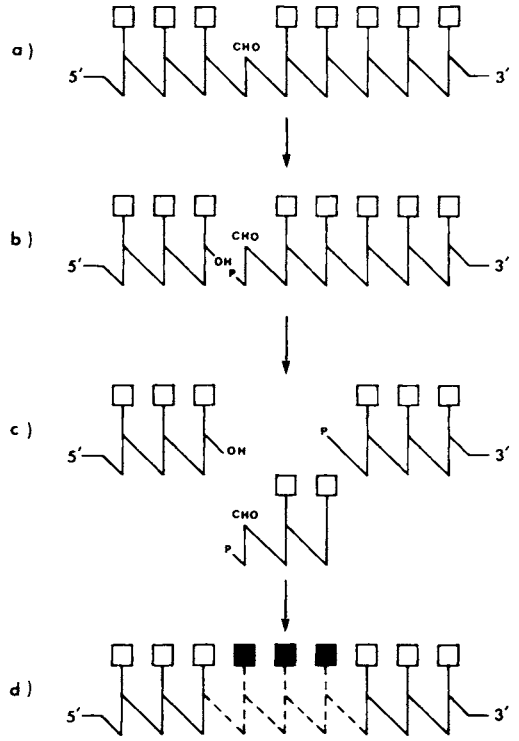

Fig. 1. Excision of AP sites as part of an oligonucleotide fragment. Only one strand of a DNA duplex is shown. a) Polynucleotide strand containing an AP site produced by spontaneous base loss or by the action of a DNA glycosylase. b) The AP site is attacked by an AP endonuclease creating hydrolysis of the phosphodiester backbone 5′ to the AP site and leaving a 3′ OH terminus. c) An oligonucleotide containing the deoxyribose-phosphate residue is excised by a 5′→3′ exonuclease activity. d) The gap is filled by repair synthesis and covalent integrity of the polynucleotide chain is restored by DNA ligase activity.

infected E coli [25–27]. Both enzymes were thought to be pure endonucleases that directly catalyzed the hydrolysis of a phosphodiester bond immediately 5′ to pyrimidine dimer sites in DNA [28–30].

Recent experiments by Grossman, Haseltine, and their colleagues with the M luteus enzyme [31] led to the suggestion of a model in which the enzyme(s) first catalyze the hydrolysis of the 5′ glycosyl bond of the dimerized pyrimidines (pyrimidine dimer-DNA glycosylase), thereby creating apyrimidinic sites which are secondarily attacked by an AP endonuclease (Fig. 2). Further studies from a number of laboratories with both the M luteus [32] and T4 enzymes [11,33–35] have provided strong support for this mechanism in vitro. Studies from this laboratory (E.H. Radany and E.C. Friedberg, manuscript in preparation) have shown that this mechanism also operates in vivo in T4-infected cells.

Radany and Friedberg [33] have demonstrated that the T4 pyrimidine-dimer-DNA glycosylase is coded by the *den V* [36] (formerly called the *v* gene [37]) of phage T4. It has also been recently shown [McMillan S, Edenberg HJ, Radany EH, Friedberg RC, Friedberg EC, manuscript submitted] that extracts prepared from E coli infected with *den* V^+ cells contain significantly greater levels of AP endonuclease activity than extracts of cells infected with phage defective in the *den V* gene. In addition, the T4 pyrimidine dimer-DNA glycosylase activity against UV-irradiated DNA is strongly competed for by DNA containing apurinic or apyrimidinic sites, but not by native DNA. These observations indicate that there is a physical association between the pyrimidine dimer-DNA glycosylase and AP endonuclease activities and that both are coded by the *den V* gene of phage T4. A similar conclusion has been reached by H. Warner et al (personal communication). Extensive purification of the M luteus pyrimidine dimer - DNA glycosylase activity has failed to separate it from AP endonuclease activity. However, there is as yet no definitive evidence that the two activities are present in a single protein [Grossman L, personal communication].

