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DNA Repair in Cockayne Syndrome

D. I. HOAR[1] AND C. WAGHORNE

INTRODUCTION

We are interested in how cultured human fibroblasts repair DNA damage induced by a variety of mutagens. In order to differentiate DNA repair systems, the properties exhibited by mutants with altered repair must be studied. We, therefore, searched the literature for human genetic disorders with defects in DNA repair for clues to the basic defect in the disorder.

Cockayne syndrome (CS), a rare autosomal recessive disorder whose clinical course usually begins in the second year, is characterized by cachectic dwarfism, retinal degeneration, progressive mental retardation, deafness, and typical facies [1]. These patients also exhibit photosensitive skin [1], similar to patients with xeroderma pigmentosum (XP). The early age of onset and progressive nature of CS suggest an environmental stimulus, possibly exposure to sunlight.

Several reports on ultraviolet (UV) sensitivity and UV-induced repair in CS patients have appeared in the literature. Robbins et al. [2] reported a patient with both XP and CS in which they attribute the reduced unscheduled DNA synthesis (UDS) to the XP entity, since an unrelated patient with CS demonstrated a "normal rate of DNA repair." Chu et al. [3] reported reduced incorporation into the low molecular weight single strand DNA observed in alkaline sucrose gradients. More recently, Schmickel et al. [4] and Andrews et al. [5] provided additional data supporting UV sensitivity in CS cells in culture. They report normal UV-induced UDS for several patients.

We examined cells from five CS patients from four unrelated families for sensitivity to UV, mitomycin C (MMC), actinomycin D, and methyl methanesulfonate (MMS). We also examined UV and MMC-induced UDS, and the kinetics of repair of damage induced by these agents in the presence and absence of caffeine (an agent believed to interfere with normal post-replication repair (PRR) [6]). Although CS cells are hypersensitive to both UV and MMC, they show normal UDS and repair normally in the presence of caffeine. However, pulse-labeled DNA from CS patients is smaller and more uniform than that of controls when examined in alkaline sucrose gradients after UV irradiation. We will discuss the implications of these findings.

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[1] Both authors: Department of Medical Genetics, University of Toronto, Toronto, Ontario M5S 1A8, Canada.

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MATERIALS AND METHODS

Cell strains

Fibroblasts were obtained from skin biopsies using standard explant techniques [7] and stored in liquid nitrogen prior to these experiments. All cell strains underwent less than 30 doublings after their primary outgrowth. Table 1 lists the suspected genotype and other pertinent data for these cell strains. Growth medium, culture conditions, and cell harvest techniques have been described [8]. The control cell strains were obtained from the Genetics Department, Hospital for Sick Children, Toronto.

Mutagen Killing Curves

All cells were treated in the log phase of growth at approximately 5×10^5 cells/100 mm petri dish. For all UV experiments, separate dishes of cells were washed with phosphate buffered saline (PBS). The PBS was removed, and the petri dishes were irradiated 60 cm below a UV source with three 15 watt Germicidal tubes. The dose rate was 1.6 $JM^{-2}sec^{-1}$ as calibrated on a Black-Ray meter (Model J225 Ultra-Violet Products, Inc., San Gabriel, Calif.). Irradiated dishes were washed with PBS and harvested only from the central portion of irradiated 100 mm petri dishes using a 6.4 cm diameter heavy brass ring to eliminate cells shielded by proximity to the edge of the petri dish. The procedure used for chemical mutagen treatment, the plating regimes, and methods of scoring survivors have been described [8]. We observed considerable variation in preweighed samples of MMC sold by various companies and have determined all MMC concentrations by optical density (OD) at 365 nM. We assumed an OD_{365} of 0.6 to equal approximately 10 μgMMC/ml.

