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TERMINAL TECHNICAL REPORT

on

"Studies on the radiation and chemical-induced molecular damages, their repair and biological expression in mammalian cells."*

INVESTIGATOR

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MASTER

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INTRODUCTION

Since leaving Oak Ridge National Laboratory in 1966 to take a teaching-research position at Michigan State University, I have been solely supported by the A.E.C. for research funds during the last five years. The report summarizes the details of this last year's (1971-72) research efforts.

The research objectives, which were supported in part by this contract, were designed to delineate the molecular basis for UV and chemical induced mutagenesis, cell killing and cancer in mammalian (including human) cells. The research was designed to test the hypothesis that the lack of repair of damaged DNA molecules, either due to genetic (e.g., xeroderma pigmentosum) or environmental (e.g., hormones, co-carcinogens or caffeine) means is the basis for the induction or modification of mutagenic and carcinogenic frequencies. Also, techniques were to be developed to get a human mutation assay system in tissue culture similar to the one developed by Chu (1). Also, once developed, an experiment was to be designed to test if pyrimidine dimers are responsible for mutations in human cells. This was to be accomplished by the use of the acetophenone technique described by Lamola (2).

Several other experiments were outlined in the original proposal. An examination of repair in a UV-sensitive strain of cattle was to be accomplished. If the human assay system was worked out, the potential molecular and mutagenic effects of the clinical phototherapy treatment for hyperbilirubinemia was to be undertaken. Lastly, completion of a study by Dr. R.B. Setlow (Oak Ridge National Laboratory) and myself was planned. This study was to examine how microbial repair enzymes could effect the repair of mammalian DNA when added exogenously to isolated mammalian cell nuclei.

Because my original contract budget was not funded in full (e.g., 50% of the budget was cut), it was impossible to accomplish several of the proposed objectives. As a matter of fact, the whole research effort this year was seriously curtailed by inadequate funding.

At the funded budget, I was only able to hire a 3/4 time technician from June 1 - October 1971. I had no dishwashing help during most of this time and only a small amount during the remainder of the year. This forced me and my technician to spend a significant portion of each work week to wash dishes, vials, to make tissue culture medium, etc. Obviously, to do tissue culture work and molecular biology on this type of schedule is almost impossible. Also, this inadequate funding made it impossible to purchase the type of supplies needed to develop a human mutation assay system. Consequently, the funded budget forced me to deal with only one aspect of my research contract adequately.

In spite of these technical problems related to the budget, I was able to accomplish a few of the contracted objectives, as well as opened up a potential exciting new area of research on DNA repair and cancer induction. It is unfortunate, therefore, that the A.E.C. support could not continue because many very potentially valuable research leads will now have to be left unexplored from my laboratory.

RESULTS

I. Biochemical basis for synergism between UV radiation and caffeine in Chinese hamster and human cells.

Caffeine has been shown to increase both the frequency of mutations and killing in bacteria, treated with ultraviolet light (3,4). The mechanism by which caffeine sensitizes bacteria to UV has been attributed to the inhibition of the excision of pyrimidine dimers (5,6). In mouse 'L' and Chinese hamster cells irradiated with UV or X-rays, caffeine further decreases the colony-forming ability (7-9). These observations have been interpreted as indirect evidence that caffeine may effect a dark repair of damage in DNA of mammalian cells.

Dr. Ernest Chu (Oak Ridge National Laboratory) and I were able to demonstrate the following about the caffeine synergism with mammalian cells under this contract.

A. UV, X-ray and Caffeine synergism with mutagenesis in Chinese hamster cells.

We were able to repeat the experiments published (10) demonstrating a synergism between UV and caffeine. Table I and II demonstrate that caffeine does not only increase UV-induced killing, but also decreases the frequency of UV-induced mutations. Table III illustrates that caffeine also synergistically acts with X-ray induced mutations in the same way as it does with UV light (e.g., it decreases the X-ray induced mutations).

We were also able to demonstrate that caffeine had to be present in the cells during the first 18 hours after the UV irradiation to reduce the mutation frequency. These results Table IV confirm the observation by Domon and Rauth (8) that caffeine acts synergistically with UV during the first S-phase of the cell cycle.

Table V demonstrates that the performed 8-azaquinine resistant mutants are not selected against in the presence of caffeine.

