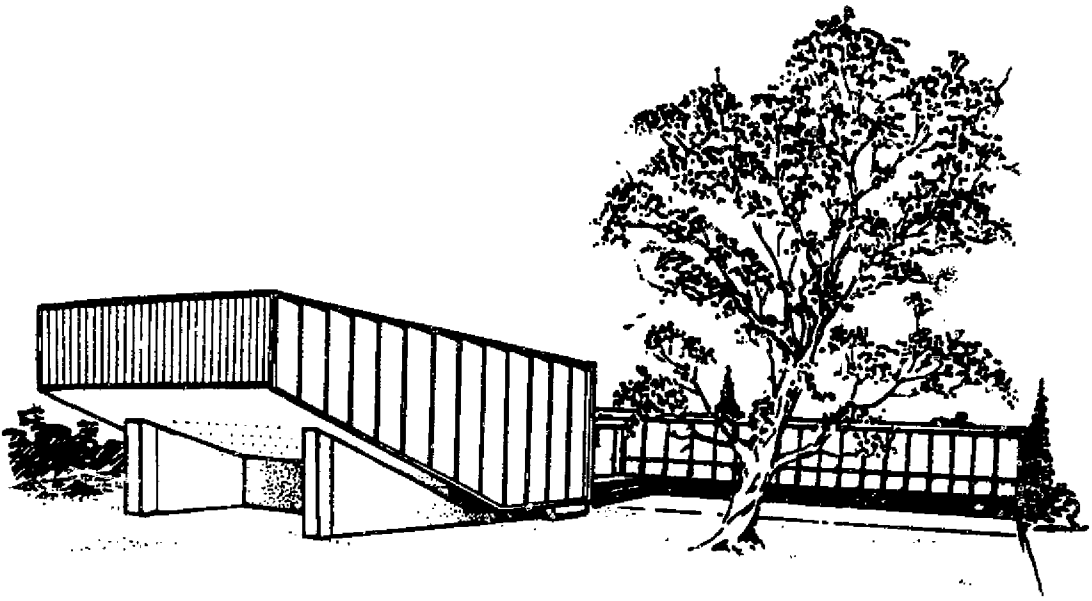


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AUSTRALIAN INSTITUTE OF NUCLEAR SCIENCE
AND ENGINEERING

12th AINSE RADIATION BIOLOGY CONFERENCE
22-24 SEPTEMBER, 1989

LUCAS HEIGHTS - AINSE THEATRE



CONFERENCE HANDBOOK

(Programme, Abstracts and General Information)

AUSTRALIAN INSTITUTE OF NUCLEAR SCIENCE AND ENGINEERING

12TH AINSE RADIATION BIOLOGY CONFERENCE 1989

LUCAS HEIGHTS N.S.W.

<u>Friday 22nd September 1989</u>	Commencing	10.30 a.m.
	Conference Luncheon	1.00 p.m.
	Symposium	4.00 p.m.
	Conference Dinner	7.00 p.m.
<u>Saturday 23rd September 1989</u>	Commencing	9.00 a.m.
	Technical Tours	1.30 p.m.
	BBQ	6.00 p.m.
	Concluding	9.00 p.m.
<u>Sunday 24th September 1989</u>	Commencing	9.00 a.m.
	Closing Discussions	1.00 p.m.
	Tour	1.15 p.m.

Conference President

Dr. R.F. Martin

Peter MacCallum Cancer Institute

Conference Committee

Mr. J.K. Brown	ANSTO
Mr. D.R. Davy	ANSTO
Dr. M. Fenech	CSIRO
Professor M.F. Lavin	Q.I.M.R.
Dr. D.G. MacPhee	La Trobe University
Professor P.A. Parsons	University of Adelaide
Dr. R.B. Gammon	AINSE

Conference Secretary

Ms J. Watson

AINSE

C O N T E N T S

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S U M M A R YFriday 22nd September 1989

10.30 - 10.40

Opening RemarksAINSE President:Prof. D.R. Miller
(Univ. of Adelaide)Conference President:Dr. R.F. Martin
(Peter MacCallum C.I.)Session I

10.40 - 11.40

Mammalian Radiation Biology I

Chairman: Dr. R. Martin

11.40 - 12.00

Morning Tea

Session II

12.00 - 1.00

Mammalian Radiation Biology II

1.00 - 2.00

Chairman: Dr. M. Fenech (CSIRO)

Conference Lunch

Session III

2.00 - 3.40

Radiation and Clinical Effects

3.40 - 4.00

Chairman: Dr. D.G. MacPhee (La Trobe Univ.)

Afternoon Tea

Session IV

4.00 - 6.00

Symposium

Radiation Risk - Prospective for Industry

Chairman: Mr. M.W. Carter (Office of the
Supervising Scientist)Session V

6.00 - 7.00

Poster Session

7.00

Conference Dinner

Saturday 23rd September 1989Session VI

9.00 - 10.30

Environmental Radiation

Chairman: Dr. R. Rosen (Univ. of N.S.W.)

