POSTREPLICATION REPAIR IN MAMMALIAN CELLS AFTER ULTRAVIOLET IRRADIATION

A MODEL

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ABSTRACT A model is presented for bypass of ultraviolet-induced damage in DNA during replication. The overall process is initiated by the introduction of a single-strand break into parental DNA near the point of arrest of synthesis, followed by a transient crossing-over step similar to that envisaged in genetic recombination. The mechanism proposed provides an alternative explanation to existing models and is entirely consistent with available data on postreplication repair in mammalian cells. In addition the model explains the low level of recombination repair observed in mammalian cells.

INTRODUCTION

A dose-dependent reduction in the rate of DNA synthesis after ultraviolet (UV) irradiation has been demonstrated in a variety of mammalian cells (Cleaver, 1967; Djordjevic and Tolmach, 1967; Domon and Rauth, 1968; Meyn et al., 1976; Rasmussen and Painter, 1964). However, while moderate UV doses reduce the rate of DNA synthesis, they do not prevent the ultimate replication of almost the entire genome (Meyn et al., 1976). A considerable body of evidence indicates that the DNA synthesized shortly after UV irradiation is of lower molecular weight than that in unirradiated cells (Buhl et al., 1972*a*; Cleaver and Thomas, 1969; Fujiwara and Kondo, 1972; Lavin et al., 1977; Lehmann, 1972; Meyn and Humphrey, 1971). However, it has been demonstrated in L cells that, at moderate UV doses, the newly synthesized DNA after irradiation is of molecular weight comparable to that of unirradiated cells (Rauth et al., 1974). In bacteria, gaps formed in newly synthesized DNA after UV irradiation are filled in by recombinational exchanges (Ganesan, 1974; Rupp et al., 1971). In UV-irradiated mammalian cells, the elongation of short fragments of newly synthesized DNA proceeds primarily by *de novo* synthesis (Lehmann, 1972), although UV-induced recombination repair has been demonstrated to occur at a low level (Buhl and Regan, 1973; Meneghini and Hanawalt, 1976; Walters and Regan, 1976).

It is generally accepted that base damage in DNA blocks or delays synthesis (Lehmann, 1972; Buhl et al., 1972*a*; Lehmann, 1974; Edenberg, 1975; Painter, 1974). Edenberg (1976) suggests that this damage is later bypassed, allowing adjacent replicons to fuse and form high molecular weight DNA. Other results indicate that reinitiation of

synthesis occurs at some time later, beyond the damaged site, giving rise to discontinuities (approximately 1,000 nucleotides long) in the newly synthesized DNA (Lehmann, 1972; Buhl et al., 1972*b* Doniger, 1978). Several models have been proposed to account for bypass of damage and subsequent replication of the damaged strand (Fujiwara, 1975; Fujiwara and Tatsumi, 1976; Higgins et al., 1976; Meneghini, 1976).

BASIC PROPOSITION

I wish to propose a model for postreplication repair in mammalian cells consistent with the findings that gaps or single-strand regions are formed in newly synthesized DNA shortly after UV irradiation (Lehmann, 1972; Buhl et al., 1972*a*; Meneghini, 1976). My model does not require a DNA polymerase activity to synthesize past damage in DNA, as might be expected in a gap-filling process by *de novo* synthesis (Lehmann, 1972; Buhl et al., 1972*b*). It provides an explanation for the involvement of recombinational exchange in postreplication repair in mammalian cells (Buhl and Regan, 1973; Meyn et al., 1976). It can also be applied to a postreplication repair mechanism in which the damaged site block's DNA synthesis (Edenberg, 1976). This model has some features in common with other models that invoke strand displacement as a means of carrying out replication past damaged regions (Fujiwara, 1975; Fujiwara and Tatsumi, 1976; Higgins et al., 1976; Meneghini, 1976). However, in this case the model proposed involves the introduction of a single-strand interruption into one of the parental DNA strands, followed by strand crossing-over, like that envisaged in genetic recombination (Broker and Lehman, 1971; Holliday, 1974; Meselson and Radding, 1975; Radding, 1973), as a means of circumventing the damage. Other models that invoke strand displacement do not provide a satisfactory mechanism to account for the dissociation of both newly synthesized strands of DNA in the region of the damage, association with one another, the subsequent dissociation of these strands, and their annealing in the original duplexes. Finally, the model proposed here is consistent with available information on postreplication repair of UV damage.