Unscheduled DNA Synthesis (UDS)

The technique of Robbins et al. [2] was used to measure UDS. Cells were plated in single chamber Lab-Tek slides (Lab-Tek Products, Westmount, Ill.) at a density of 5×10^4 cells per slide. After 24 hr, [^{3}H] thymidine ([^{3}H]dT) [46 Ci/mM; Amersham-Searle, Arlington Heights,

TABLE 1

PLATING EFFICIENCY OF CELL LINES

Cell line*	Sex	Age (yr)†	PE‡	Genotype	Relationship§
C 57 CTO	F	21	0.53	Control	Volunteer
C 62 CTO	M	35	0.35	Control	Volunteer
C 68 CTO	F	40	0.46	Control	Volunteer
C 160 CTO	F	5	0.56	Control	Trauma
C 162 CTO	M	13	0.55	Control	Burns
C 192 CTO	M	2	0.67	Control	Burns
CSH 3 WI	F	32	0.083	Heterozygote	Parent of CS 10 WI
CSH 4 WI	M	35	0.323	Heterozygote	Parent of CS 10 WI
CS 10 WI	M	4	0.258	Cockayne	···
CS 618 CTO	M	4	0.168	Cockayne	···
CS 693 CTO	F	12	0.091	Cockayne	···
CSH695 CTO	M	45	0.135	Heterozygote	Parent of 697 and 698
CSH696 CTO	F	44	0.085	Heterozygote	Parent of 697 and 698
CS 697 CTO	F	12	0.170	Cockayne	Sister of 698
CS 698 CTO	F	8	0.151	Cockayne	Sister of 697

* Cell line nomenclature follows that for xeroderma pigmentosum and ataxia telangiectasia. C = control; CS = Cockayne syndrome; CSH = CS heterozygote; CTO = Canada, Toronto, Ontario; and WI = Winnipeg, Manitoba, Canada.

† Age at time of biopsy.

‡ Average plating efficiency obtained for log phase cells obtained from zero exposure data in killing curve experiments.

§ Relationship between heterozygotes and patients, or reason for biopsy.

Ill.] was added to give 1 μCi/ml of medium, and incubation continued for 90 min so S phase cells could be identified. Cultures were washed with PBS and either UV irradiated (10 JM^{-2}) or treated with MMC (10 μg/ml for 10 min). In controls, these treatments yield relative survivals of .001 and .006, respectively. After washing twice with PBS, normal growth medium containing [^{3}H] dT (1 μCi/ml) was added for 90 min. Slides were coded, washed, fixed, and autoradiographed using standard methods. Autoradiographs were developed after 5 days exposure, stained, and grain counts were made on the coded slides.

Alkaline Sucrose Gradient Analysis

Alkaline sucrose gradient analysis was performed according to Lehmann et al. [6]. Cells were seeded at a density of 10^5 per 60 mm petri dish (Falcon Plastics) and grown for 2 days in a medium supplemented with 15% (v/v) fetal calf serum (referred to as α medium) [8]. One day later, [^{14}C] dT was added to a final concentration of 0.5 μCi/ml (59 mCi/mM). The cells were washed twice with PBS and placed in fresh α medium 30 min prior to treatment. The cells were again washed in PBS and exposed to a UV dose of 20 JM^{-2} or 50 μg MMC/ml for 30 min. After washing MMC treated cells, or immediately in the case of UV treated cells, three ml of α medium was added. After a 15 min incubation, 25 μCi/ml of [^{3}H] dT (46 Ci/mM) was added for 30 min or 1 hr. When pulse-chase experiments were performed, the labeled medium was replaced with α medium containing 10 μg/ml of deoxyribonucleotide and ribonucleotide. When caffeine or hydroxyurea were employed, they were present continuously from the time of treatment to the time of harvest. Cells were harvested after washing twice with PBS by scraping them off with a rubber policeman in 0.3 ml ice cold buffered EDTA [6]. The cells were then exposed to 2 krads of γ-irradiation from a ^{137}Cs source, at a dose rate of 104 rads/min, to prevent entanglement of DNA strands during the denaturation and centrifugation process [9].