10.30 - 11.00

Morning Tea

Session VII

11.00 - 12.30

New Developments at ANSTO - three short
presentations of exciting new developments

12.30 - 1.30

Lunch

Session VIII

1.30 - 5.00

Technical Tours - ANSTO or Australian Museum

6.00 - 7.30

BBQ

Session IX

7.30 - 9.00

Biomedical Applications

Chairman: Dr. M.F. Lavin (Q.I.M.R)Sunday 24th September 1989Session X

9.00 - 10.30

Bacterial Mutagenesis

Chairman: Dr. L.A. Burgoyne (Flinders Univ.)

10.30 - 11.00

Morning Tea

Session XI

11.00 - 12.20

Poster Summary

Chairman: A.Prof. J.M. Gebicki (Macquarie Univ.)

12.00 - 1.00

Lunch

1.00 - 1.10

Closing Discussions

1.15

Tour - Royal National Park

Friday 22nd September 1989 - Lucas Heights

<u>TIME</u>	<u>PAPER</u> <u>NO.</u>	
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<u>SESSION I</u>		<u>MAMMALIAN RADIATION BIOLOGY I</u> <u>Chairman:</u> Dr. R.F. Martin (Peter MacCallum C.I.)
10.40 - 11.00	1	Characterization of a γ -Radiation-Activated DNA-Binding Protein which is Constitutively Present in Ataxia-Telangiectasia Nuclear Extracts. <u>S.P. Singh</u> , P. Le Poidevin, M.F. Lavin (Q.I.M.R.)
11.00 - 11.20	2	DNA Binding Protein Induced by Ionizing Radiation. <u>M.F. Lavin</u> , S.P. Singh, K. Hobson, I. Myoshi, B. Teale (Q.I.M.R.)
11.20 - 11.40	3	Detection of Ataxia-Telangiectasia Heterozygotes: Methods based on Radiosensitivity. <u>P. Le Poidevin</u> , S. Singh, M.F. Lavin (Q.I.M.R.)
11.40 - 12.00		MORNING TEA
<u>SESSION II</u>		<u>MAMMALIAN RADIATION BIOLOGY II</u> <u>Chairman:</u> Dr. M. Fenech (CSIRO)
12.00 - 12.20	4	Detection of Ionizing Radiation-Induced DNA Double-Strand Breakage in Mammalian Cells. I.R. Radford (Peter MacCallum C.I.)
12.20 - 12.40	5	Radiation Induced DNA Damage - Protection by DNA Ligands. <u>L. Denison</u> , R. Martin (Peter MacCallum C.I.)
12.40 - 1.00	6	Molecular Changes during Apoptosis. <u>G. Baxter</u> , P. Smith, M.F. Lavin (Q.I.M.R.)
1.00 - 2.00		CONFERENCE LUNCH - Stevens Hall Lounge

Friday 22nd September 1989 - Lucas Heights

<u>TIME</u>	<u>PAPER NO.</u>	
<u>SESSION III</u>		
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<u>Chairman:</u> Dr. D.G. MacPhee (La Trobe Univ.)		
2.00 - 2.20	7	Death by Cell Cycle Arrest. S.J. Davis (Oxford Univ., U.K.), <u>L.A. Burgoyne</u> (Flinders Univ.)
2.20 - 2.40	8	Amino Acid and Protein Peroxides. <u>J.M. Gebicki</u> , S. Baumgartner (Macquarie Univ.)
2.40 - 3.00	9	Relationship between the Levels of Vitamin E and Oxidizability of Human LDL. A.V. Babiy, J.M. Gebicki (Macquarie Univ.)
3.00 - 3.20	10	Bilirubin as an Antioxidant. R. Stocker (Heart Research Institute)
3.20 - 3.40	11	Radium Intestinal Transfer Studies. <u>R.U. Domei</u> (ANSTO), A.M. Beale (Univ. of N.S.W.)
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<u>SESSION IV</u>		
<u>SYMPOSIUM:</u> Radiation Risk - Prospective for Industry		
<u>Chairman:</u> Mr. M.W. Carter (Office of the Supervising Scientist)		
4.00 - 4.30	12	Risk Employment Misbeliefs. F.P.J. Robotham (Univ. of Melbourne)
4.30 - 5.00	13	Radiation Doses via Inhalation and Ingestion under the Current and Proposed ICRP Models. J.R. Twining (ANSTO)
5.00 - 5.30	14	Radiation Risks in the Mineral Sands Industry. <u>G.S. Hewson</u> , B. M. Hartley (Dept. of Mines, Perth)
5.30 - 6.00		Symposium Discussion