MECHANISM

The following steps are proposed (Fig. 1): (*a*) UV irradiation gives rise to pyrimidine dimers in DNA; (*b*) Gaps are formed opposite pyrimidine dimers or other forms of base damage after DNA replication; (*c*) A nick is introduced into the complementary parental strand; (*d*) The nicked strand of a duplex molecule, by strand migration, switches to pair with the other parental chain; (*e*) Reciprocal crossing over involving polymerization at the 3′ end of the interrupted daughter strand follows; (*f*) The linkage point (crossing-over point) is free to migrate in either direction (in the process envisaged here movement occurs to the right); (*g*) As the linkage point moves to the right, restoration of the original helices occurs; (*h*) The overall effect is closure of the discontinuity opposite the lesion in DNA without the exchange of DNA strands or the requirement for a polymerase activity to read over the damaged region.

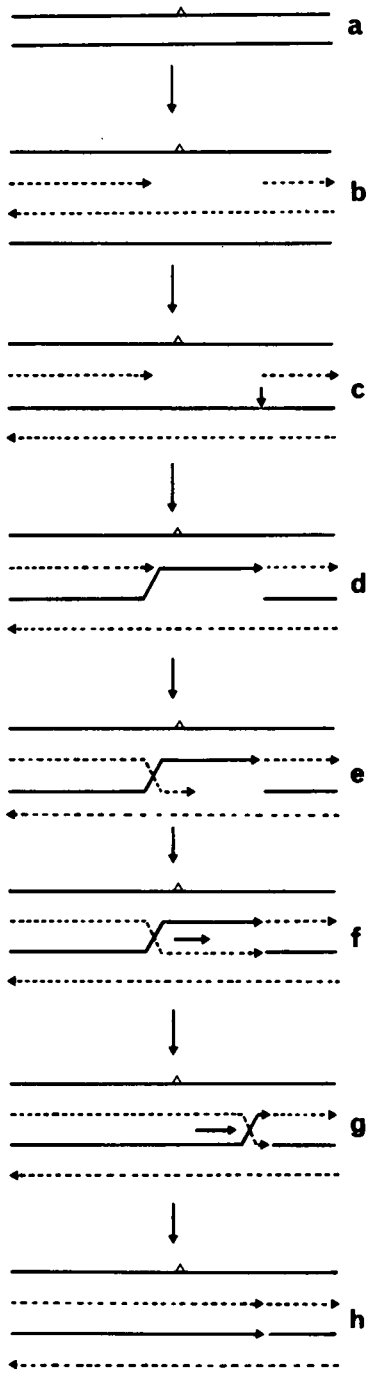

FIGURE 1 Proposed mechanism for postreplication repair of UV damage in mammalian cells. Synthesis of DNA is interrupted by a pyrimidine dimer. Incision occurs on the complementary undamaged parental strand, followed by strand migration and reciprocal crossing-over. The overall effect is the bypassing of the damaged site. Details of the steps involved are outlined in the text.

