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XERODERMA PIGMENTOSUM—PROGRESS AND REGRESS*

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INTRODUCTION

I first came across xeroderma pigmentosum (XP) in 1967 at a time when I was interested in radiation damage to DNA and its enzymatic repair. It seemed reasonable to suppose that XP was a radiation-sensitive hereditary disease, analogous to radiation-sensitive mutants well known in microorganisms (Cleaver, 1968). To prove or disprove this supposition we had only to apply the reasonably well-advanced techniques for study of the excision-repair system in bacteria (Fig. 1) to XP. Now that experiments on most aspects of repair in XP have been performed, we can accurately regard XP as a human analog of the bacterial strains designated as UVR^-, HCR^- (Cleaver, 1968, 1969, 1970a, b, 1971a, b, 1972b; Reed et al., 1969; Setlow et al., 1969; Bootsma et al., 1970; Cleaver and Trosko, 1970; Epstein et al., 1970; Goldstein, 1971).

In a subject like this, which ranges widely over the fields of medicine, genetics, radiobiology, virology, and biochemistry, the complications, strengths, and weaknesses of every experiment are hard to assess fully. I shall therefore briefly allude to some areas in which the work done on XP is misleading or equivocal.

OBSERVATIONS AND DISCUSSION

Biochemical Systems Involved in Repair of Ultraviolet (UV) Damage

There are three genetically determined UV repair systems in bacteria: the excision repair system (mutants of this system include UVR^-, HCR^- and POL^-), the recombination repair system (REC^-), and the photoreactivation system (PHR^-). Photoreactivation need not concern us since the system is completely absent in man and other mammals except marsupials (Cleaver, 1966; Cook and McGrath, 1967). Since mutants of the REC^- system have reduced viability even in the absence of UV (Haefner, 1968), such mutations in man would hardly be viable. The cases described by Jung (1970) can be discounted because their clinical symptoms of UV sensitivity are very slight, and he has yet to show that the cells from such patients exhibit increased UV sensitivity or any biochemical features that would correspond to an REC^- mutation.

Mutations in the excision repair system have been identified in cases of XP, although many of the cases investigated probably represent different mutations. Considerable differences exist among unrelated patients (Bootsma et al., 1970; Cleaver, 1970b, 1971a, 1972a) and three distinct variants are now known. All the variants appear to be autosomal recessive diseases characterized by greatly increased sensitivity of the skin to UV light; the skin of exposed regions shows a high incidence of UV-induced malignancies of all forms: keratoacanthomas, squamous carcinomas, sarcomas, and melanomas (Hebra and Kaposi, 1874; El-Hefnawi et al., 1965; Rook et al., 1968). Two less common variants have similar skin symptoms: one, which is also defective in repair, has additional severe neurologic involvement (the DeSanctis-Cacchione syndrome) (DeSanctis and Cacchione, 1932); the other appears to have no defect in the excision repair system (Burk et al., 1971; Cleaver, 1972a). Except where explicitly described, this latter variant is excluded from most of the general discussion of the characteristics of XP.

Detection of Excision Repair

A number of experimental tests have been made of the model of excision repair originally derived for bacteria (Fig. 1) (Boyce and Howard-Flanders, 1964; Pettijohn and Hanawalt, 1964; Setlow and Carrier, 1964).

1. Are individual fibroblasts sensitive to UV light (Cleaver, 1970b; Goldstein, 1971)?
2. How well do fibroblasts support the growth of UV-damaged viruses (host cell reactivation) (Rabson et al., 1969; Aaronson and Lytle, 1970)?
3. Are UV photoproducts (cyclobutyl pyrimidine dimers) formed and removed from DNA (Setlow et al., 1969; Cleaver, 1970a; Cleaver and Trosko, 1970)?
4. Are single-strand gaps made and joined during excision?
5. Are short regions of new bases inserted into DNA (unscheduled synthesis, repair replication) to replace excised dimers (Cleaver, 1968, 1969, 1970a; Reed et al., 1969; Bootsma et al., 1970; Epstein et al., 1970)?