Friday 22nd September 1989 - Lucas Heights

<u>TIME</u>	<u>PAPER</u> <u>NO.</u>	
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<u>SESSION V</u>		
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	16	The Effects of Cell Cycle on the Molecular Basis of X-ray Induced Mutations at an Autosomal Locus. <u>J. Condon</u> , D.R. Turner (Flinders Medical Centre)
	17	Gadolinium Neutron Capture. <u>R.F. Martin</u> , G. D'Cunha, A. Haigh, M. Pardee (Peter MacCallum C.I.), A. Whittaker, D.P. Kelly (Univ. of Melbourne), B.J. Allen (ANSTO)
	18	Thresholds in the Assessment of Chemical Carcinogens. F.P. Imray (Dept. of Community Services and Health, Canberra)
	19	Are Oxidised Proteins Damaging Species? <u>J.A. Simpson</u> , R.T. Dean (Heart Research Institute)
	20	Morphological Changes in Melanoma Cells Following Irradiation. D.H. Barkla (Monash Univ.), <u>B.J. Allen</u> , J.K. Brown, S. Buck (ANSTO)
	21	Cloning the Rad4 Gene of Schizosaccharomyces Pombe. M. Fenech (CSIRO), A. Carr, A.R. Lehmann, F.Z. Watts (Univ. of Sussex, U.K.)
	22	Sensitisation of Photo-Cleavage of DNA by an Iodinated DNA Ligand - Mechanistic Studies. <u>L.E. Bennett</u> , R.F. Martin (Peter MacCallum C.I.), R. Cooper (Univ. of Melbourne)
	23	Death (Apoptosis) of Cells Irradiated in S-Phase in Neonatal Tissues. <u>J. Allen</u> , B.V. Harmon, D.J. Alien, G.C. Gobé (Univ. of Queensland)
7.00		CONFERENCE DINNER - ANSTO Canteen

Saturday 23rd September 1989 - Lucas Heights

<u>TIME</u>	<u>PAPER NO.</u>	
<u>SESSION VI</u>		<u>ENVIRONMENTAL RADIATION</u> <u>Chairman:</u> Dr. R. Rosen (Univ. of N.S.W.)
9.00 - 9.30	24R <u>Review</u>	Extremely Low Frequency Electromagnetic Fields and Cancer. M.H. Repacholi (Royal Adelaide Hospital)
9.30 - 9.50	25	Review of the Epidemiological Studies Linking Elf Electromagnetic Radiation with Cancer. A.J. Christophers (Univ. of Melbourne)
9.50 - 10.10	26	Impact of Reduced Radiation Limits on Environmental Measurements. <u>M.W. Carter</u> , A. Johnston (Office of the Supervising Scientist)
10.10 - 10.30	27	Experimental Studies of ^{226}Ra and Radiocalcium Accumulation from the Aquatic Medium by Freshwater Turtles. R.A. Jeffree (ANSTO)
10.30 - 11.00		MORNING TEA
<u>SESSION VII</u>		<u>NEW DEVELOPMENTS AT ANSTO</u> <u>Chairman:</u> Dr. R.B. Gammon (AINSE)
11.00 - 11.20		AINSE Facilities and Services. R.B. Gammon (AINSE)
11.20 - 11.40		8MV Tandem Accelerator. J.W. Boldeman (ANSTO)
11.40 - 12.00		Australian Small Angle Neutron Scattering Facility (AUSANS). R.B. Knott (ANSTO)
12.00 - 12.20		National Medical Cyclotron Facility. R. Boyd (ANSTO)
12.20 - 12.30		Discussion
12.30 - 1.30		LUNCH - Stevens Hall Lounge
<u>SESSION VIII</u>		Technical Tours
1.30 - 5.00		ANSTO or Australian Museum
6.00 - 7.30		BBQ - Adjacent Swimming Pool

Saturday 23rd September 1989 - Lucas Heights

<u>TIME</u>	<u>PAPER NO.</u>	
<u>SESSION IX</u>		<u>BIOMEDICAL APPLICATIONS</u>
		<u>Chairman:</u> Dr. M.F. Lavin (Q.I.M.R.)
7.30 - 8.00	28 <u>Review</u>	Radiation Biology and Radiotherapy. H.R. Withers (Prince of Wales Hospital)
8.00 - 8.20	29	Micronuclei in Cytokinesis-Blocked Lymphocytes of Cancer Patients Following Fractionated Partial-Body Radiotherapy. <u>M. Fenech</u> (CSIRO), J. Denham (Newcastle Mater Hospital), W. Francis (Royal Adelaide Hospital), A.A. Morley (Flinders Medical Centre)
8.20 - 8.40	30	Regression of Melanoma Xenografts by Neutron Capture Therapy. <u>S. Buck</u> , B.J. Allen (ANSTO)
8.40 - 9.00	31	DNA Ligands as Radiomodifiers. <u>R.F. Martin</u> , V. Murray, L. Dension, G. D'Cunha, M. Pardee, A. Haigh, G.S. Hodgson (Peter MacCallum C.I.), E. Kampouris, D.P. Kelly (Univ. of Melbourne)