Seven-drop alkaline sucrose fractions were collected on Whatman 3 mm paper strips. The acid-insoluble radioactivity was determined by scintillation counting after soaking the paper

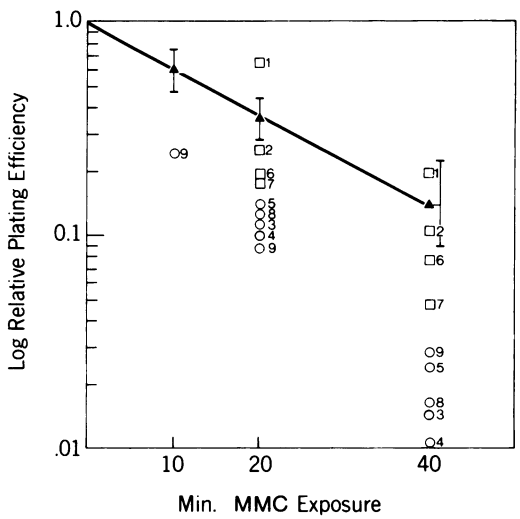

FIG. 1.—Killing by MMC of six normal control lines listed in table 1 (one repeated twice), five patients (*circles*) and four heterozygotes (*squares*). *Triangles* and *error bars* show control averages ± 2 standard deviations. Cells were exposed to MMC at a concentration of 1 μg ml^{-1} for times shown. No. = cell lines: 1 = CSH 3 WI; 2 = CSH 4 WI; 3 = CS 10 WI; 4 = CS 618 CTO; 5 = CS 693 CTO; 6 = CSH 695 CTO; 7 = CSH 696 CTO; 8 = CS 697 CTO; and 9 = CS 698 CTO. Plotted points are averages of five or more determinations.

strips 20 min in ice cold 5% trichloro acetic acid (TCA) followed by 20 min soaking in cold 95% ethanol and drying in a 100°C oven for 20 min. Blank strips of paper carried through this process were used to determine the background counts which have been subtracted.

RESULTS

All cell lines in table 1 were tested for sensitivity to MMC. The results are presented in figure 1. Average and 95% confidence limits are given for controls. CS cells show a MMC sensitivity twofold greater than controls and greater than any of the heterozygous parents although two parents show slight sensitivity. UV sensitivity has previously been reported in CS patients [3–5]. Figure 2 presents data on two affected siblings and their presumed heterozygous parents. The parents show identical UV sensitivities to controls (average for four), whereas the CS patients are similar (i.e., they are threefold more UV sensitive). With the exception of CS 618 CTO, all CS patients, their parents, and controls have similar MMS sensitivities (data not shown). It is possible that the MMS sensitivity observed in CS 618 CTO is due to an unrelated cause, similar to the familial MMS sensitivity unrelated to any known syndrome reported previously [10]. In addition, we tested six control lines—CSH 3 WI, CSH 4WI, CS 10 WI, and CS 618 CTO—for sensitivity to actinomycin D and found all were within 2 standard deviations of the mean suggesting a normal response (data not shown).

Table 2 presents the results of UDS studies on patients and heterozygotes. The UDS levels in affected individuals from each sibship were similar to those observed for controls and heterozygotes. The level of MMC-induced UDS is low (three patients and one heterozygote) and of the same order of magnitude as observed for actinomycin D-induced UDS at doses giving similar survivals.

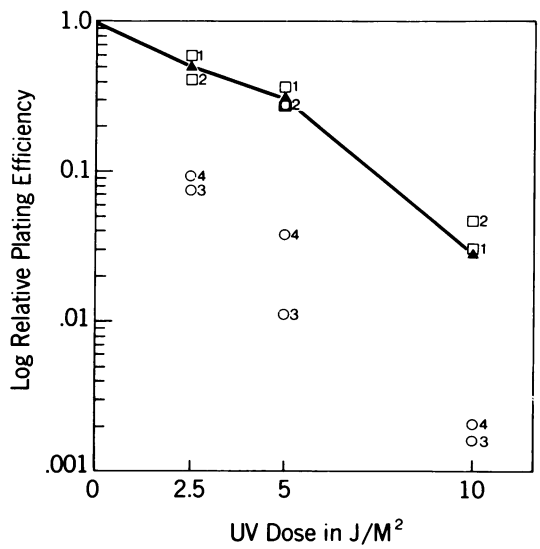

FIG. 2.—Killing by UV of two CS patients and their normal parents. Plotted line shows average survival of four independent normal control lines. No. = cell lines: 1 = CSH 695 CTO; 2 = CSH 696 CTO; 3 = CS 697 CTO; and 4 = CS 698 CTO. Plotted points are averages of five or more determinations.