I believe that definite answers to all of these questions except 4 are now available. Although we know what to expect as an answer to that question, the one reported attempt to study single-strand breaks in XP cells failed because of complications in the techniques and extreme variability in the published data (Setlow et al., 1969).

Similar results have been obtained in skin fibroblasts (Cleaver, 1968, 1969, 1970a, b, 1971a, 1972b; Reed et al., 1969; Setlow et al., 1969; Bootsma et al., 1970; Goldstein, 1971), epithelial cells (Epstein et al., 1970), and lymphocytes (Burk

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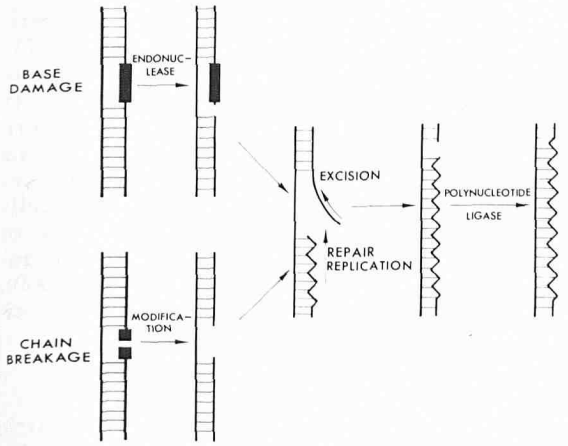

FIG. 1. Model for excision repair of UV and other damage to DNA bases. In this form of the model, excision and repair replication proceed in concert so that large single-strand regions of DNA are never exposed. The excised region in human DNA is subsequently degraded to short acid-soluble lengths (less than 15 bases) (Cleaver and Boyer, 1972), but the patch is considerably larger (up to about 300 bases) (Cleaver, 1971a, 1972b; Cleaver et al., 1972). Reproduced from Cleaver (1971a), by permission of publisher.

et al., 1971) from XP, and presumably the biochemical defect is present in all cells of the body.

Sensitivity of XP Cells

The major clinical symptom of XP is a high incidence of UV-induced skin cancers, which could be due to systemic factors other than the inherent properties of individual cells (Rook et al., 1968). It is important to demonstrate that the genotype has some phenotypic expression in individual cells. The main method at our disposal is colony formation by single cells, but unfortunately primary fibroblasts have a low plating efficiency (a maximum of 10 to 20 percent) (Cleaver, 1970b, 1972a; Goldstein, 1971). Use of this method presupposes that the cells that form colonies are a random sample of the population and are typical of the whole population in terms of their UV sensitivity. Granting these assumptions XP fibroblasts are, with few exceptions, much more sensitive to UV light than normal cells (Fig. 2). However, cells from certain cases of XP (three identified to date) (Burk et al., 1971; Cleaver, 1972a) differ in that their UV sensitivity is normal This is an indication that they are not defective in any repair system since defects in any repair system in bacteria invariably result in increased UV sensitivity (Kondo et al., 1970).

If we consider the sensitivity of normal cells (D_{37}† about 30 ergs/mm², Fig. 2) and the dose rate of UV at the earth's surface, we can see that we are exposed to a hazard from solar radiation to which we are quite sensitive. Solar radiation contains UV equivalent to about 1 to 2 ergs/mm²/min of 254 nm wavelength (Harm, 1969; Trosko et al., 1970). Thus, most unprotected human fibroblasts would be killed after 30 to 60 min in direct sunlight. This illustrates how crucial the various shielding and protective mechanisms in the skin are and how potentially dangerous are any large-scale technological ventures that might alter the UV dose rate at the earth's surface.

Biochemical Aspects of Excision Repair

The two main aspects of excision repair that can be studied biochemically are the excision of UV photoproducts from DNA (Fig. 3) and their replacement by the insertion of new bases into DNA. The latter can be studied either by tritiated thymidine (³HTdR) labeling and autoradiography (unscheduled synthesis) or by density labeling with the heavy analog of TdR, bromouracil deoxyriboside (BrUdR) (repair replication). Another method of studying repair replication has recently been introduced whereby the BrUdR-containing repair regions are selectively broken (BrU photolysis) (Regan et al., 1971), but I will concentrate on the two former methods.