How ubiquitous is this mechanism for the incision of UV-irradiated DNA containing pyrimidine dimers? To date, the two enzyme activities just described appear to be unique examples. However, it is of obvious interest to extensively survey both other prokaryotes as well as eukaryotes for DNA glycosylases active on pyrimidine dimers in DNA. Studies in our laboratory have failed to detect convincing evidence of pyrimidine dimer-DNA glycosylase activity in extracts of M radiodurans, the yeast S cerevisiae, or human KB cells [Love JD, McMillan S, Radany EH, Friedberg EC, unpublished observations].

The UV Endonuclease of E coli

The genetics of the excision repair of pyrimidine dimers in uninfected E coli has been established for many years; however, the products of the *uvrA*, *uvrB*, and *uvrC* genes have only recently been isolated [38–42]. Unlike the "UV endonucleases" of M luteus and phage T4, the E coli enzyme is a multiprotein complex. The *uvrA* protein has been purified to physical homogeneity and has a Mr = 114,000 [39–42]. It binds to unirradiated single-stranded DNA, UV-irradiated single-stranded DNA, and UV-irradiated duplex DNA [40,42]. The protein also has a DNA-dependent ATPase activity. The *uvrB* and *uvrC*

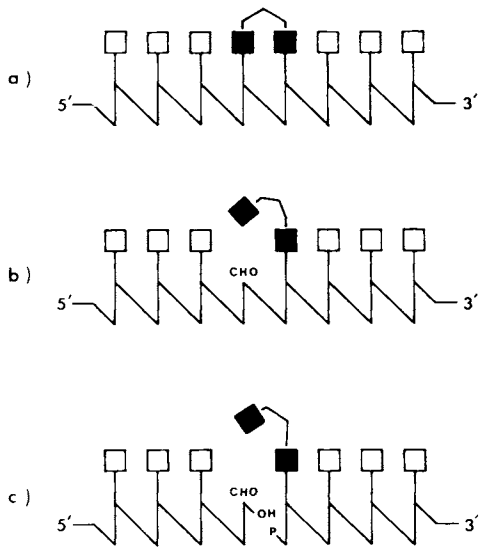

Fig. 2. Incision of UV-irradiated DNA at pyrimidine dimer sites by the combined action of a DNA glycosylase and AP endonuclease. Only one strand of a DNA duplex is shown. a) Polynucleotide chain containing a pyrimidine dimer. b) The 5′ glycosyl bond of the dimer is attacked by a specific DNA glycosylase. c) The resulting AP site is attacked by an AP endonuclease shown here to catalyze phosphodiester bond hydrolysis 3′ to the AP site and creating a 3′ OH terminus. Excision of the dimer still requires the action of a 5′→3′ exonuclease.

proteins have not yet been separated, but together with the *uvrA* protein they catalyze incision of UV-irradiated DNA [38–42]. The amount of these gene products constitutively present in extracts of E coli is very small. It has been estimated that E coli may normally have as few as 12 copies of the *uvrC* polypeptide/cell [43]. This has made the purification of the *uvr* complex an extraordinarily difficult task. Although recent evidence indicates that the *uvrA* and *uvrB* genes are inducible as part of the "SOS" cascade [44,45], the amplification of gene expression is less than an order of magnitude, and there is as yet no evidence that the *uvrC* gene is also inducible. A highly significant advance in the potential for characterizing the E coli UV DNA incising activity is the successful cloning of the *uvrA*, *uvrB*, and *uvrC* genes [43,46–49]. The molecular weight of the expressed *uvrA* gene product [48] is in excellent agreement with that obtained by study of the protein purified from extracts of E coli [41,42]. Studies with the cloned *uvrB* [46,49] and *uvrC* genes [43] indicate that their products are polypeptides of Mr = 84,000 and 68,000, respectively. Thus the *uvrA*, *uvrB*, *uvrC* protein complex has a Mr $>$ 250,000.