Endonuclease Attack

The model proposed here does not require a polymerase with damaged DNA as template. In Fig. 1 *c* it is postulated that a nick is introduced into the parental strand, complementary to that containing the lesion, at a point opposite or nearly opposite the gap, by a site-specific endonuclease. Indeed there is now evidence for an essential role for endonucleases in eukaryote cells in the transfer of genetic material (Badman, 1972; Holloman, 1973; Holloman and Holliday, 1973; Stern and Hotta, 1973). Alternatively, a protein similar to the omega protein (Wang, 1971), the gene 32 protein of bacteriophage T4 (Alberts and Frey, 1970), or the eukaryotic unwinding proteins (Basse and Wang, 1974; Champoux and Dulbecco, 1972; Vosberg et al., 1975) might initiate the sequence of events proposed. It is not envisaged that a particular base sequence is involved in the cleavage process, since UV damage would be distributed randomly along the DNA and thus also the resulting interruptions. The introduction of such a break into DNA may result from a close alignment of the homologous region of the undamaged duplex with the single-stranded region containing the damaged site (Fig. 1 *c*). Alternatively, the presence of single strand breaks in parental DNA in the vicinity of the replication fork, as has been postulated in models for DNA replication, might fulfil this requirement. The presence of such a nick would allow strand migration like that proposed to account for intermediate forms in genetic recombination (Broker and Lehman, 1971; Holliday, 1974; Radding, 1973; Potter and Dressler, 1976). This would lead to single-stranded attack on a recipient duplex (Holliday, 1974; Holloman et al., 1975), in this case a complementary single-stranded region within such a duplex (Fig. 1 *d*). It has been calculated that long, hybrid DNA tracts can be formed by rotary diffusion of the initial exchange point along the molecule (Meselson, 1972). Free or nearly free rotation would occur about single-strand interruptions, giving rise to rapid hetero-duplex formation. Any of the unwinding proteins (Alberts and Frey, 1970; Basse and Wang, 1974; Champoux and Dulbecco, 1972; Vosberg et al., 1975) that remove rotary strain from twisted circular DNA would have an overall effect similar to that of a DNA single-strand interruption in such a process.

Crossing Over

Reciprocal crossing over followed by polymerization opposite the other daughter strand is then initiated (Fig. 1 *e*). Atomic models indicate that transfer of a strand from one helix to another can be achieved within one length of sugar-phosphate backbone (Sigal and Alberts, 1972). This means that hydrogen bonding can be completely preserved on each side of such a switch point. Since the linkage point may migrate in either direction (Holliday, 1974; Potter and Dressler, 1976; Holloman et al., 1975), it becomes obvious that movement to the right by rotary diffusion will restore the original pairing positions (Fig. 1 *f*).

Ligation

It is proposed here that the original nick is similar to that observed in the case of untwisting enzyme that does not act as a substrate for DNA ligase (Champoux, 1976),

possibly because the enzyme remains covalently bound to one or both of the free ends. In this case it is suggested that both free ends are not active in the ligation reaction. Once the linkage point has moved to such free ends, endonucleolytic cleavage would not be necessary to restore the two daughter strands to their initial arrangement in separate duplexes. Restoration of the daughter strands to their original arrangement would then allow the ligation to occur.

CONSISTENCY OF MODEL WITH PUBLISHED DATA

Gap-Filling

The model presented here is consistent with published data using photoreversal of 5′-bromodeoxyuridine (BUdR) substituted regions as evidence for the presence of gaps (Lehmann, 1972; Buhl et al., 1972*b*; Lavin et al., 1977). However, in this case, the process of gap-filling by *de novo* synthesis occurs effectively in the undamaged duplex (Fig. 1 *e*). In the process described, the interruption occurs in the ongoing daughter strand (5′ → 3′), but the model is equally applicable when the damage exists on the other parental strand, where replication is occurring discontinuously in a reverse direction to that of fork movement (Edenberg and Huberman, 1975).

Nuclease Data

The model is consistent with recent findings using a single-strand specific nuclease from *N. crassa,* which indicate that gaps are formed along the newly synthesized strand (Meneghini, 1976). In Fig. 1 *c–e* areas of single-stranded, newly synthesized DNA occur that would be susceptible to the single-strand nuclease giving rise to an effective double-strand break, as observed (Meneghini, 1976). In addition, the model explains the failure to detect gaps opposite dimers using the T_4 endonuclease V (Meneghini and Hanawalt, 1976) and the UV endonuclease from *Micrococcus luteus* (Clarkson and Hewitt, 1976), which specifically nick DNA at positions adjacent to pyrimidine dimers (Friedberg and King, 1971; Kaplan et al., 1971). If strand migration is initiated rapidly after gap formation, then the structures illustrated from Fig. 1 *d* onward would predominate. This model would allow for the detection of single-strand breaks in the vicinity of pyrimidine dimers after sedimentation on alkaline sucrose gradients. However, no double-strand breaks would be detected using the T_4 endonuclease V or the micrococcal enzyme, on the expectation that gaps existed opposite pyrimidine dimers (Fig. 1 *c*). This was found to be the case (Meneghini and Hannawalt, 1976) and it was assumed that gaps did not exist opposite pyrimidine dimers.