In XP, UV photoproducts (cyclobutyl pyrimidine dimers) are formed in DNA but, unlike those in normal cells, few are excised after irradiation (Fig. 3). A small amount of excision may still occur because the method has low resolution. As a consequence of the reduced excision, fewer bases are inserted into DNA by unscheduled synthesis (Fig. 4) and repair replication (Fig. 5). Excision

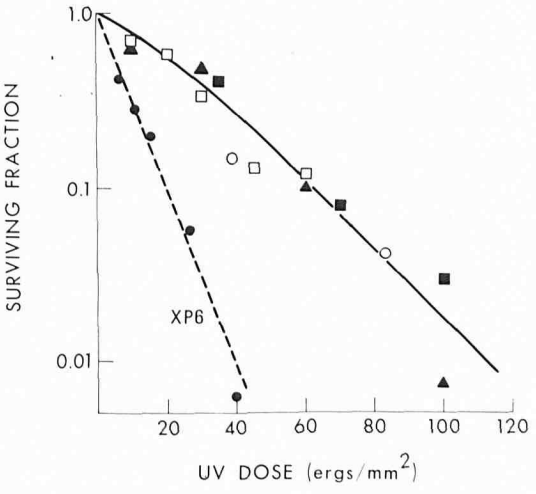

FIG. 2. Survival curve for normal and XP human fibroblasts irradiated with UV light (254 nm). Normal cells ■, ▲; XP6 (low repair) ●; XP14 (normal repair) □; XP16 (normal repair) ○. Reproduced from Cleaver (1972a), by permission of publisher.

†D_{37} is the dose at which 37 percent of the irradiated population survives.

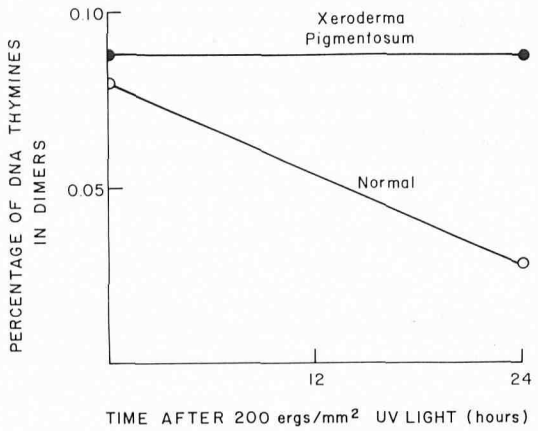

FIG. 3. Fraction of thymine-containing cyclobutyl dimers in DNA of normal and XP fibroblasts immediately and 24 hours after irradiation. Normal cells O; XP cells ●.

repair appears to be quantitatively reduced, but only in a small number of cases is it completely undetectable (Cleaver, 1968, 1969, 1970a, b, 1971a, 1972b; Bootsma et al., 1970; Parrington et al., 1971).

When agents other than UV light are used to damage DNA, the response of XP cells indicates that these cells can repair only radiation or chemical damage that involves chain breaks (Table). The responses to various agents (Table) are analogous to *Escherichia coli* mutants UVR^-, HCR^- (Kondo et al., 1970). This, together with the known details of excision repair of UV damage in XP cells, is consistent with the hypothesis that XP cells lack an enzyme that initiates excision of base damage by endonucleolytic attack (Cleaver, 1969; Setlow et al., 1969). There is no direct evidence on isolated enzymes to confirm this hypothesis, but at present it is the simplest hypothesis consistent with all the available evidence. Recent assays of DNA and RNA polymerase activities in XP tissue were done with extracts that were, unfortunately, too impure to allow any definitive conclusions to be reached (Müller et al., 1971a,b).

Attempts at Therapy In Vitro

XP patients can be given only palliative and preventive treatment for their disease; several attempts at experimental therapy of XP cells *in vitro* have thus far been unsuccessful. The first attempt was to integrate SV40 virus into XP cells and assay excision repair in the transformed cells. Although several characters under viral control are expressed (T antigen, loss of contact inhibition), the genetic defect characteristic of XP remained unchanged (Bootsma et al., 1970; Cleaver, 1970b; Parrington et al., 1971). Moreover, the rate of transformation of XP cells by SV40 was similar to that in normal cells (Aaronson and Lytle, 1970).