In further contradistinction to the M luteus and T4 enzymes, the *uvrA*, *uvrB*, *uvrC* gene product complex has an absolute requirement both for Mg^{++} and for ATP. In addition, whereas the pyrimidine dimer-DNA glycosylases are apparently strictly specific for dimers in DNA, the complex attacks psoralen/UV-treated DNA in vitro, and strains of E coli defective in *uvr* A, B, or C genes are abnormally sensitive to mitomycin C, 4-nitroquinoline-1-oxide, and

other chemical agents [50]. Thus it appears that the E coli enzyme is a more general DNA repair endonuclease that presumably recognizes conformational distortions in the DNA duplex produced by a variety of forms of DNA damage. However, the presence of conformational distortion of the secondary structure of DNA may not be the sole basis for the substrate specificity of this enzyme complex, since it apparently discriminates between the strand containing base damage and the opposite DNA strand.

It remains to be clearly established whether or not the incision of DNA containing pyrimidine dimers (as opposed to other forms of base damage) is catalyzed by a direct-acting endonuclease or by a DNA-glycosylase/AP endonuclease mechanism in E coli. Recent studies in our laboratory (preliminary results of which have been published [51]) suggest that some thymine-containing pyrimidine dimers are attached by a DNA glycosylase in vivo. In these experiments *uvr*$^+$ strains of E coli were incubated following UV irradiation and oligonucleotides in the acid-soluble fraction, including those containing excised pyrimidine dimers, were isolated free of contaminating thymine and thymidine. Monomerization of pyrimidine dimers was effected by direct photoreversal as described by Radany and Friedberg [33]. When glycosyl bonds in thymine-containing pyrimidine dimers are hydrolyzed in vivo, monomerization of the dimer by re-irradiation (direct photoreversal) results in the release of free thymine. This is the assay by which we routinely measure pyrimidine dimer-DNA glycosylase activity both in vivo and in vitro. By these criteria we have observed that about 20% of the excised thymine-containing pyrimidine dimers in E coli contain hydrolyzed glycosyl bonds. The question as to why only a fraction of thymine-containing pyrimidine dimers are apparently so affected is under active investigation.

Incision of UV-Irradiated DNA in Eukaryotes

Current information on the enzymology of excision repair in eukaryotes is not as advanced as in the prokaryote systems discussed above. The equivalent of the E coli *uvrA*, *uvrB*, and *uvrC* proteins has not been isolated from any eukaryote, and if the cellular-biological and genetic evidence from these systems is to be taken as any indicator, the enzymology of DNA incision in eukaryotes may be even more complex than in E coli. For example, it is now established that there are seven complementation groups in the human disease xeroderma pigmentosum (see [52] for a recent review). A direct analysis of the capacity of cells from each of these complementation groups to carry out incision of their DNA during post-UV incubation has revealed a severe or complete defect in five of the seven [53]. One possible interpretation of these data is that the products of at least five genes constitute a complex required for the incision of damaged DNA in human cells.

A striking parallel to the data from human cells comes from recent studies with the yeast S cerevisiae. This organism has been very thoroughly investigated with respect to the genetics of DNA repair, and all loci controlling sensitivity to radiation are called *RAD* [54]. A number of *rad* mutants fall into a discrete group referred to as the *rad3* class, of which the principal phenotypes are an abnormal sensitivity to UV radiation and to UV-mimetic chemicals, as well as a severe defect in the excision repair of pyrimidine dimers. Studies in

this laboratory have shown that mutants defective at five different *RAD* loci are defective in their ability to catalyze the formation of single-strand breaks in their DNA at pyrimidine dimer sites during post-UV incubation in vivo [55]. In addition, no *rad* mutants yet examined have been found to be defective in their ability to excise thymine-containing pyrimidine dimers in vitro from UV-irradiated DNA *preincised* with M luteus UV DNA-incising activity [55]. Collectively these data suggest that the genetic control of the incision of UV-irradiated DNA at pyrimidine dimers in S cerevisiae is as complex as in human cells.