TABLE 2

UNSCHEDULED DNA SYNTHESIS IN COCKAYNE PATIENTS AND THEIR PARENTS

SUBJECTS	No. CELLS	AVERAGE GRAIN COUNT			STIMULATION	
		Control	UV	MMC	UV	MMC
Parents:						
CSH 3 WI	100	2.0	49.7	4.5	47.7	2.5
695	100	5.1	39.4	n.t.*	34.3	···
Patients:						
CS 10 WI	100	1.1	51.2	5.9	50.1	4.8
618	100	3.9	38.2	5.5	34.3	1.6
693	100	2.3	54.1	n.t.	51.8	···
698	100	0.6	42.1	2.7	41.5	2.1

* n.t. = not tested.

Because the normal UDS rates suggest that the defect in CS might be in PRR, alkaline sucrose gradient analysis of DNA followed UV and MMC treatment. Also, since caffeine is thought to affect PRR in humans [6], we used it to further probe this process.

Pulse-chase experiments using [^{3}H] dT were performed on cells from all CS patients, three CS heterozygotes (CSH) and two controls following UV and MMC treatment. Figures 3*A*–3*C* show representative 60 min pulse gradient profiles obtained with a CS patient and her parent. The four other CS patients behaved like the patient shown in figure 3; four controls, including two heterozygotes, behaved similarly to the heterozygote shown. There is an initial relative deficiency in higher molecular weight DNA following UV (fig. 3*B*) or MMC (fig. 3*C*) treatment of CS cells; however, after a

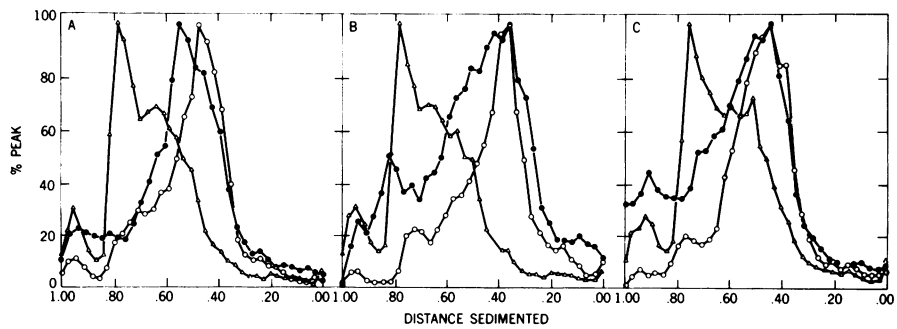

FIG. 3.—Tritium pulse profiles from heterozygote CSH 695 CTO (*solid circles*) and her affected daughter CS 698 CTO (*open circles*). *Open triangles* show ^{14}C bulk DNA profile from heterozygote. *Panel A*, untreated; *panel B*, UV irradiated (20 JM^{-2}); *panel C*, MMC treated (50 μg/ml, 30 min). Total CPM (× 10^{-3}) for pulse of heterozygote followed by CS patient (*A*) 17, 37; (*B*) 4.5, 8.1; and (*C*) 9.8, 9.0. Sedimentation from *right* to *left*; abscissa, relative distance sedimented; ordinate, percent of peak fraction. These axes are normalized by computer analysis to permit accurate comparisons between experiments. Resulting profiles are the same as plots of percent total incorporation.