Sunday 24th September 1989 - Lucas Heights

<u>TIME</u>	<u>PAPER NO.</u>	
<u>SESSION X</u>		<u>BACTERIAL MUTAGENESIS</u>
		<u>Chairman:</u> Dr. L.A. Burgoyne (Flinders Univ.)
9.00 - 9.30	32R <u>Review</u>	Antimutagenesis. D.G. MacPhee (La Trobe Univ.)
9.30 - 9.50	33	Spontaneous and Ionizing Radiation- Induced Mutagenesis in Prokaryotes. <u>D. Liaskou</u> , D.G. MacPhee (La Trobe Univ.)
9.50 - 10.10	34	The Effect of Mismatch Repair and Glucose Depression on 9AA-Induced Mutagenesis in Bacteria. <u>G. Kopsidas</u> , D.G. MacPhee (La Trobe Univ.)
10.10 - 10.30	35	The Effect of 9-Amino Acridine, ICR191 and Dexon on Reversion of Frameshift Mutations in Salmonella Typhimurium. <u>J. D'Costa</u> , D.G. MacPhee (La Trobe Univ.)
10.30 - 11.00		MORNING TEA
<u>SESSION XI</u>		<u>POSTER SUMMARY</u>
11.00 - 12.00		<u>Chairman:</u> Assoc. Professor J.M. Gebicki (Macquarie Univ.)
12.00 - 1.00		LUNCH - Stevens Hall Lounge
1.00 - 1.10		<u>Closing Discussions</u>
1.15		Tour - Royal National Park

A B S T R A C T S

CHARACTERIZATION OF A γ -RADIATION-ACTIVATED DNA-BINDING PROTEIN
WHICH IS CONSTITUTIVELY PRESENT IN ATAXIA-TELANGIECTASIA NUCLEAR EXTRACTS

S.P. Singh, Priscilla Le Poidevin and M.F. Lavin

Molecular Oncology, Queensland Institute of Medical Research, Herston Qld 4006

Ataxia-telangiectasia A-T is a rare human genetic disorder characterized by cerebellar ataxia, oculocutaneous telangiectasia, immunodeficiency and developmental abnormalities. This disorder is also associated with a predisposition to development of cancer, in particular, leukaemias and lymphomas (Spector *et al.*, 1982). Increased sensitivity to ionizing radiation *in vivo* and in cells in culture together with evidence of defective DNA repair in some cases (Cornforth and Bedford, 1985), chromosomal instability, specific gene rearrangements and altered DNA topoisomerase II activity (Aurias *et al.*, 1985, Singh *et al.* 1988), all point to a DNA processing defect in A-T.

In this report we describe the presence of a DNA-binding activity in the nuclear extracts from A-T cells capable of specifically binding to the PvuII-SphI (270-199 nucleotides) fragment of the SV40 enhancer element. Characterization of the DNA-binding activity in terms of the size of the protein and its DNase 1 and DMS footprints revealed that the size and binding site are different from the AP family of transcription factors. Furthermore this binding protein was only detected in normal cells after exposure to γ -radiation. These results demonstrate the presence of a constitutively active protein in A-T cells which normally plays an important role in response to radiation damage.

A. Aurias, J. Courturier, A.M. Dutrillaux, B. Dutrillaux, F. Herpin, E. Lamoliatte, M. Lombard, M. Muleris, M. Paravatou and M. Priur (1985) *Hum. Genet.*, 71, 19-21.

M.N. Cornforth, and J.S. Bedford (1985) *Science* 227, 1589-1591.

S.P. Singh, R. Mohamed, C. Salmond and M.F. Lavin (1988) Reduced DNA topoisomerase II activity in ataxia-telangiectasia. *Nucleic Acids Res.* 16, 3919-3926.

B.D. Spector, A.H. Filipovich, G.S. Perry III and J.H. Hersey (1982) In: B.A. Bridges and D.G. Harnden (Eds.), *Ataxia-telangiectasia: A Cellular and Molecular Link between Cancer, Neuropathology and Immune Deficiency*, Wiley, New York, pp. 133-146. Session I Friday 10.40 - 11.00 a.m.

DNA BINDING PROTEIN INDUCED BY IONIZING RADIATION

M.F. Lavin, S.P. Singh, K. Hobson, I. Myoshi and B. Teale

Molecular Oncology, Queensland Institute of Medical Research, Herston Qld 4006

Exposure of mammalian cells to a number of stress-causing agents leads to activation of existing proteins and preferential transcription of certain genes. A recent report by Glazer *et al* (1989) showed that UV radiation led to induction of several DNA-binding proteins by a mechanism that did not involve *de novo* protein synthesis.