INDUCIBLE ERROR—FREE DNA REPAIR: THE ADAPTIVE RESPONSE

In 1977 Samson and Cairns first reported a new DNA repair pathway in E coli which is inducible and apparently error free [56]. This repair pathway (sometimes referred to as the adaptive response) is essentially characterized by a reduction in mutation frequency and an increase in survival in E coli cells pre-exposed to very low levels of certain mutagenic alkylating agents, prior to exposure to mutagenic and lethal challenging doses of the agent. The protection against mutation and cell killing requires *de novo* protein synthesis and is also very critically dependent on the doses of alkylating agents used for the pre-exposure (adaptation).

Continued investigation of this system in a number of laboratories [57–61] has provided evidence that the adaptive response in E coli involves the induction of functions for the repair of O^6-methylguanine in DNA. A good correlation between the mutation frequency and the presence of O^6-methylguanine in adapted and nonadapted cells has been demonstrated. In addition, mutant strains defective in the adaptive response *(ada⁻)* are defective in their ability to remove O^6-methylguanine from DNA and demonstrate a loss of protection against its mutagenic effects. A curious feature of the response in E coli is that it has a finite capacity. Thus, adapted cells can rapidly remove only a limited number of O^6-methylguanine residues per cell following exposure to a challenging dose of a given alkylating agent. Those lesions generated in excess of the induced repair capacity are removed at a much slower rate, typical of the kinetics of the repair of these lesions in unadapted cells.

The isolation by Barbara Sedgwick of a mutant of E coli that constitutively expresses the adaptive response (unpublished data) facilitated the isolation and partial purification of a protein fraction by Lindahl and his co-workers [62] that appears to be responsible for the rapid limited repair of O^6-methylguanine residues in DNA. This fraction contains a protein of Mr ~ 16,000 which functions as a methyltransferase activity that removes methyl groups from the O^6 position of guanine. The methyl groups are covalently bound to cysteine residues of protein as S-methylcysteine. Thus the loss of radioactive methyl groups in O^6-methylguanine from the acid-insoluble fraction of DNA incubated with extracts of adapted E coli cells is not accompanied by the recovery of radioactivity in the acid-soluble fraction. The demethylation reaction has been independently confirmed by Foote et al [63], who constructed a synthetic polymer containing O^6-methyl [8^{-3}H] deoxyguanosine. The enzyme-catalyzed removal of the methyl group results in the formation of radiolabeled guanine in

the deoxypolymer, which can be readily quantitated. Whether or not the acceptor protein and the transferase are a single physical entity has not yet been definitely established. However, the current working hypothesis is that once a transferase molecule accepts a methyl group it loses its catalytic activity. This provides a rational biochemical explanation for the finite property of the induced response described above.

Does an adaptive response formally analogous to that in E coli exist in eukaryotes? There is considerable evidence in the literature that mammalian cells, including human cells and tissues, do carry out the repair of O^6-alkylguanine in DNA [64–70]. However, the only published evidence for possible enhanced repair associated with specific adaptive pretreatment of cells comes from a recent report by Samson and Schwartz [71]. These investigators have shown that the exposure of Chinese hamster ovary cells or of SV40-transformed human skin fibroblasts to defined small doses of N-methyl-N′-nitro-nitrosoguanidine renders them more resistant to induction of sister chromatid exchanges and to cell killing by challenge doses of the alkylating agent.

The question of an adaptive response in higher eukaryotes to small doses of certain chemical mutagens is of obvious importance to a consideration of the role of chemical exposure in neoplastic transformation. If such a response does exist, clearly those levels of exposure that elicit an daptive response would be protective against somatic mutations. Similarly, if mammalian cells possess an inducible repair mode, mutants that express this repair constitutively would be expected to be relatively resistant to certain chemical carcinogens.