Density Gradient Centrifugation

Recent findings using BUdR as a heavy label indicate that, in addition to hybrid DNA, both intermediate and heavy density DNA are found in the process of replicative bypass (Rommelaere and Miller-Faures, 1975; Higgins et al., 1976; Moore and Holliday, 1976; Fujiwara and Tatsumi, 1976). This intermediate and heavy density DNA disappears with a chase period, and hydroxyurea inhibits the process (Fujiwara and

Tatsumi, 1976; Higgins et al., 1976). The authors suggest that the newly synthesized DNA complementary to the undamaged parental strand is displaced and undergoes branch migration. The next step calls for a dissociation of the interrupted daughter strand from the damaged parental strand and a subsequent annealing with the second daughter strand, followed by synthesis of complementary DNA. This complex series of rearrangements ultimately provides a means of replicating past the damage site. The model presented here does not require the folding back of daughter strands and the subsequent energy-requiring dissociation and annealing with parental strands, and yet it is entirely consistent with the appearance of both intermediate and high density DNA. When BUdR is used to label the daughter strands, the structures outlined in Fig. 1 *e* and *f*, on shearing, would give rise to both heavy-heavy DNA and intermediate density DNA, postulated to result from the association of replicated hybrid DNA and as yet unreplicated parental DNA (Fujiwara and Tatsumi, 1976).

Electron Microscopy

The model is consistent with the finding, using electron microscopy, in which branched molecules of both "X" and "H" configuration were found (Higgins et al., 1976). These data were obtained under conditions that do not allow good distinction between single- and double-strand DNA (Davis et al., 1971). Branched molecules of the X configuration with a short fourth arm of approximately the right length would arise from the structures in Fig. 1 *d* and *e* by breakage of the single-strand region in the daughter strand, while molecules with an H configuration could arise in Fig. 1 *e* and *f*, due to incomplete hybridization in the region of the lesion (Broker and Lehman, 1971).

RECOMBINATION REPAIR

In bacteria it is suggested that free ends resulting from gaps formed opposite pyrimidine dimers initiate recombination (Rupp et al., 1971; Howard-Flanders, 1975). Since gaps or single-strand regions are also observed in mammalian cells, it might be expected that a similar process existed in these cells. Since the model outlined here involves a transient crossing-over process, some of the enzymes involved could be similar to those in recombination. Fig. 1 *d* illustrates the reannealing of two parental strands in the region containing the damage in a manner similar to that predicted in the initiation of recombination. Strand breakage occurring at the crossing-over point or as the point of linkage moved to the left, would result in the transfer of parental DNA into the region opposite the damaged site (Fig. 2). The model would be consistent with the exchange of pyrimidine dimers observed between parental and daughter strands (Fujiwara and Tatsumi, 1977; Ganesan, 1974, Meneghini et al., 1978), if movement of the crossing-over point and subsequent breakage occurred sufficiently far to the left to include a dimer site already bypassed (Fig. 2 *b*, *c*).

The model outlined here is an attempt to describe the mechanism of bypass of UV-induced damage in DNA by the replication machinery of the cell. However, it does not assume to be all-embracing with respect to type of damage or in relation to cell

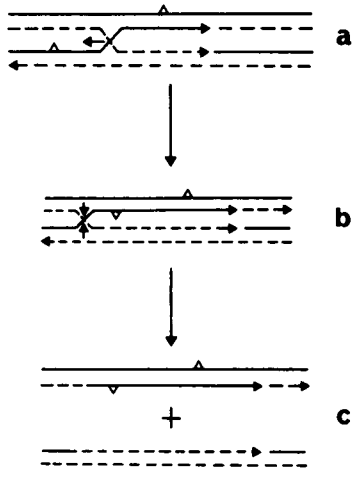

FIGURE 2 Exchange of pyrimidine dimers between parental and daughter strands by recombination. (*a*) The linkage point (see Fig. 1) moves to the left. (*b*) Breakage occurs at the crossing-over point to the left of a damaged site previously bypassed. (*c*) This gives rise to equal ratios of recombinant molecules, giving rise to the appearance of pyrimidine dimers in daughter strands.