A recent report (Singh *et al* 1989) describes the presence of a constitutively active DNA-binding protein in extracts from ataxia-telangiectasia cells. This syndrome is characterized by radiosensitivity and predisposition to cancer. The DNA-binding protein observed in A-T extracts binds to a region of the SV40 enhancer located between the binding site for transactivating factors AP-3 and AP-5. It was only possible to detect the same binding activity in normal cells after exposure to γ -radiation. We describe here radiation dose-dependence and time course of activation of this protein and some of its characteristics using the SV40 enhancer sequence for binding studies. It is not clear at this stage whether this activity protein is involved in DNA repair or DNA replication.

P.M. Glazer, N.A. Greggio, J.E. Methherall and W.C. Summers (1989) *Proc. Natl. Acad. Sci. U.S.A.* 86, 1163-1167.

S.P. Singh, P. Le Poidevin and M.F. Lavin *Proc. Aust. Bioch. Soc.* 1989.

**Detection of ataxia-telangiectasia
heterozygotes: Methods based on radiosensitivity**

Priscilla Le Poidevin, Surinder Singh and Martin F Lavin
Molecular Oncology, Queensland Institute of Medical Research,
Bramston Terrace, Herston, Queensland 4006.

A-T has aroused interest not only because of the relationship between a defect in coping with damage to DNA and predisposition to malignancy but also because A-T heterozygotes or carriers of the gene have an elevated risk of developing several forms of cancer (Swift *et al* 1976). It has been estimated that A-T heterozygotes represent about 1% of the general population. Swift *et al* (1976) demonstrated an elevated risk of malignant neoplasms in the families of patients with A-T and suggested that up to 5% of deaths from cancer under the age of 45 may be due to A-T heterozygosity. Swift *et al* (1987) have recently determined that the relative risk of cancer was 2.3 for men ($P = 0.014$) and 3.1 for women ($P = 0.084$) amongst persons heterozygous for ataxia-telangiectasia. The cancer most clearly associated with A-T heterozygosity was breast cancer, showing an estimated relative risk of 6.8. With a frequency of 1-3% in the general population anything from 7-20% of breast cancer patients could be A-T heterozygotes. A recent British study has also shown a statistically significant ($P < 0.05$) excess of deaths from breast cancer in A-T heterozygotes (Pippard *et al* 1988).

Clearly a sensitive, reliable and simple assay would be useful in the detection of A-T heterozygotes amongst cancer patients. Recently two important developments in this laboratory in the study of the biochemical defect in A-T have paved the way for the establishment of reliable assays for A-T heterozygotes. These assays are based on G2 phase delay and DNA protein binding.

Pippard, E.C., Hall, A.J., Parker, D.J.P. and B.A. Bridges (1988) *Cancer Res.* 48, 2929-2932.

Swift, M., Reitnour, P.J., Morrell, D. and C. Chase. (1987) *New Engl. J. Med.* 316, 1289-1294.

Swift, M., Sholman, L., Perry, M. and C. Chase (1976) *Cancer Res.* 36, 209-215.

DETECTION OF IONIZING RADIATION-INDUCED DNA
DOUBLE-STRAND BREAKAGE IN MAMMALIAN CELLS

by

Ian R. Radford

Molecular Sciences Group
Peter MacCallum Cancer Institute
481 Little Lonsdale Street
Melbourne, Australia

Abstract

Results obtained using two different methods to measure radiation-induced DNA double-strand breakage (dsb) will be presented.

Non-denaturing filter elution has shown a non-linear induction of DNA dsb by low let radiation. The validity of this result and possible explanations for its occurrence will be examined.

Pulsed field gel electrophoresis has been used to examine DNA repair and degradation following irradiation of mouse lymphoma lines that do or do not display rapid interphase death.