I have recently attempted to apply the experimental design of Ashkenazi and Gartler (1971) who showed that crude sonicates of normal fibroblasts could replace the missing enzyme activity of cells from Lesch-Nyhan patients. Such experiments, repeated under almost identical conditions but with XP cells, failed to reveal any replacement of missing enzymatic activity in XP cells (Cleaver, unpublished experiments). The use of the UV-specific endonuclease, which initiates repair in *Micrococcus luteus* (Kaplan et al., 1969), has also failed (Cleaver, unpublished experiments).

Prenatal Diagnosis

Recently, in cooperation with the Pediatric Department (Dr. R. R. Howell) of Johns Hopkins University and Oak Ridge National Laboratories (Drs. R. B. Setlow and J. D. Regan), we developed a method for prenatal diagnosis of XP. Since this disease is asymptomatic in heterozygous carriers, prenatal diagnosis is of use for pregnancies only when an XP child has already been diagnosed in the family. Consequently, in view of the rarity of XP, prenatal diagnosis of this entity is a technique useful in only a few clinical situations. From our experience in this initial trial, we know that the major delay in diagnosis is the period required for tissue culture of cells obtained by amniocentesis. Once cells have been cultured, any of the methods used for studying excision repair can be used to determine the nature of the cells. The most sensitive method is, without doubt, autoradiography for unscheduled synthesis: this requires a few dozen cells in an autoradiograph and an exposure time of 2 or 3 days (with high specific activity ^{3}HTdR, above 15 Ci/mmole). Other feasible methods include isopycnic gradients (which require some 10^6 cells) and BrU photolysis (which requires between 10^3 and 10^4 cells) (Regan et al., 1971). Since the techniques of unscheduled synthesis measurement and isopycnic density gradient centrifugation might be used directly on cells obtained by amniocentesis, the delay involved in establishing tissue cultures may be avoided.

In general, I believe that in terms of precision and ease of application prenatal diagnosis is best executed by means of autoradiography.

Homozygous and Heterozygous XP Variants

In most cases of XP, excision repair is reduced in the homozygotes but unaffected in the parents (presumed to be heterozygous) (Cleaver, 1969, 1970b, 1971a, 1972b; Bootsma et al., 1970). There are, however, some exceptions. In three homozygous cases, repair replication has apparently been normal (Burk et al., 1971; Cleaver, 1972a) (Fig. 5). Two of these cases are male siblings (XP13, XP14). These variants of XP could represent mutations in a later stage of repair than repair