type. While the model may explain the elongation of daughter DNA strands in a variety of mammalian cells after UV (Buhl et al., 1972*a*; Lavin et al., 1976*b*; Meyn and Humphrey, 1971), it cannot be applied to other results, using similar UV doses, which fail to detect discontinuities in newly synthesized DNA (Rauth et al., 1974). A further constriction on the model is that it applies only at short times after UV irradiation, since gaps are not detected at longer postirradiation periods. It has been suggested that failure to detect gaps in newly synthesized DNA at longer times after irradiation is due to correction of conformational anomalies without the necessity for excision repair (Buhl et al, 1973). No requirement for the mechanism described here would exist in the presence of such a modification system, which becomes apparent only at longer times after UV irradiation. The model is compatible with results that demonstrate a greater reduction in molecular weight of newly synthesized DNA in excision-defective xeroderma pigmentosum cells when compared to normal cells (Lehmann et al., 1975). Fig. 1 *d* represents a transient crossing-over giving rise to a duplex structure in the area of the damaged site. Repair of this damage could occur at this stage by an excision system closely linked to the process of postreplication repair. Bridges (1977) presents evidence for the presence of an excision-dependent postreplication repair system in excision-proficient bacteria. If such a system played a partial role in postreplication repair in mammalian cells, then excision-defective cells would be expected to show some defects in synthesis of DNA after UV irradiation.

The apparent discrepancies outlined above can be explained by the presence of several postreplication repair mechanisms in mammalian cells or by the modification of damaged sites so that they no longer act to interrupt DNA synthesis. Results with

Escherichia coli indicate that at least two postreplication repair mechanisms are operative after UV (Bridges, 1977; Sedgwick, 1975; Tait et al., 1974; Youngs and Smith, 1976).

CONCLUSION

The intermediate structures described in the model are consistent with results from density label experiments (Fujiwara and Tatsumi, 1976; Higgins et al., 1976), electron microscopy (Higgins et al., 1976), and enzymology (Meneghini and Hanawalt, 1976; Meneghini, 1976; Clarkson and Hewitt, 1976). If the crossing-over system featured in my model employed recombination enzymes, then it might be possible to isolate recombination-deficient cells deficient in postreplication repair. Alternatively, the postreplicative repair mechanism outlined here might be expected to proceed more efficiently in cells with a high level of recombination, on the assumption that both processes have common intermediates. Since the introduction of a nick into parental DNA is a central part of the scheme I have proposed, then clearly the identification of an endonuclease or an untwisting enzyme with this required degree of specificity is important. Recent reports (Champoux, 1976; Lavin et al., 1976*a*; Wang et al., 1975; Pedrini et al., 1976) reveal the presence of enzymes in mammalian cells that could be candidates for this role.

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REFERENCES

ALBERTS, B. M., and L. FREY. 1970. T_4 bacteriophage gene 32. A structural protein in the replication and recombination of DNA. *Nature (Lond.).* **227**:1313–1317.

BADMAN, R. 1972. Deoxyribonuclease-deficient mutants of *Ustilago maydis* with altered recombination frequencies. *Genet. Res.* **20**:213–229.

BASSE, W. A., and J. C. WANG. 1974. An ω protein from *Drosophila melanogaster*. *Biochemistry.* **13**:4299–4303.

BRIDGES, B. A. 1977. Recent advances in basic mutation research. *Mutat. Res.* **44**:149–164.

BROKER, T. R., and I. R. LEHMAN. 1971. Branched DNA molecules. Intermediates in T_4 recombination. *J. Mol. Biol.* **60**:131–149.

BUHL, S. N., and J. D. REGAN. 1973. Repair of endonuclease-sensitive sites in daughter DNA of ultraviolet-irradiated human cells. *Nat. New Biol.* **246**:484.

BUHL, S. N., R. M. STILLMAN, R. B. SETLOW, and J. D. REGAN. 1972*a*. DNA chain elongation and joining in normal human and Xeroderma Pigmentosum cells after ultraviolet irradiation. *Biophys. J.* **12**:1183–1191.