RADIATION INDUCED DNA DAMAGE - PROTECTION BY DNA LIGANDS

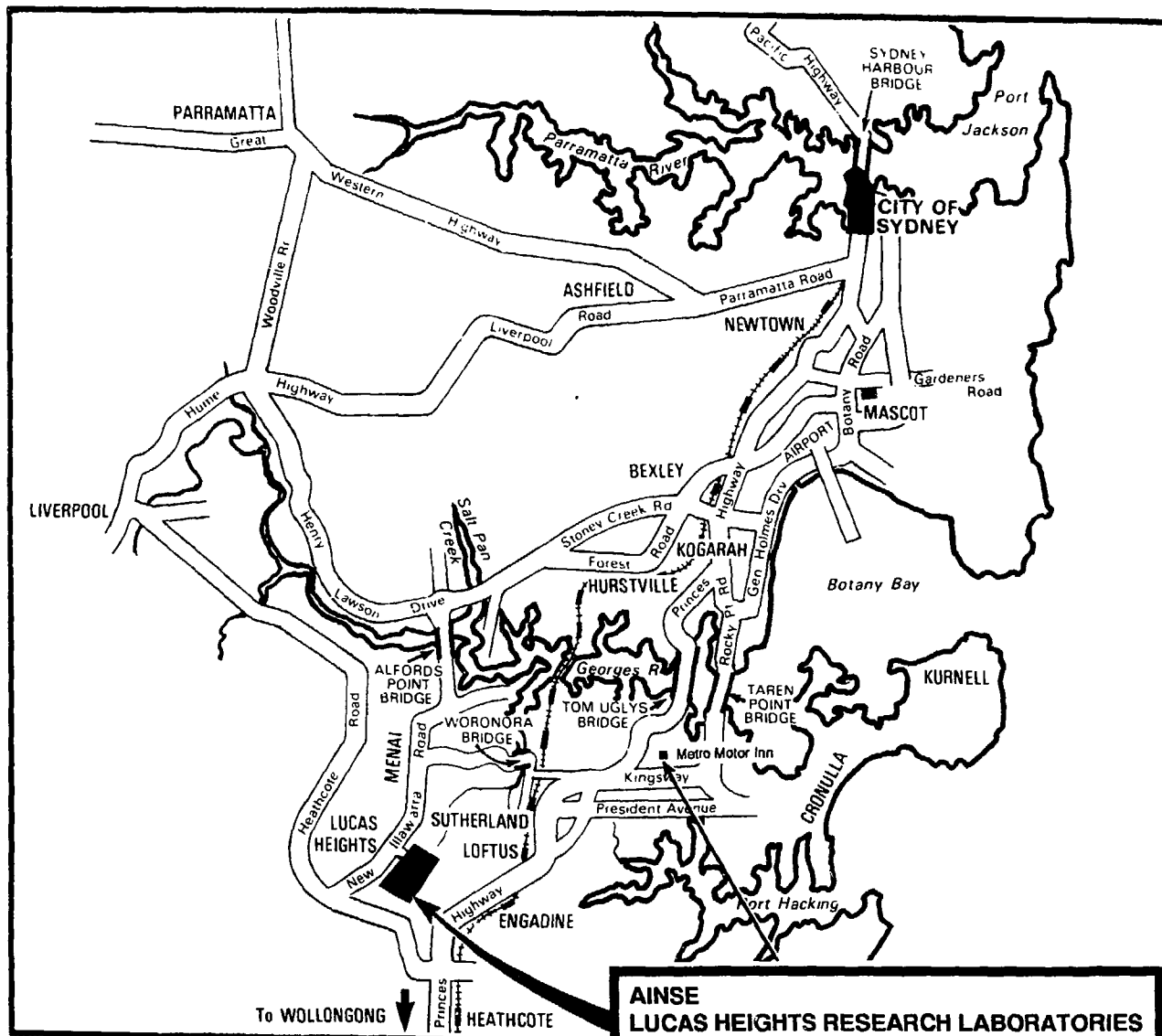
L. Denison and R.F Martin

Molecular Sciences Group, Peter MacCallum Cancer Institute
Melbourne

The death of cells induced by ionizing radiation is considered to be primarily due to lesions produced in DNA, and in particular, double strand breaks. This damage is due partly to a direct effect and partly to an indirect effect. The indirect effect is caused by ionization in the vicinity of DNA, and subsequent reaction between DNA and the reaction of OH radicals or other products of water radiolysis. The direct effect is caused by ionization of the DNA itself with the subsequent formation of a radical cation in the nucleobases. For DNA in dilute aqueous solution, the effects of irradiation by ionizing radiation are caused by the indirect effect.

Using a ^{60}Co -gamma source, we have undertaken a study of a particular group of DNA ligands as radioprotectors against radiation-induced strand breaks in plasmid (pBR322) DNA. Production of single-strand breaks are detected as nicked circles and double-strand breaks as linear molecules. All three plasmid DNA species can be resolved from each other by agarose gel electrophoresis. Laser densitometry provides a convenient method to quantitate the production of both types of strand breaks. The results of these experiments indicate that at a concentration of 25 μM of ligand, the dose modification factor is approximately 4.

Sequencing gel experiments have also been undertaken to ascertain whether the protection observed is specific to the binding sites of the ligand or if it is more generally distributed along all the sites of radiation-induced strand breaks. Results of experiments carried out using 3'- ^{32}P -100bp fragment of pBR322, indicates the presence of both types of protection.



AINSE
LUCAS HEIGHTS RESEARCH LABORATORIES
New Illawarra Rd, Lucas Heights
Postal Address: Private Mail Bag 1,
Menai Nsw 2234
TEL (02) 543 3388, 543 3411
FACSIMILE (02) 543 7802

DEATH BY CELL CYCLE ARREST

by

Simon J. Davis and Leigh A. Burgoyne

Sir William Dunn School of Pathology, South Parks Road,
University of Oxford, United Kingdom, OX1 3RE and School of
Biological Sciences, Flinders University, Bedford Park, South
Australia, 5042.