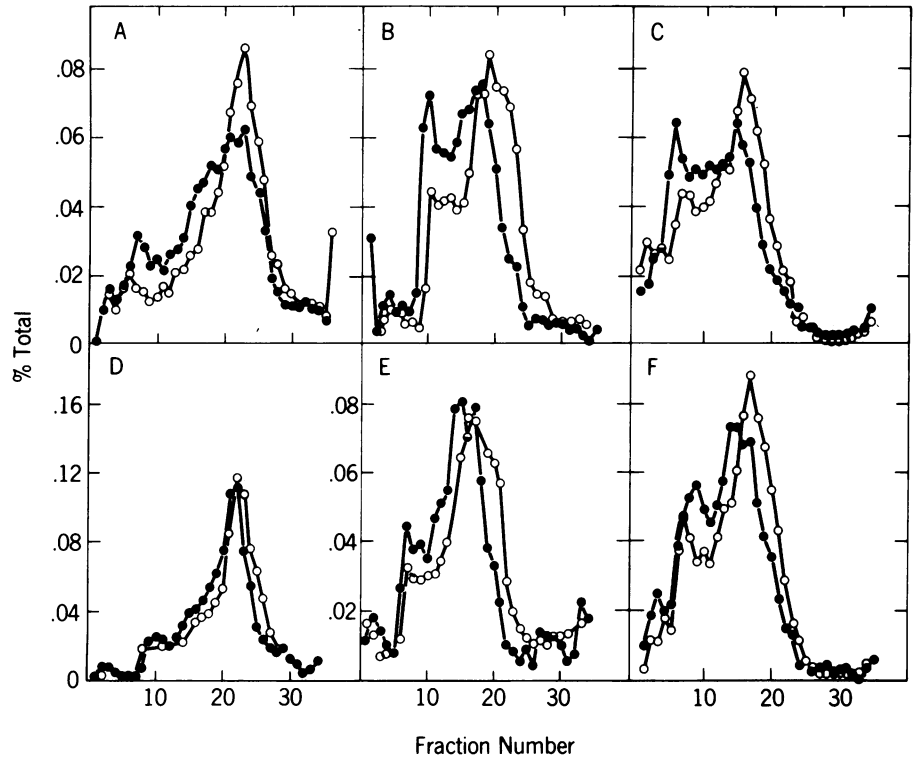

FIG. 4.—Effects of caffeine on pulse-labeled UV irradiated or MMC treated DNA. *A* and *D*, UV treated pulse; *B* and *E*, UV treated pulse, chased 3.5 hr; *C* and *F*, MMC treated pulse, chased 3.5 hr. *Upper panels* from heterozygote CSH695CTO and *lower panels* from affected daughter CS698CTO. *Closed symbols*, no caffeine; *open symbols*, caffeine treated. Total CPM ($\times 10^{-3}$) for untreated, followed by caffeine treated cells, (*A*) 4.5, 6.7; (*B*) 6.6, 11.4; (*C*) 9.9, 16.9; (*D*) 8.1, 10.5; (*E*) 2.1, 5.7; and (*F*) 4.0, 12.4. Sedimentation is from *right* to *left*. Abscissa, fraction number; ordinate, fraction of total incorporation. Note that profiles in (*A*) and (*D*) are identical to those in fig. 3 (*A*) and (*B*) although the axes are not normalized here.

3.5 hr chase, the DNA shows an appreciable increase in molecular weight (fig. 4). When graded UV doses of 10, 20, and 40 JM^{-2} are used to treat CS and CSH cells and 30 min pulse profiles are analyzed, a dose-dependent decrease in DNA size from CS cells is observed; however, heterozygotes or normal controls do not show a marked decrease in DNA size at low doses, and an apparent threshold effect of UV exists (fig. 5*A*). The apparent threshold in normal cells lies between 10 and 15 JM^{-2} and is probably related to the inhibitory effect of dimers on DNA replication. Here again the deficiency in pulse-labeled DNA sedimenting near that of prelabeled bulk DNA is evident with the CS patient.

The effect of caffeine on the ability of pulse-labeled UV irradiated or MMC-treated DNA to increase in molecular weight was also examined. Pulse-chase experiments were performed in the absence and presence of 0.3 mg/ml caffeine. Figure 4 shows the results obtained for one CS patient and one of her parents. In two control lines, three heterozygotes, and all patients, we observed a consistent, small, but significant,