BUHL, S. N., R. B. SETLOW, and J. D. REGAN. 1972*b*. Steps in DNA chain elongation and joining after ultraviolet irradiation of human cells. *Int. J. Radiat. Biol.* **22**:417–442.

BUHL, S. N., R. B. SETLOW, and J. D. REGAN. 1973. Recovery of the ability to synthesize DNA in segments of normal size at long times after ultraviolet irradiation of human cells. *Biophys. J.* **13**:1265–1275.

CHAMPOUX, J. J. 1976. Evidence for an intermediate with a single-strand break in the reaction catalyzed by the DNA untwisting enzyme. *Proc. Natl. Acad. Sci. U.S.A.* **73**:3488–3491.

CHAMPOUX, J. J., and R. DULBECCO. 1972. An activity from mammalian cells that untwists superhelical DNA. A possible swivel for DNA replication. *Proc. Natl. Acad. Sci. U.S.A.* **69**:143–146.

CLARKSON, J. M., and R. R. HEWITT. 1976. Significance of dimers to the size of newly synthesized DNA in UV-irradiated Chinese hamster ovary cells. *Biophys. J.* **16**:1155–1164.

CLEAVER, J. E. 1967. The relationship between the rate of DNA synthesis and its inhibition by ultraviolet light in mammalian cells. *Radiat. Res.* **30**:795–810.

CLEAVER, J. E., and G. H. THOMAS. 1969. Single strand interruptions in DNA and the effects of caffeine in Chinese hamster cells irradiated with ultraviolet light. *Biochim. Biophys. Res. Commun.* **36**:203–208.

DAVIS, R. W., M. SIMON, and N. DAVIDSON. 1971. Electron microscope heteroduplex methods for mapping regions of base sequence homology in nucleic acids. *Methods Enzymol.* **21**:413–428.

DJORDJEVIC, B., and L. J. TOLMACH. 1967. Responses of syncronous populations of HeLa cells to ultraviolet irradiation at selected stages of the generation cycle. *Radiat. Res.* **32**:327–346.

DOMON, M., and A. M. RAUTH. 1968. Ultraviolet irradiation of mouse L cells. Effects on DNA synthesis and progression through the cell cycle. *Radiat. Res.* **35**:350–368.

DONIGER, J. 1978. DNA replication in ultraviolet light irradiated Chinese hamster cells. The nature of replicion inhibition and post-replication repair. *J. Mol. Biol.* In press.

EDENBERG, H. 1975. Inhibition of DNA synthesis by ultraviolet light. *In* Molecular Mechanisms for Repair of DNA, Part B. P. C. Hanawalt, and R. B. Setlow, editors. Plenum Press, New York. 631–633.

EDENBERG, H. J. 1976. Inhibition of DNA replication by ultraviolet light. *Biophys. J.* **16**:849–860.

EDENBERG, H. J., and J. A. HUBERMAN. 1975. Eukaryotic chromosome replication. *Annu. Rev. Genet.* **9**: 245–284.

FRIEDBERG, E. C., and J. J. KING. 1971. Dark repair of ultraviolet-irradiated deoxyribonucleic acid by bacteriophage T_4. Purification and characterization of a dimer-specific phage-induced endonuclease. *J. Bacteriol.* **106**:500–507.

FUJIWARA, Y. 1975. Postreplication repair of alkylation damage to DNA of mammalian cells in culture. *Cancer Res.* **35**:2780–2789.

FUJIWARA, Y., and T. KONDO. 1972. Caffeine sensitive repair of ultraviolet light-damaged DNA of mouse L cells. *Biochim. Biophys. Res. Commun.* **47**:557–564.

FUJIWARA, Y., and M. TATSUMI. 1976. Replicative bypass repair of ultraviolet damage to DNA of mammalian cells. Caffeine sensitive and caffeine resistant mechanisms. *Mutat. Res.* **37**:91–110.

FUJIWARA, Y., and M. TATSUMI. 1977. Low-level DNA exchanges in normal human and xeroderma pigmentosum cells after UV irradiation. *Mutat. Res.* **43**:279–290.