B. UV and caffeine synergism on the molecular weight of DNA in UV irradiated Chinese hamster cells.

To determine the molecular basis of the biological synergism of caffeine and UV in Chinese hamster cells, the molecular weight of the pre-existing DNA that had been UV-irradiated and incubated for 6 hours in the presence or absence of caffeine was determined by alkaline sucrose gradient centrifugation (Figure 1 and 2). It can be clearly seen that the molecular weight of DNA that had been UV-irradiated with high and low doses of UV radiation had not been altered by 6 hours postirradiation incubation in 1×10^{-3} caffeine. These observations could be interpreted to mean that caffeine completely inhibited the first step of excision repair (therefore no small fragmented resulting from single strand breaks would occur). However, since caffeine does not seem to inhibit excision repair in human cells (11), these results may mean that excision repair of pre-existing UV-irradiated DNA repairs via excision all the damage in the presence of caffeine. Since very few breaks resulting from repair are open at

Figure 1.

Figure 2.

any single moment, no major shift in the molecular weight would be observed in the UV-controls. Results demonstrate that few were available.

When the molecular weight of newly synthesized DNA in UV irradiated Chinese hamster cells was examined after caffeine or no caffeine posttreatment, I observed a drastic synergism. Figure 3 demonstrates that caffeine or UV alone do not significantly alter the molecular weight spectrum in the alkaline-sucrose gradient. However, after UV, caffeine somehow caused a drastic reduction in the molecular weight of the DNA synthesized after UV. Caffeine did not effect the incorporation of ^3H -Thymidine into the DNA of control or UV-irradiated cells (Fig. 4).

These results confirm again the observation made by Domon and Rauth (8) that caffeine had to be present during the first S-phase of the cell cycle after UV-irradiation to be effective.

One interpretation of the caffeine-induced lowered molecular weights in UV-irradiated cells is that caffeine inhibits excision of dimers, and the small fragments of DNA represent pieces of DNA made up to an unremoved pyrimidine dimers in the UV-irradiated DNA template. Another interpretation is that the caffeine induced the enzymatic breakdown of newly synthesized DNA in UV-irradiated cells. Alternatively, caffeine might inhibit a recombination-repair type mechanism in Chinese hamster cells. We favor the latter because on the basis of inhibited repair at the first step of repair (e.g., $\text{B}_{\text{S-1}}$ and xeroderma pigmentosum) we would predict that caffeine ought to act synergistically by increasing the UV-induced mutation frequency. It does not. If we assume that the recombination-repair mechanism, an inhibition of it's action ought to increase killing and decrease the mutation frequency.

These results have far reaching implications, in that if we assume most mutations in higher organisms are due to recombination-repair or the lack of excision repair, and if mutations can be one of the biological basis for carcinogenesis, then a caffeine-posttreatment of a radiation or chemical induced lesion of DNA ought to act as an anti-mutagen and anti-carcinogen.

Figure 3.

Figure 4.

Experiments were initially started to test this hypothesis in mice with Dr. Barnett Rosenberg of Michigan State University's Biophysics Department. Results of the experiment will not be available for several months. Unfortunately because of the termination of this grant, follow up on this line of research will have to terminate.

II. Repair of UV-induced pyrimidine dimers in *Drosophila melanogaster*.

In an attempt to develop a system whereby molecular lesions of DNA, repair systems and mutations could be analyzed, I decided that, with the development of *Drosophila* cells in tissue culture (12), *Drosophila* ought to be examined for its repair mechanisms. Tissue culture cells of *Drosophila melanogaster* were given various doses of ultraviolet light. The results indicate that *Drosophila* cells do have a dark-repair mechanism (Table II) and that the relative amount of excision is a function of the amount of UV-irradiation given to the cells (Figure 5a and 5b). Then cells were also capable of direct photoreactivation of UV-induced pyrimidine dimers (Figure 6).

III. Kinetics of Repair of UV-induced dimers in human cells.

One of the first experiments which we did this year was to determine the relative amount of repair of UV-induced pyrimidine dimers from DNA of human cells given various doses of UV radiation. Figure 7 demonstrates that the proportion of pyrimidine dimers to thymine removed by excision in UV-irradiated human cell DNA decreases with increasing doses.

IV. Excision repair in cattle showing hereditary predisposition to active skin cancer of the eye and eye lids.

Collaborating with Dr. James Cleaver, University of California Medical Center's Radiation Laboratory, I was able to confirm his results which indicated that that genetic disorder was not similar to xeroderma pigmentosum. Figure 8 demonstrates that these cattle excised their UV-induced pyrimidine dimers as well as the control cattle.