ABSTRACT

DNAase-I based probes, of various types, attack nuclear DNA in a manner that is now well known to be sensitive to the higher order structure of chromatin. Thus, normally organised nuclear chromatin, has in a variety of organisms, a mode of digestion that is "disomal" in character. Such chromatin produces a very diffuse series of DNA fragments, that on gel analysis are principally characterised by an arithmetic series, the disomal series, $2N, 4N, 6N$ etc. Where N is the average length of the DNA associated with one nucleosome, hence the series based on $2N$ is referred to as disomal.

On exposure of cultured HL-60 cells to the drug colchicine, two events were noted. The first is that the cells rapidly became inviable although apparently still intact. The second was that the disomal digestion "signature" of normal chromatin changed into a monosomal signature, indicating a major change of structure had occurred at the supranucleosomal level.

Colchicine is well known to cause arrest of the cell cycle and lethality but is known to have little or no rapid effects on transcription, translation or energy supplies and, further, our studies did not find any evidence of proteolysis of the chromatin or direct nucleolysis of the DNA.

Thus it appears that some sort of loss of higher-order structure of chromatin appears to be one of the earliest symptoms of this particular type of lethal arrest of the cell cycle.

AMINO ACID AND PROTEIN PEROXIDES

by

J.M. Gebicki and S. Baumgartner

School of Biological Sciences, Macquarie University

North Ryde, Australia

The last two decades have witnessed a great expansion of interest in free radical-induced oxidation of biomolecules. Virtually all reported studies concentrated on the formation and reactions of lipid peroxides, which have a demonstrated role in general tissue damage and onset or development of many diseases. In comparison with lipids, peroxidation of amino acids and proteins was neglected, in spite of brief reports of its occurrence over 30 years ago [1,2].

We have found recently that an assay technique developed for the measurement of lipid peroxides can be applied to other biomolecules. Oxidation of two proteins - BSA and lysozyme - was followed in molecules exposed to gamma rays in presence of air. Hydroperoxide groups generated were identified by reduction with a variety of reagents. The oxidizing radical was the hydroxyl while superoxide was ineffective. Presence of transition metals gave no significant increase of the degree of protein peroxidation.

We have also tested all the common amino acids for their susceptibility to peroxidation. Only those possessing a tertiary carbon or a side-chain with two or more CH_2 groups formed stable peroxides. At present it is not known whether susceptibility of amino acids to free radical-induced peroxidation is altered by their incorporation in a protein.

- [1] R. Latarjet and J. Loiseleur, *Comp. Rend. Soc. Biol.* 136, 60 (1942)
- [2] S. Okada in "Organic Peroxides in Radiobiology"
"(R. Latarjet, ed) pp. 46-48, Pergamon Press (1958)

RELATIONSHIP BETWEEN THE LEVELS OF VITAMIN E AND
OXIDIZABILITY OF HUMAN LDL.

by

A.V. Babiş and J.M. Gebicki

School of Biological Sciences, Macquarie University
North Ryde, Australia

A crucial phenomenon in the development of atherosclerotic plaques is the accumulation of lipids in the intima region of arteries. These lipids are made up principally of cholesterol esters, derived from low density lipoproteins (LDL) circulating in blood, which accumulate in monocyte derived macrophages migrating to the site of lesion.

Normally these cells only take up sufficient LDL for their cholesterol requirements. However, under some conditions the regulation of LDL uptake can break down, lipid uptake becomes uncontrolled, and the affected cells are converted to lipid - laden foam cells.

Oxidative modification of LDL is believed to increase its uptake by macrophages and monocytes and enhance their transformation into foam cells.

A number of studies have suggested that vitamin E can prevent these events by protecting LDL lipids from oxidation. However, there are indications that other factors also contribute to the antioxidant potential of LDL in vivo. We have tested the role of vitamin E in protecting the LDL, using improved methodology for the assay of lipid peroxides.

Human LDL was exposed to oxygen free radicals generated by gamma rays and the formation of peroxides and changes in levels of vitamin E were measured. The results showed that there was no correlation between the initial levels of vitamin E and the amount of peroxide formed after exposure of the LDL to a standard quantity of oxygen radicals. The vitamin performed its antioxidant role by conferring some early protection to the lipids, being consumed in the process. However, it is clear that additional factors are also instrumental in determining the total antioxidant potential of the human LDL.