GANESAN, A. K. 1974. Persistence of pyrmidine dimers during post-replication repair in ultraviolet light-irradiated *Escherichia coli* K12. *J. Mol. Biol.* **87**:103–119.

HIGGINS, N. P., K. KATO, and B. STRAUSS. 1976. A model for replication repair in mammalian cells. *J. Mol. Biol.* **101**:417–425.

HOLLIDAY, R. 1974. Molecular aspects of genetic exchange and gene conversion. *Genetics.* **78**:273–287.

HOLLOMAN, W. K. 1973. Studies on a nuclease from *Ustilago maydis. J. Biol. Chem.* **248**:8114–8119.

HOLLOMAN, W. K., and R. HOLLIDAY. 1973. Studies on a nuclease from *Ustilago maydis. J. Biol. Chem.* **248**:8107–8113.

HOLLOMAN, W. K., R. WIEGAND, C. HOESSLI, and C. M. RADDING. 1975. Uptake of homologous single-stranded fragments by superhelical DNA. A possible mechanism for initiation of genetic recombination. *Proc. Natl. Acad. Sci. U.S.A.* **72**:2394–2398.

HOWARD-FLANDERS, P. 1975. Repair by genetic recombination in bacteria. Overview. *In* Molecular mechanisms for repair of DNA, Part A. P. C. Hanawalt, and R. B. Setlow, editors. Plenum Press, New York. 265–274.

KAPLAN, J. C., S. R. KUSHNER, and L. GROSSMAN. 1971. Enzymatic repair of DNA. III. Properties of the UV-endonuclease and UV-exonuclease. *Biochemistry.* **10**:3315–3324.

LAVIN, M. F., T. KIKUCHI, C. COUNSILMAN, A. JENKINS, D. J. WINZOR, and C. KIDSON. 1976*a*. A mammalian nicking endonuclease. *Biochemistry.* **15**:2409–2414.

LAVIN, M. F., P. MCCOMBE, and C. KIDSON. 1976*b*. DNA replication and post-replication repair in UV-sensitive mouse neuroblastema cells. *Int. J. Radiat. Biol.* **30**:31–40.

LAVIN, M. F., G. M. WILLETT, A. H. CHALMERS, and C. KIDSON. 1977. DNA replication and repair in a human melanoma cell-line resistant to ultra-violet-radiation. *Int. J. Radiat. Biol.* **31**:101–111.

LEHMANN, A. R. 1972. Postreplication repair of DNA in ultraviolet-irradiated mammalian cells. *J. Mol. Biol.* **66**:319–331.

LEHMANN, A. R. 1974. Postreplication repair of DNA in mammalian cells. *Life Sci.* **15**:2005–2016.

LEHMANN, A. R., S. KIRK-BELL, C. F. ARLETT, M. C. PATERSON, P. H. M. LOHMAN, E. A. DE WEERD-KASTELEIN, and D. BOOTSMA. 1975. Xeroderma pigmentosum cells with normal levels of excision repair have a defect in DNA synthesis after UV-irradiation. *Proc. Natl. Acad. Sci. U.S.A.* **72**:219–223.

MENEGHINI, R. 1976. Gaps in DNA synthesized by ultraviolet light-irradiated W138 human cells. *Biochim. Biophys. Acta.* **425**:419–427.

MENEGHINI, R., and P. HANAWALT. 1976. T_4-endonuclease V-sensitive sites in DNA from ultraviolet-irradiated human cells. *Biochim. Biophys. Acta.* **425**:428–437.

MENEGHINI, R., C. F. M. MENCK, R. I. SCHUMACHER, and M. CORDERIO-STONE. 1978. DNA replication halt by pyrimidine dimers and its resumption in mammalian cells. *In* DNA repair mechanisms, vol. 9. P. C. Hanawalt, E. C. Friedberg, and C. F. Fox, editors. Academic Press, Inc. New York. In press.

MESELSON, M. 1972. Formation of hybrid DNA by rotary diffusion during genetic recombination. *J. Mol. Biol.* **71**:795–798.

MESELSON, M. S., and C. M. RADDING. 1975. A general model for genetic recombination. *Proc. Natl. Acad. Sci. U.S.A.* **72**:358–361.