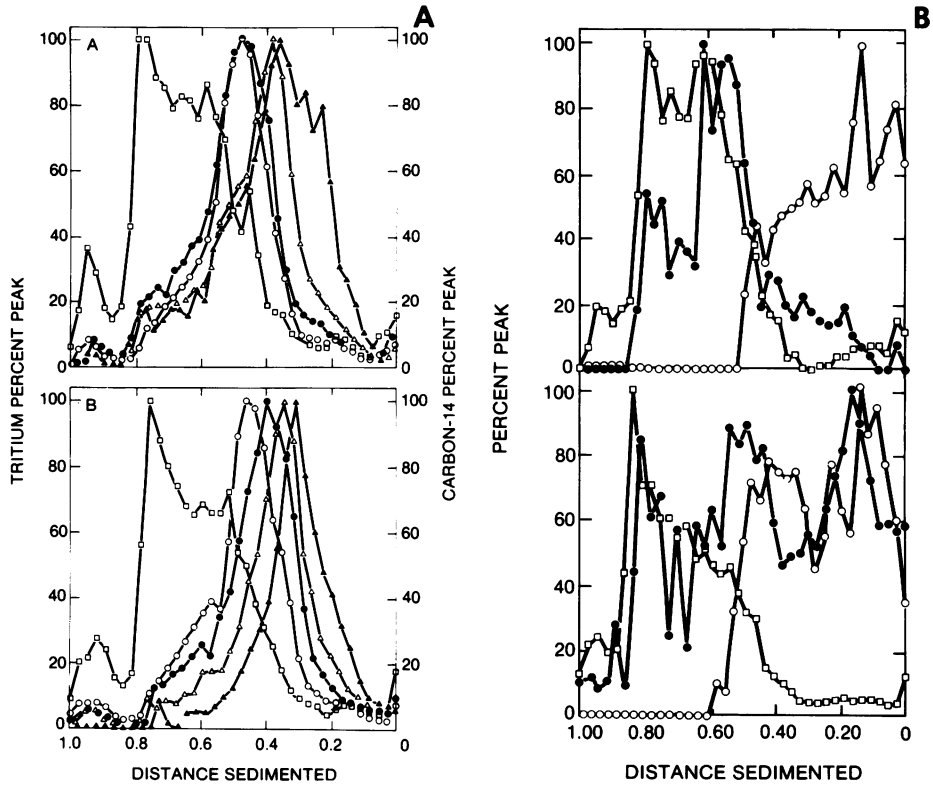

FIG. 5.—*A*, Effect of increasing UV dose on CSH696CTO (top) and CS10WI (bottom). Alkaline sucrose gradient analysis of 30 min pulse following OJ (*open circle*), 10J (*closed circle*), 20J (*open triangle*), and 40J (*closed triangle*). *Open squares* mark the ^{14}C-labeled bulk chromosomal DNA used as an internal marker in each gradient. Axes as in figure 3; total CPM ($\times 10^{-3}$); *top*, OJ (4.2), 10J (2.1), 20J (15.1), and 40J (5.5); *bottom*, 0J (9.7), 10J (12.3), 20J (15.3), and 40J (14.7). *B*, Effect of hydroxyurea on 1 hr pulse label incorporation with or without prior UV treatment. Heterozygote CSH696CTO (*top*) and patient CS10WI (*bottom*). *Open squares*, untreated bulk prelabeled ^{14}C; *open circles*, tritium pulse in absence of UV with 2mM HU present throughout the pulse; and *closed circles*, tritium pulse following $40JM^{-2}$ of UV with HU present throughout. Axes as in figure 3; total incorporation $X10^{-3}$ in absence of UV followed by presence of UV; *top*, 1.0, 2.0; *bottom*, 2.1, 5.4.

inhibition of molecular weight increase for UV treated DNA in the presence of caffeine. When caffeine is present alone without prior mutagen treatment, there is a slight inhibition of molecular weight increase observed in all cell lines (data not shown). The magnitude of this effect cannot account for the differences shown here; hence, these differences are assumed to be a reflection of caffeine effects on repair. The molecular weight increase in MMC-treated DNA was also somewhat sensitive; however, clearly MMC repair is not totally inhibited by caffeine. There were no consistent differences betweeen patients and controls or heterozygotes.

To establish that the defective production of higher molecular weight DNA in CS patients was repair related and not due to a defect in semiconservative replication alone, we performed pulse labeling studies in the presence of hydroxyurea (HU). HU

inhibits elongation of semiconservatively replicating DNA; however, it does not inhibit repair replication [11]. During a 60 min pulse in the presence of HU, untreated CSH 696 CTO and CS 10 WI cells incorporate little radioactivity which appears as a broad class of small DNA at the top of the gradient (fig. 5*B*). Treated with 40 JM^{-2} of UV, CSH cells incorporate all radioactivity into DNA as large as the prelabeled bulk DNA (fig. 5*B*, top). When the percentage of DNA in the bottom half of the gradient is calculated, 84.5% of prelabeled carbon and 68.4% of pulse-labeled tritium appear in the heterozygote as in normal repair replication. In CS cells treated identically, although some incorporation appears in larger DNA (83.9% of carbon and only 39.6% of tritium sediment below half on the gradient), a substantial proportion appears as small DNA (fig. 5*B*, bottom). Identical studies performed plus and minus HU at 10 and 20 JM^{-2} of UV indicate the large DNA class size substantially missing in CS cells following UV due to an abnormality in HU-resistant DNA synthesis.