Figure 5a.

Figure 5b.

Figure 6.

Figure 7.

Figure 1

Figure 2

V. Environmental modification of the repair of damaged DNA in human cells.

Several natural and "man-made" chemicals are known to sensitize the biological response of mammalian cells to radiation or chemical assault. In our attempt to determine if these drugs caused their sensitization effect by inhibiting DNA repair, I irradiated human cells in culture with UV radiation, I then added various classes of chemicals (DNA synthesis inhibitors, radiation sensitizers, co-carcinogens, hormones, DNA repair inhibitors). After posttreatment with these various drugs, I measured the amount of excision repair that took place in the presence of these drugs. Tables VII and VIII demonstrate that FUDR, Caffeine, Quinacrine do not inhibit excision. However, all the hormones, at 1 µg/ml concentration or higher, and co-carcinogens inhibited the excision process. We will have to repeat these experiments with the hormones, however, since we suspect that the observations may be artifacts.

At the time of this report, we have preliminary evidence that both cyclic AMP and caffeine can ameliorate the hormone inhibition to the excision repair. If these observations are real and can be repeated, the biological implications of these results are very exciting and profound. The biochemical nature of the co-carcinogen and hormone induced excision inhibition are not known at the present time, however, assuming the observations are not artifacts, we think we have a clue. The biological manifestations of co-carcinogen and hormone inhibition of repair will have to be tested on mutation assay systems and on animal cancer systems.

VI. Repair of DNA damage in other animal systems.

Preliminary studies were started to demonstrate whether either the excision repair or photoreactivation of UV-induced dimers occurred in pig cells. Also, we wanted to develop a tissue culture of brain cells in order to study repair.

One experiment indicated that pig cells do not have an excision repair system similar to human cells, and that they do not have the photoreactivation repair mechanism. Further work needed to be done to finish these studies.

We were only able to develop a tissue culture of 9 day old mice in culture. Figure 9 and 11 demonstrate the type of neuronal cells found in our cultures after 2 months. Again, with the termination of this contract, we will have to drop this line of research to investigate the nature of DNA repair in brain cells.

VII. Acetophenone-induced pyrimidine dimers in human cells.

In order to determine if pyrimidine dimers were responsible for UV-induced biological damages such as mutations, we originally thought that by producing pyrimidine dimers under conditions which presumably produced only pyrimidine dimers, we might examine the biological consequences of the induced dimers. Several experiments were performed to determine the toxicity of acetophenone and acetone on AV₃ human cells. We were able to induce pyrimidine dimers by 3130Å irradiation on acetophenone or acetone treated cells, however, only at doses or concentrations, which were highly lethal to the control-non irradiated cells. Because of this and of the report (13) that 3130 Å - irradiated acetophenone treated cells also have other molecular lesions, I decided to stop this line of investigation.

ACCOMPLISHMENTS

During my service at Michigan State University, the Atomic Energy Commission has been my main research support. Because of my unique faculty position at Michigan State University, I did not have any graduate or undergraduate research support. Because of the level of AEC funding, I was also unable to have any postdoctoral support. Therefore, I, alone, was responsible for all of the research contributions that were made during the AEC funding.

I had a huge teaching load during the first four years of the AEC support. Since I taught in an area in which few scientists dare tread (philosophical, social and ethical impact of science), and since I felt this is an absolutely critical area of teaching today, I am extremely grateful to the AEC for their support which enabled me to do this kind of teaching and also kept me intellectually

Figure 9.

Figure 10.

Figure 11.

and scientifically active in a very important area of research the repair of DNA damage in mammalian cells and in other higher organisms. Because of your support, I was able to accomplish a few significant objectives in this area.

I only regret that, after all your support which enabled me to establish a laboratory where molecular assays for DNA damage, the repair of DNA damage, and mutagenic and other tissue culture assays are all routine assays in my laboratory, I will not be funded by the A.E.C. to continue research on many potentially fruitful areas of research.

Because of your earlier support of my research which enabled me to have this unique teaching situation, I was given a Michigan State University Teacher-Scholar Award (1971). Also, it is ironic that after your support and my research accomplishments under that support, I was given an N.I.H. Career Development Award to spend at least 80% of my time for research.