MEYN, R. E., R. R. HEWITT, L. F. THOMSON, and R. M. HUMPHREY. 1976. Effects of ultraviolet irradiation on the rate and sequence of DNA replication in synchronized Chinese hamster cells. *Biophys. J.* **16**: 517–526.

MEYN, R. E., and R. M. HUMPHREY. 1971. Deoxyribonucleic acid synthesis in ultraviolet-light-irradiated Chinese hamster cells. *Biophys. J.* **11**:295–301.

MOORE, P. D., and R. HOLLIDAY. 1976. Evidence for the formation of hybrid DNA during mitotic recombination in Chinese hamster cells. *Cell.* **8**:573–579.

PAINTER, R. B. 1974. DNA damage and repair in eukaryotic cells. *Genetics.* **78**:139–148.

PEDRINI, A. M., G. RANZANI, G. C. F. PREDRALI NOY, S. SPADARI, and A. FALASCHI. 1976. A novel endonuclease of human cells specific for single-stranded DNA. *Eur. J. Biochem.* **70**:275–283.

POTTER, H., and D. DRESSLER. 1976. On the mechanism of genetic recombination. Electron microscopic observation of recombination intermediates. *Proc. Natl. Acad. Sci. U.S.A.* **73**:3000–3004.

RADDING, C. 1973. Molecular mechanisms in genetic recombination. *Annu. Rev. Genet.* **7**:87–111.

RASMUSSEN, R. E., and R. B. PAINTER. 1964. Evidence for repair of ultra-violet damaged deoxyribonucleic acid in cultured mammalian cells. *Nature (Lond.).* **203**:1360–1362.

RAUTH, A. M., M. TAMMEMAGI, and G. HUNTER. 1974. Nascent DNA synthesis in ultraviolet light-irradiated mouse, human, and Chinese hamster cells. *Biophys. J.* **14**:209–220.

ROMMELAERE, J., and A. MILLER-FAURES. 1975. Detection by density equilibrium centrifugation of recombinant-like DNA molecules in somatic mammalian cells. *J. Mol. Biol.* **98**:195–218.

RUPP, W. D., C. E. WILDE, D. L. RENO, and P. HOWARD-FLANDERS. 1971. Exchanges between DNA strands in ultraviolet-irradiated *Escherichia coli*. *J. Mol. Biol.* **61**:25–44.

SEDGWICK, S. G. 1975. Genetic and kinetic evidence for different types of postreplication repair in *Escherichia coli* B. *J. Bacteriol.* **123**:154–161.

SIGAL, N., and B. ALBERTS. 1972. Genetic recombination. The nature of a crossed strand-exchange between two homologous DNA molecules. *J. Mol. Biol.* **71**:789–793.

STERN, H., and Y. HOTTA. 1974. DNA metabolism during pachytene in relation to crossing over. *Genetics.* **78**:227–235.

TAIT, R. C., A. L. HARRIS, and D. W. SMITH. 1974. DNA repair in *Escherichia coli* mutants deficient in DNA polymerases I, II, and/or III. *Proc. Natl. Acad. Sci. U.S.A.* **71**:675–679.

VOSBERG, H. P., L. I. GROSSMAN, and J. VINOGRAD. 1975. Isolation and partial characterization of the relaxation protein from nuclei of cultured mouse and human cells. *Eur. J. Biochem.* **55**:79–94.

WANG, J. C. 1971. Interaction between DNA and an *Escherichia coli* protein ω. *J. Mol. Biol.* **55**:523–533.

WANG, E. C., D. HENNER, and J. J. FURTH. 1975. An endonuclease from calf thymus which introduces a limited number of single strand breaks into DNA. *Biochem. Biophys. Res. Commun.* **65**:1177–1183.

WATERS, R., and J. D. REGAN. 1976. Recombination of UV-induced pyrimidine dimers in human fibroblasts. *Biochem. Biophys. Res. Commun.* **72**:803–807.

YOUNGS, D. A., and K. C. SMITH. 1976. Genetic control of multiple pathways of post-replication repair in *UVR* B strains of *Escherichia coli* K-12. *J. Bacteriol.* **125**:102–110.