CONCLUSIONS

Advances in the past decade have significantly increased awareness of the multiplicity of biochemical mechanisms for the repair of base damage to DNA. It is now evident that many types of monoadduct base damage are repaired by a class of enzymes consisting of small proteins with limited biochemical complexity (DNA glycosylases), each of which is very specific for a given type of damaged or inappropriate base.

The recent discovery that both the T4 and M luteus "UV endonucleases" (correndonucleases) are also DNA glycosylases suggests that these two enzymes are not prototypic examples of general repair endonucleases. The latter, which have a much broader substrate specificity than the DNA glycosylases, have not as yet been extensively characterized from any biological source. One obvious explanation for this is that they are only catalytically active as high molecular weight multiprotein complexes, as exemplified by the *uvr* A, *uvr* B, or *uvr* C gene products of E coli and by the genetic complexity of excision repair in both lower and higher eukaryotes. Such multiprotein complexes may be difficult to reconstitute in cell-free systems.

Another singularly exciting area of active current research is the inducible adaptive response of E coli to selective methylation of guanine in the O^6 position. This type of repair system appears to have evolved to deal very rapidly and with great efficiency with a limited specific damage to DNA. It is of distinct interest to determine whether further examples of this mode of DNA repair exist in nature.

Finally, it is worth noting that the available evidence suggests that all of the DNA repair processes discovered in lower organisms (notably E coli) are represented in eukaryotes, including mammalian cells. Though this observation should not be over-generalized, it is singularly encouraging to recognize that prokaryotes continue to serve as sources of fundamental information of the molecular mechanisms by which living cells maintain genetic fidelity.

This brief review has focused on certain limited aspects of recent developments in the field of DNA repair, with an admitted bias for areas that are of specific interest to the authors. Due to the limited space available we have omitted a consideration of the postulated repair of sites of purine loss by DNA-purine insertases and refer the interested reader to the relevant literature [72–74]. A second notable omission is the topic of the repair of mismatched bases in DNA, an area in which exciting new genetic and cellular-biological information is available [75]. However, as yet there are no published reports of specific enzymes and/or other proteins involved in this process. Finally, the reader should be aware that while we have chosen to review DNA repair as defined in the opening statement, significant progress has been made in recent years in the understanding of the molecular mechanisms involved in the tolerance of damage in DNA, particularly that associated with the induction of *error-prone* responses controlled by the *rec* A and *lex* A genes of E coli.

ACKNOWLEDGMENTS

The authors wish to acknowledge the participation of Dr. R.J. Reynolds, School of Public Health, Harvard University, in some of the experimental results quoted from this laboratory. Research performed in the senior author's laboratory was supported by research grants CA-12428 from the USPHS and 1-672 from the Foundation-March of Dimes, as well as by contract DE-AS03-76SF00326 with the US Department of Energy. JDL is supported by USPHS Postdoctoral National Services Award CA-06441; SM is supported by Postdoctoral Fellowship DRG-407-F from the Damon Runyon-Walter Winchell Cancer Foundation; RAS is a postdoctoral trainee in the Stanford Cancer Biology Program funded by USPHS grant CA-09302; and EHR is a predoctoral trainee in the Stanford Medical Scientist Training Program funded by USPHS grant GM-07365.