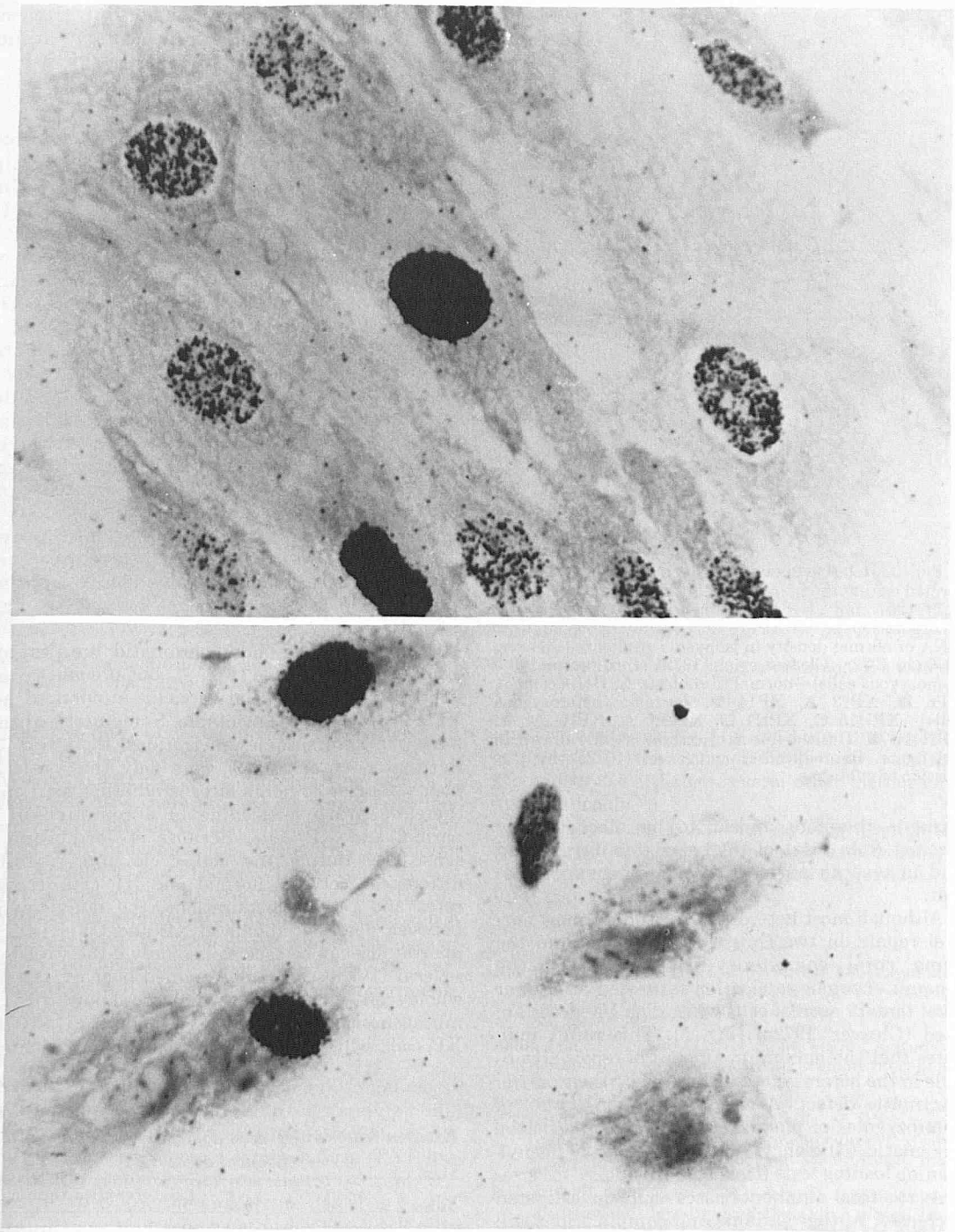

FIG. 4. Unscheduled synthesis (DNA repair) demonstrated autoradiographically in heterozygous and homozygous XP fibroblasts labeled with ^{3}HTdR (10 μCi/ml, 15 Ci/mmole) for 3 hours after 260 ergs/mm^2 UV light (254 nm) Exposure time approximately 7 days. *Top:* heterozygous XP cells; *bottom:* homozygous XP cells.

replication (see Fig. 1) or in some other UV repair system, or they could be mosaics. Cultured cells of these variants have normal UV sensitivity (Fig. 2), which would exclude the possibility of any defects in DNA repair. Studies on lymphocytes from XP16 show no distinct classes of repairing and nonrepairing cells, which make mosaicism an unlikely possibility (Burk et al., 1971). Such XP