DISCUSSION

Our observation of MMC sensitivity in five CS patients and the corroboration of the reported UV sensitivity in patients with this syndrome [3, 4] suggest that these properties may be characteristic of the syndrome. We presented evidence of normal UDS in patients from each of the sibships examined, and using alkaline sucrose gradient analysis, we revealed abnormal pulse-labeled DNA profiles following UV or MMC treatment. Repair during a 3.5 hr chase is normal in the presence or absence of caffeine. Hence, the defect is only apparent early after mutagen treatment.

Previous reports of UV repair in CS have been published. The normal UDS we observed in four unrelated CS patients agrees with Robbins et al. [2] and Andrews et al. [5]. The combined MMC and UV sensitivity with normal UDS levels yet abnormal pulse-labeled DNA patterns provide clues to where the defect is. We must, however, make certain assumptions about how MMC damage is repaired in humans.

Mitomycin C is an alkylating agent capable of forming both mono-alkyl derivatives [12] and alkylated cross-links [13]. The repair of the mono-alkyl derivatives is probably accomplished by the gamma excision repair system, as ataxia telangiectasia cells, which are believed to have a defect in this repair system [14], are sensitive to MMC and other mono-alkylating agents incapable of cross-link formation [8]. The repair of cross-links in human fibroblasts may require a sequence of processes as in *E. coli*. The first step involves unhooking one side of the cross-link and requires endonuclease activity of the UVR excision repair system. The *polA* exonuclease [15–17] and subsequent PRR controlled by the *rec A* system accomplishes the second step [15]. This proposed system leaves the remaining "half-link" (the covalently linked bases with only one side detached from the duplex DNA), which is probably removed by an excision repair sequence [15]. Mutant studies cannot resolve this in *E. coli*, as the same system, (UVR), must be involved in both steps. Since two repair systems are required for MMC and UV repair, a common sensitivity to MMC and UV could result from a defect in either system.

MCC-induced UDS levels are markedly lower than the UV-induced UDS levels, yet they are obtained with doses giving similar survival rates (table 2). This may represent gamma excision repair (short patch repair [18]) as the UDS levels are similar to those

obtained with equivalent doses of actinomycin D (unpublished results). The cross-links produced by MMC would not initially induce UDS (assuming an *E. coli* repair sequence) because the first step is nucleolytic and does not involve polymerization. If the terminal step (removal of the remaining "half-link") is accomplished by an excision system, this would only occur after completion of the PRR sequences necessary for MMC repair.

Pulse-labeled DNA in untreated cells (fig. 3*A*) is synthesized semiconservatively and represents label incorporated at growing points and in recently completed replicons during the 1 hr pulse. There is a slight reduction in average DNA size in this patient and her affected sib. This is not found with all patient-parent pairs, and when untreated, these may be indistinguishable as shown in figure 5. Short (5 min) pulse and pulse-chase experiments designed to examine relative replication rates fail to show a consistent difference between patients and heterozygoes but do reveal delayed DNA elongation in Bloom syndrome (data not shown).

Following UV treatment, the heterozygote synthesizes much larger DNA than the affected child. This becomes more pronounced at higher UV doses (fig. 5*A*). The larger pulse-labeled DNA has been interpreted to be excision repair patches, occurring in existing large DNA [19], and our studies on HU resistant repair (fig. 5*B*) substantiate this. If this large DNA is in fact the result of excision patches, then the deficiency of higher molecular weight DNA occurring in CS patients suggests that they are deficient in excision repair. As the UDS levels are normal (table 2), indicating normal gap filling, a defect could exist in either the polymerization or the final ligation reaction. With defective gap closure, excision repaired DNA should contain numerous gaps and appear small. The consequences of MMC damage would be similar although normal gamma excision repair of mono-alkylated lesions should generate some higher molecular weight DNA. The data in figures 3, 5*A*, and 5*B* are consistent with these expectations. The existence of larger DNA in CS cells following UV treatment in the presence of HU indicates that during the 60 min pulse, some completed repair has occurred (fig. 5*B*). Similar tests done with ½ hr pulses and chases up to 3.5 hr indicate that by 3.5 hr, virtually all HU resistant incorporation appears with prelabeled DNA in heterozygotes and patients (data not shown). This indicates that if a block in repair exists as the data suggest, it can be bypassed by an alternative system.