Since my involvement in radiation repair in mammalian cells at Oak Ridge National Laboratory in 1963-64, I was able to accomplish the following:

I was the first person to demonstrate UV-induced pyrimidine dimers in mammalian cells. I was one of the first to demonstrate that a dark repair excision mechanism exists in human cells, as well as the first to demonstrate directly, that human cells do not photoreactivate UV-induced dimers.

I was also a member of a team that first demonstrated a lack of a UV-endonuclease repair enzyme in the human mutant, xeroderma pigmentosum.

I was also the first to directly demonstrate the sunlight induction of pyrimidine dimers in human cells. Also, I demonstrated the biochemical basis of visible light-induced psoralen sensitization in human cells. The lack of a postulated LSD-UV synergism and DNA damage in human cells was also demonstrated by me.

I have also demonstrated the induction and photorepair of pyrimidine dimers in several higher plant systems. Now, I have demonstrated both light and dark-repair excision mechanisms in Drosophila melanogaster tissue culture cells, as well as dark repair in cattle.

I was also a member of a team which demonstrated a synergism between caffeine and UV damage on a molecular and biological level.

JET/psw
June 9, 1972

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Table 1: Caffeine Effect on UV-Induced Mutations ($A_{zg}^s \rightarrow A_{zg}^r$) and Killing in Chinese Hamster Cells.

UV Dose ergs/mm ²	% Survival		Mutation Freq./10 ⁵ Survivors	
	<u>No caffeine</u>	<u>Caffeine</u>	<u>No caffeine</u>	<u>Caffeine</u>
0	100	90	1.6	.67
50	73	65		
65	64	34	4.60	3.85
75	29	12		
100	19	6		
150	5	4		

Table II: Caffeine Effect on UV-Induced Mutation ($A_{zg}^s \rightarrow A_{zg}^v$) and Killing in Chinese Hamster Cells.

UV Dose <u>ergs/mm²</u>	% Survival		Mutation Freq./10 ⁵ Survivors	
	<u>No Caffeine</u>	<u>Caffeine</u>	<u>No caffeine</u>	<u>Caffeine</u>
0	100	129	.17	.02
50	127	8.4		
65	86	4.9	11.7	1.43
80	67	6.7		
100	36	1.6		
150	7	.09		

Table III: Caffeine Effect on X-ray Induced Mutations ($A_{zg}^s \longrightarrow A_{zg}^r$) and Killing of Chinese Hamster Cells.

X-ray Dose <u>Roentgens</u>	% Survival		Mutation Freq./ 10^5 Survivors	
	<u>No caffeine</u>	<u>Caffeine</u>	<u>No caffeine</u>	<u>Caffeine</u>
0	100	123	1.5	.93
50	94	120	6.3	.75
100	90	97	5.5	.92
200	73	80	5.9	.75

Table IV: Caffeine Effect on UV-Induced Mutations ($A_{zg}^s \longrightarrow A_{zg}^r$) and
Killing in Chinese Hamster Cells During Different Postirradiation
Times.

UV Dose	Caffeine	% Survival	Mutation Freq./10 ⁵ Survivors
<u>ergs/mm²</u>			
0	0	100	8.7
0	0-18 hrs.	63	9.6
0	18-42 hrs.	77	6.9
0	0-200 hrs.	74	1.9
65	0	46	25.4
65	0-18 hrs.	5	17.5
65	18-42 hrs.	8	15.8
65	0-200 hrs.	.4	15.6

Table V: Effect of Caffeine ($1 \times 10^{-3}M$) on A_{zg}^s and A_{zg}^r cells.

	EM-15 Medium			EM-15 Medium + $1 \times 10^{-3}M$ Caffeine		
Number and Types of Cells Plated	Average number colonies/plate	Mutation Freq./ 10^5 Survivors		Average number colonies/plate	Mutation Freq./ 10^5 Survivors	
100 A_{zg}^r	89.8			79.0		
$1 \times 10^5 A_{zg}^s$						
100 A_{zg}^r	103.9			89.4		
$4 \times 10^4 A_{zg}^s$						
$1 \times 10^5 A_{zg}^s$	19.0	19.0		3.1	3.5	
	Average number colonies/plate	P.E.	% Survival	Average number colonies/plate	P.E.	% Survival
A_{zg}^s	112.6	112.6	100	100.6	100.6	89.3
A_{zg}^r	105.4	105.4	100	95.4	95.4	90.5

BLE VI:

Dark Repair (DR) of Ultraviolet Light-Induced Pyrimidine Dimers ($\hat{X}\hat{T}$)* in *Drosophila Melanogaster*

Cells Grown In Vitro.