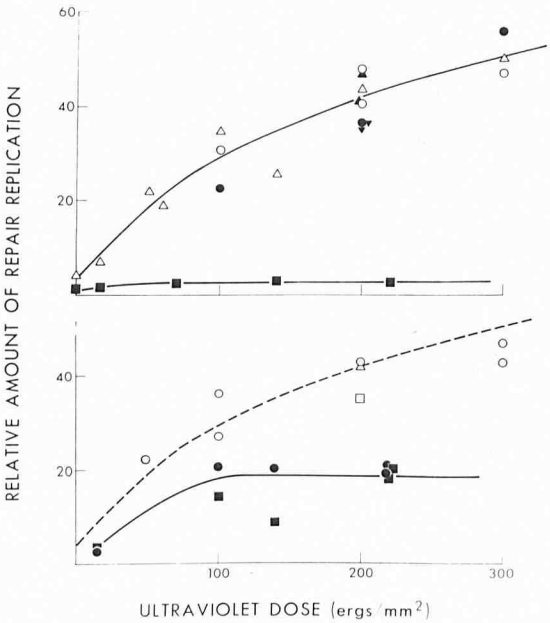

FIG. 5. Relative amounts of repair replication performed during the first 4 hours after irradiation with UV light (254 nm). Repair replication measured by the incorporation of ^{3}HBrUdR (20 μCi/ml, 3 μg/ml) into DNA of normal density in isopycnic gradients (Cleaver, 1970a,b, 1972a; Cleaver et al., 1972). *Top:* (normal and homozygous cells)—normal fibroblasts △, HeLa cells ○, XP6 ■, XP13 ▲, XP14 ●. *Bottom:* (heterozygous cells)—XPH15 ○, XPH1 □, XPHK △, XPH11M ●, XPH11F ■. Dashed line is the same as line drawn in top figure. Reproduced from Cleaver (1972a), by permission of publisher.

variants therefore appear to be biochemically distinct from most of the cases thus far studied and involve an as yet unknown biochemical defect.

Although most heterozygotes studied show normal repair, in two (husband and wife from the same rural community—H11M, H11F) the amount of repair replication saturated at a lower level than in normal cells when high UV doses are used (Cleaver, 1972a) (Fig. 5). This result indicates that the maximum amount of repair attainable in the heterozygotes is limited by their partial enzymatic defect. A similar situation occurs in heterozygotes of phenylketonuria, where a partial enzymatic deficiency is detectable with phenylalanine loading tests (Hsia et al., 1956).

As the total number of cases of XP investigated increases, further variants and complications will probably be uncovered. Variability is the norm in human hereditary diseases, and we have only begun to explore this facet of XP. Several of the cases unambiguously diagnosed as the DeSanctis-Cacchione syndrome cannot perform any detectable amounts of repair replication (Cleaver, 1968, 1969, 1970a,b, 1971a, 1972b) and thus may represent large deletions in the affected gene, whereas other cases with partial repair capacity could represent base change mutations. But the two main forms of XP are complementary defects (deWeerd-Kastelein et al., 1972).

Carcinogenesis in XP

We cannot leave the subject of XP without some comments on carcinogenesis, because the high level of actinic skin cancer is the outstanding clinical symptom of this disease. Now that the euphoria that greeted the identification of the major biochemical defect in XP has faded, we must admit that only limited insights into actinic carcinogenesis in XP have been gained. One possibility, in view of the normal repair seen in many malignant cells and in XP variants, is that defective repair is irrelevant to carcinogenesis. Granted that genetic changes of some sort underlie carcinogenesis and that defective repair has some clinical relevance in XP, XP data can be extrapolated in two directions: (1) genetic changes may arise through mutations or chromosomal changes resulting from unrepaired damage in DNA; (2) unrepaired damage to DNA may potentiate the transformation of cells by oncogenic viruses. Both of these directions are experimentally testable and some evidence has already been advanced.

UV light induces both chromatid breaks and exchanges in XP cells (Fig. 6), but precise quantitative data on the relative yields in normal and XP cells are not yet available. Some preliminary work on chromosome aberrations reported by Parrington et al. (1971) gave only the yield of aberrations at 30 hours after irradiation and may therefore prove misleading in a comparison of normal and XP cells. Because of variations in sensitivity during the cell cycle and possible differences between normal and XP cell growth rates and cell cycle durations, the relationship between defective repair in XP and UV-induced aberrations can be ascertained only if the yields at several UV doses are determined over at least a whole cell cycle. From what we know of UV mutagenesis in *E. coli* UVR$^-$ (Kondo et al., 1970), XP cells will probably show a high UV-induced

TABLE I

Excision repair in XP cells damaged by radiation and chemical agents

Agent	Level of excision repair
UV light	Reduced (Cleaver, 1968, 1969)
Methoxypsoralen plus visible light	Reduced (Parrington et al., 1971)
X-rays	Normal (Cleaver, 1969)
BrUdR plus UV light	Normal (Cleaver, 1969)
Methylmethane sulfonate	Normal (Cleaver, 1971b)
Methyl-nitro-nitrosoguanidine	Normal (Cleaver, 1971b)