Since a combined UV and MMC sensitivity might also be expected if the CS patients had a defect in a PRR system that is required for the repair of lesions caused by both agents, we attempted to resolve this. The data in figure 4 show that near normal transitions to higher molecular weight DNA do occur in the CS cells in the presence or absence of caffeine. The relative deficiency of high molecular weight DNA in the patients, compared to their parents, would be expected because of their initial deficiency in this material. Although the mode of action of caffeine on PRR is unclear at present, data from *Drosophila* mutants with defective UV repair indicate that at least two PRR systems exist—one is very caffeine sensitive, and the other is essentially caffeine resistant [20]. At least two similar PRR systems exist in humans. Lehmann et al. [6] showed caffeine sensitivity of PRR in xeroderma pigmentosum (XP) variants. Arlett et al. [21] demonstrated their UV sensitivity in the presence of caffeine which implies first, that at least two PRR pathways exist for UV repair, and second, that one

is sensitive to caffeine. In these XP variants, we observed normal MMC sensitivity in the absence of caffeine and a caffeine enhanced MMC sensitivity (unpublished results), indicating that caffeine inhibitable repair is involved in the resolution of both UV and MMC damage. Using the techniques of Lehmann et al. [6], we observed a consistent small caffeine-sensitive repair component in normal cell lines, the CS heterozygotes, and the CS patients.

Our observations of normal PRR, normal UDS, UV, and MMC hypersensitivity and decreased amounts of large pulse-labeled DNA following UV or MMC exposure suggest that cells from CS patients have a defect in DNA metabolism. Since the defect is evident in the presence of HU, it appears that there is a defect in DNA repair. The deficiency in high molecular weight pulse-labeled DNA observed following mutagen treatment suggests that the defect could be in a late step in UV excision repair or some mechanism, as yet undefined, that is involved with linking together of the gapped parental DNA produced following UV irradiation.

Since the defect can be bypassed with sufficient time, we assume an alternate mechanism exists for completing these repair patches. As two forms of DNA ligase have been recognized in mammalian cells and one has been suggested to be associated with DNA repair [22], a deficiency in one of the DNA ligases might result in the observed phenotype.

Cockayne syndrome would differ from excision deficient XP in that at least some of the classical XP mutants have UV endonuclease activity and may be defective in the preparation of DNA for UV excision mechanisms [23]. The existence of normal UDS and normal caffeine sensitive PRR in Cockayne syndrome clearly differentiates this syndrome from the classical and variant forms of XP.

SUMMARY

Cockayne syndrome (CS) is a rare recessive genetic disease characterized in part by premature ageing and photosensitive skin. Because of the latter characteristic, this syndrome was considered to be an example of a UV-sensitive DNA repair-defective human disorder. We demonstrated normal levels of UV-induced unscheduled DNA synthesis (UDS) in four unrelated CS patients that show hypersensitivity to both UV and Mitomycin C (MMC). At low UV exposure, CS DNA shows a dose-dependent decrease in size. By contrast, heterozygotes appear to have a threshold below which there is little change in size of single strand DNA. Immediately following UV or MMC treatment, CS DNA is deficient in high molecular weight species, but undergoes a normal transition to larger DNA during a chase interval in the presence or absence of caffeine. This suggests a defect in replication or excision repair and no defect in post-replication repair (PRR). Pulse studies performed in the presence of hydroxyurea (HU) also reveal a deficient production of large DNA, suggesting the defect is in repair. As these cells have normal UDS and normal PRR, the basis for their UV sensitivity must be distinct from that observed in xeroderma pigmentosum (XP).

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