REFERENCES

1. Hanawalt PC, Friedberg EC, Fox CF (eds): "DNA Repair Mechanisms." New York: Academic press, 1978.
2. Hanawalt PC, Cooper PK, Ganesan AK, Smith CA: Ann Rev Biochem 98: 783, 1979.
3. Lindahl T: Nature 259: 64, 1976.
4. Friedberg EC, Anderson C, Bonura T, Cone R, Simmons R: In Hanawalt PC, Friedberg EC, Fox CF (eds): "DNA Repair Mechanisms." New York: Academic Press, 1978, pp 163–173.
5. Lindahl T: Prog Nuc Acid Res Mol Biol 22: 135, 1979.
6. Duncan BK: In Boyer PD (ed): "The Enzymes." Vol. 14. New York: Academic Press (in press).
7. Lindahl T, Ljungquist S, Seigert W, Nyberg B, Sperens B: J Biol Chem 252: 3286, 1977.
8. Karran T, Lindahl T: J Biol Chem 253: 5877, 1978.
9. Riazuddin S, Lindahl T: Biochem 17: 2110, 1978.

10. Chetsanga CJ, Lindahl T: Nucleic Acids Res 6: 3673, 1979.
11. Demple B, Linn S: Nature 287: 203, 1980.
12. Breimer L, Lindahl T: Nucleic Acids Res 8: 6199, 1980.
13. Laval J, Pierre J, Laval F: Proc Natl Acad Sci USA 78: 852, 1981.
14. Friedberg EC, Bonura T, Radany EH, Love JD: In Boyer PD (ed): "The Enzymes." Vol. 14. New York: Academic Press (in press).
15. Hadi S-M, Goldthwait DA: Biochemistry 10: 4986, 1971.
16. Paquette Y, Crine P, Verly WG: Can J Biochem 50: 1199, 1972.
17. Yajko DM, Weiss B: Proc Natl Acad Sci USA 72: 688, 1975.
18. Weiss B: J Biol Chem 251: 1896, 1976.
19. White BJ, Hochhauser SJ, Citron NM, Weiss B: J Bacteriol 126: 1082, 1976.
20. Linn S, Demple B, Mosbaugh DW, Warner HR, Deutsch WA: In Seeberg E, Kleppe K (eds): "Chromosome Damage and Repair." New York: Plenum (in press).
21. Warner HR, Demple BF, Deutsch WA, Kane CM, Linn S: Proc Natl Acad Sci USA 77: 4602, 1980.
22. Nakayama H, Okubo S, Sekiguchi M, Takagi Y: Biochem Biophys Res Commun 27: 217, 1967.
23. Kaplan JC, Kushner SR, Grossman L: Proc Natl Acad Sci USA 63: 144, 1969.
24. Carrier WL, Setlow RB: J Bacteriol 102: 178, 1970.
25. Friedberg EC, King JJ: Biochem Biophys Res Commun 37: 646, 1969.
26. Yasuda S, Sekiguchi M: Proc Natl Acad Sci USA 67: 1839, 1970.
27. Friedberg EC, King JJ: J Bacteriol 106: 500, 1971.
28. Riazuddin S, Grossman L: J Biol Chem 252: 6280, 1977.
29. Riazuddin S, Grossman L: J Biol Chem 252: 6287, 1977.
30. Minton K, Durphy M, Taylor R, Friedberg EC: J Biol Chem 250: 2823, 1975.
31. Grossman L, Riazuddin S, Haseltine WA, Lindan C: Cold Spr Harbor Symp Quant Biol 43: 947, 1979.
32. Haseltine WA, Gordon LK, Lindan CP, Grafstrom RH, Shaper NL, Grossman L: Nature 285: 634, 1980.
33. Radany EH, Friedberg EC: Nature 286: 182, 1980.
34. Seawell PC, Smith CA, Ganesan AK: J Virol 35: 790, 1980.
35. Gordon LK, Haseltine WA: J Biol Chem 255: 12047, 1980.
36. Wood WB, Revel HR: Bacteriol Rev 40: 847, 1976.
37. Harm W: Virology 19: 66, 1963.
38. Seeberg E, Nissen-Meyer J, Strike P: Nature 263: 524, 1976.
39. Seeberg E: Proc Natl Acad Sci USA 75: 2569, 1978.
40. Seeberg E: In Hanawalt PC, Friedberg EC, Fox CF (eds): "DNA Repair Mechanisms." New York: Academic Press, 1978, pp 225–228.
41. Seeberg E: Adv Nuc Acids Res Mol Biol 26: 217, 1981.
42. Seeberg E, Steinum, A-L: In Seeberg E, Kleppe K (eds): "Chromosome Damage and Repair." New York: Plenum (in press).
43. Yaokum GH, Grossman L: Nature (in press).
44. Kenyon CJ, Walker GC: Proc Natl Acad Sci USA 77: 2819, 1980.
45. Fogliano M, Schendel PF: Nature 289: 196, 1981.
46. Pannekoek H, Noordermeer I, van de Putte P: J Bacteriol 139: 48, 1979.
47. Sancar A, Rupp WD: Biochem Biophys Res Commun 90: 123, 1979.
48. Sancar A, Wharton RP, Seltzer S, Kacinski BM, Clarke ND, Rupp WD: J Mol Biol 148: 45, 1981.
49. Sancar A, Clarke ND, Griswold J, Kennedy WJ, Rupp WD: J Mol Biol 148: 63, 1981. and Mutagenesis in Eukaryotes." New York: Plenum, 1980, pp 121–139.
50. Murray ML: Environ Mutagen 1: 347, 1979.
51. Radany EH, Friedberg EC: J Supramol Struct Supplement 5. (abstr), 10th Ann. ICN-UCLA Symposia, p 176, 1981.
52. Friedberg EC, Ehmann UK, Williams JI: Adv Rad Biol 8: 85, 1979.
53. Zelle B, Lohman PHM: Mutat Res 62: 363, 1979.
54. Haynes RH, Kunz BA: In Strothers J, Broach J, Jones EW (eds): "The Molecular Biology of the Yeast Saccheromyces." New York: Cold Spring Harbor Press (in press).
55. Reynolds RJ, Friedberg EC: In Generoso W, Shelby MD, de Serres FJ (eds): "DNA Repair and Mutagenesis in Eukaryotes." New York: Plenum, 1980, pp 121-139.
56. Samson L, Cairns J: Nature 267: 281, 1977.