Experiment	UV Treatment	0 hr.		24 hr. - DR**	
		$\frac{\text{Counts in } \hat{X}\hat{T}}{\text{Counts in } \hat{T}}$	$\hat{X}\hat{T} (\%)$	$\frac{\text{Counts in } \hat{X}\hat{T}}{\text{Counts in } \hat{T}}$	$\hat{X}\hat{T} (\%)$
A.	None	0/473,600	0.00		
	15 sec.***	681/931,200	0.07	113/414,600	0.03
	20 sec.	664/611,900	0.11	350/602,300	0.06
	30 sec.	1,448/1,015,200	0.14	353/551,900	0.06
	45 sec.	-----	----	450/267,000	0.17
	60 sec.	2,251/787,300	0.29	288/109,500	0.26
B.	15 sec.	257/240,700	0.11	142/198,300	0.07
	20 sec.	891/647,300	0.14	184/215,400	0.09
	30 sec.	775/319,900	0.24	709/352,300	0.20
	60 sec.	1,226/312,100	0.39	562/162,000	0.35

* $\hat{X}\hat{T}$ refers to both $\hat{T}\hat{T}$ and $\hat{U}\hat{T}$ dimers, since chromatography procedures used here do not separate them from each other.

**DR refers to post radiation dark repair incubation.

***Cells were irradiated at 2537 Å. The dose rate for experiment A was not determined accurately. The incident dose rate to cells in experiment B was 35 ergs/mm²/sec.

TABLE VII:

The effect of various drugs on the excision of UV-induced pyrimidine dimers. These drugs are either DNA synthesis inhibitors, co-carcinogens, radiation sensitizers, or promoters of cell growth.

Treatment	$\frac{\text{Counts in XT}}{\text{Counts in T}}$	
UV	576/330,200	.17%
UV-DR	138/122,700	.11%
UV+Hydroxyurea (10^{-3}M)	213/194,400	.11%
UV+Acriflavin (10 mg/ml)	410/291,500	.14%
UV+FUDR (10^{-5}M)	156/125,000	.12%
UV+TWEEN 80	287/199,000	.14%
UV+Estradiol ($5 \times 10^{-5}\text{M}$)	431/243,300	.18%
UV+Croton Oil (.005%)	508/236,800	.21%
UV+Quinacrine (0.15 mM)	447/361,300	.12%
UV+Putrescine ($3 \times 10^{-8}\text{M}$)	259/251,300	.10%

TABLE VIII:

The effect of various drugs and concentrations of hormones, radiation, synergists, and co-carcinogens on the excision of UV-induced pyrimidine dimers.*

Treatment	XT/T	% XT/T
UV	375/373,400	0.10
UV+DR (24 hrs.)	85/145,400	0.06
UV+Caffeine ($1 \times 10^{-3}M$)	89/120,242	0.07
UV+Croton Oil (.005%)	197/194,400	0.10
UV+Tween 80 (6 hrs.)	150/167,400	0.09
UV+DR (6 hrs.)	92/122,800	0.08
UV+Estradiol (14 $\mu g/ml$)	663/426,000	0.16
UV+Estradiol (.14 $\mu g/ml$)	307/229,900	0.13
UV+Estradiol (.014 $\mu g/ml$)	157/175,800	0.09
UV+Estradiol (.0014 $\mu g/ml$)	161/231,100	0.07
UV+Estrone (14 $\mu g/ml$)	250/713,700	0.12
UV+Corticosterone (1 $\mu g/ml$)	192/175,000	0.11
UV+Progesterone (1 $\mu g/ml$)	221/231,800	0.10
UV+Testosterone (1 $\mu g/ml$)	169/166,300	0.10

*All cells treated with drugs after irradiation were placed in the dark for twenty-four hours before analyzed for pyrimidine dimers.

COMPILATION OF EQUIPMENT IN LABORATORY OF

Dr. James E. Trosko

Microvoid transfer hood
Hotpack CO₂ incubator
Hotpack CO₂ standup tissue culture incubator
New Brunswick shaker incubator
Zeiss inverted phase microscope
Zeiss research microscope
Waterbaths (2)
Freezer
Refrigerator
pH meter
Branson sonifier
Chromatography equipment
Clinical centrifuge
Yellow Springs radiometer
High temperature oven
Packard scintillation counter
Coulter cell counter

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