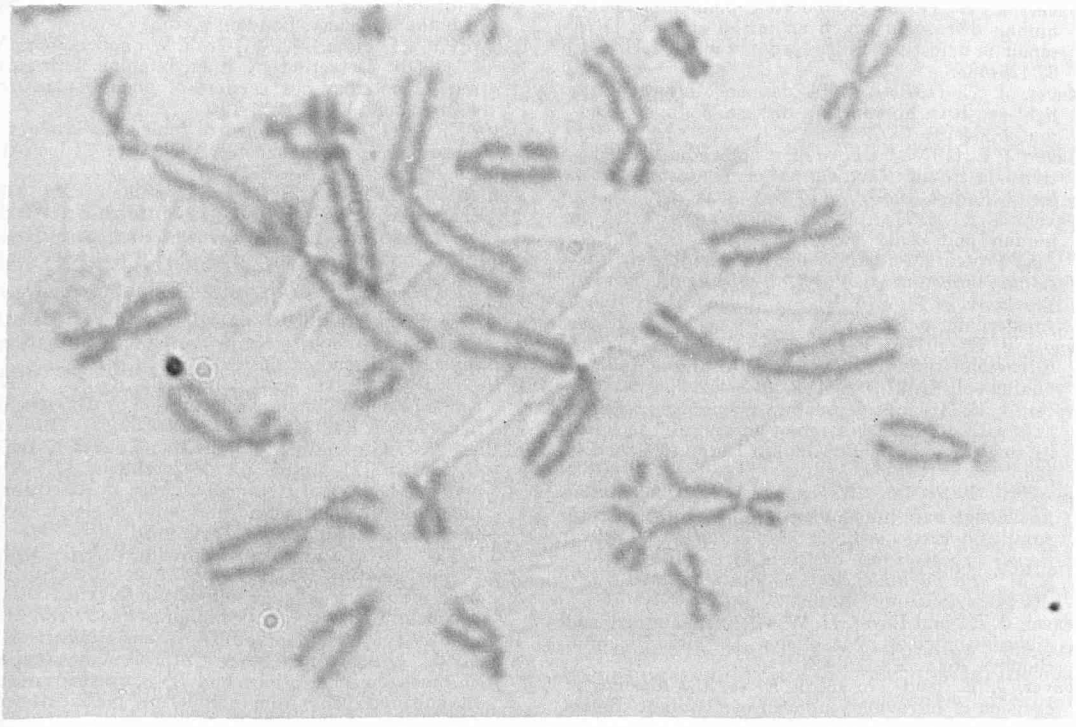

FIG. 6. Chromatid breaks and exchanges in XP cells (XP6, low repair) 28 to 35 hours after irradiation with 39 ergs/mm^2 UV light (254 nm).

mutation rate, but with present techniques this will be difficult to prove.

Many agents can act as potentiating factors in carcinogenesis; there are several examples of ionizing radiation and UV light increasing the rate at which an oncogenic virus transforms irradiated cells (Pollock and Todaro, 1968; Lytle et al., 1970). This could also be a factor in XP; unrepaired UV damage in skin could accelerate viral carcinogenesis. Whether or not genetic changes or viral transformation have importance in carcinogenesis will be a matter for future experiments to resolve.

SUMMARY

Xeroderma pigmentosum is an autosomal recessive human skin disease whose outstanding clinical symptom is an increased frequency of actinic carcinogenesis. The most common form of XP has a reduced capacity for excision repair of UV damage to DNA; the site of the defect is at the initial stage of the repair pathway. These XP cells are precisely analogous to bacterial strains UVR$^-$, HCR$^-$. Two minor variants of the disease with similar skin symptoms are known. One has a similar but complementary defect in excision repair and additional severe neurological symptoms. The other apparently has normal excision repair and normal UV sensitivity *in vitro*. From considerations of resolution and our experience in one test case, prenatal diagnosis of XP is practicable, and autoradiography (to measure unscheduled synthesis) is the most reliable and sensitive method to use although several other methods are also applicable.

Carcinogenesis in XP may develop through the unrepaired damage in DNA which leads to genetic changes (mutations, chromosome aberrations) or viral transformation.

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