57. Jeggo P, Defais M, Samson L, Schendel PF: Mol Gen Genet 152: 1, 1977.
58. Schendel PF, Robins PE: Proc Natl Acad Sci USA 75: 6017, 1978.
59. Robins P, Cairns J: Nature 279: 74, 1980.
60. Cairns J: Nature 286: 176, 1980.
61. Karran P, Lindahl T, Griffin BE: Nature 280: 76, 1980.
62. Olsson M, Lindahl T: J Biol Chem 255: 10569, 1980.
63. Foote RS, Mitra S, Pal BC: Biochem Biophys Res Commun 97: 654, 1980.
64. Kleihues P, Margison GP: Nature 259: 153, 1976.
65. Buecheler J, Kleihues P: Chem Biol Interact 16: 325, 1977.
66. Scherer E, Steward AP, Emmelot P: Chem Biol Interact 19, 1; 1977.
67. Pegg AE: Biochem Biophys Res Commun 84: 166, 1978.
68. Pegg AE: Nature 274: 182, 1978.
69. Montesano R, Bresil H, Planche-Martel T, Margison GP, Pegg AE: Cancer Res 40: 452, 1980.
70. Warren W, Lawley PD: Carcinogen 1: 67, 1980.
71. Samson L, Schwartz JL: Nature 287: 861, 1980.
72. Deutsch WA, Linn S: Proc Natl Acad Sci USA 76: 141, 1979.
73. Livneh A, Elad D, Sperling J: Proc Natl Acad Sci USA 76: 1089, 1979.
74. Duetsch WA, Linn S: J Biol Chem 254: 12099, 1979.
75. Radman M, Wagner RE Jr, Glickman BW, Meselson M: In Alecevik M (ed): "Progress in Environmental Mutagenesis." Amsterdam: Elsevier-North Holland, 1980, pp 121–130.