BILIRUBIN AS AN ANTIOXIDANT

R. Stocker

The Heart Research Institute,
145 Missenden Road, Camperdwon,
Sydney NSW 2050

Abstract

Abstract unavailable at time of printing

RADIUM INTESTINAL TRANSFER STUDIES

by

Renate U. Domel and Dr A. M. Beal*

Environmental Science Program
 Biological Impact Studies
 ANSTO
 Lucas Heights, NSW, Australia

Abstract

Previous work has shown that ^{226}Ra is concentrated within the tissues of fresh water mussels in insoluble granules. It is present as an insoluble phosphate compound together with Ca, Mg, Ba, Fe and Al. Because mussels form part of the traditional diet of Aborigines, this work has been set up to measure the transfer rate of this radium-226 species as it is found in the mussel tissue, in comparison to radium as a simple chloride, across the gut wall of rats to gain comparative information for human dose rate calculations.

FEED TRIALS

Standard rat cages were adapted to allow separate faeces and urine collection, as well as a measured food dose.

Freshwater mussels are obtained from the Northern Territory (supplied by the OSS). These are fed with algae and a radium-226 dose is added daily, after which the mussel tissue is removed from the shell, dried and blended to obtain a powder of even particle size. Pelleted laboratory animal feed (Milling Industries LTD), for which a content analysis from the company has been obtained, was blended and sieved to produce a powder of even particle size.

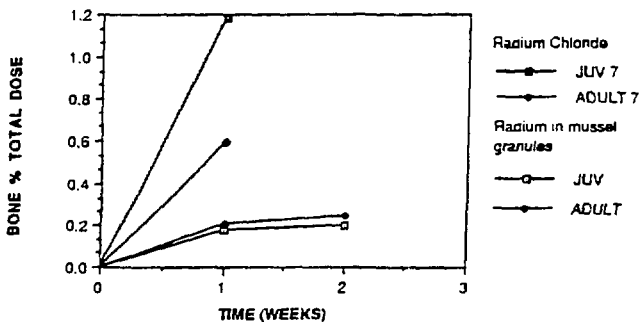
Feed trials using the above two ingredients were commenced in February 1987 and results have been obtained for 7, 14, 28, and 56 days dosage of female juvenile rats (4 weeks old) and female adult rats (12 weeks and over).

Radium as the chloride has been incorporated into the standard laboratory rat food and a gut transfer rate obtained for juvenile and adult female rats for a seven day feed period.

The results, Fig. 1., for the above work show:

- some radium from the fresh water mussel tissue is available for transport across the intestinal membrane but the transport rate is less than that for radium chloride.
- the rate of radium transport and uptake, mainly onto the bone tissue, is greater for juvenile rats than adult rats.

FIG. 1. BONE % TOTAL FED DOSE



*School of Biological Sciences,
 University of NSW,
 Kensington, Australia

RISK EMPLOYMENT MISBELIEFS

F.P.J. Robotham

Director, Safety Health and Risk Management
University of Melbourne

Abstract

The history of permissible radiation exposure levels is one of steady reduction. From the first limit of 1% of an erythema dose per day to today's complex confusion of dose limits the trend has been down, down, down.

In 1987 the International or Commission on Radiological Protection (ICRP) received the latest (final?) assessment of radiation doses by the people of Hiroshima and Nagasaki following the atomic bombing of these two cities.

There are apparent increases in risk associated with the type of acute exposure received during nuclear explosions.

Shortly after the ICRP review, the UK National Radiological Protection Board announced an interim threefold reduction in occupational whole body radiation exposures, from 50mSv/y to 15mSv/y. ICRP have declined to make any specific recommendations before the issue of their revised magnum opus due in 1990.

This paper will discuss the current radiation risk perspective, the implications of any reductions on employment and some of the misbeliefs associated with radiation.

RADIATION DOSES VIA INHALATION AND INGESTION
UNDER THE CURRENT AND PROPOSED ICRP MODELS.

by

John R. Twining

Biological Impacts Project
Environmental Science Program
Australian Nuclear Science and Technology Program

Abstract

The ICRP are considering lowering the limits for radiation exposure by at least a factor of two. In the Australian sand-mining industry the implications of this decision are that exposure limits will probably be exceeded if the current models for dose estimation are retained. In fact, the current limits are proving difficult to achieve due to the nature of the separation processes involving monazite. If default AMAD values are used and respiration protection factors are not applied using the current model some workers could be considered to be over-exposed.

However, as part of the process of redefinition, the ICRP task group on lung dynamics will also be presenting a revised inhalation exposure model which will appear fairly soon after the new recommendations are released. The biological bases for the new model are discussed as is the likely influence the new lung model will have on dose assessment via inhalation and ingestion, which are the critical pathways in the sand-mining industry.

The current and proposed models are described and the performance of the models is compared for class Y materials in which thorium (the main radiotoxic constituent of monazite) is included. Doses to lymph and bone from translocated inhaled material are considered with reference to clinical data, as are the dose implications of material translocated to the gastrointestinal tract from the lungs or from direct ingestion.

The general effect of the new model is such that by using more realistic deposition and clearance factors the committed effective dose equivalents are reduced by a factor of 5-10 thereby more than compensating for the expected reduction in ICRP exposure limits when applied with the current lung model.

RADIATION RISKS IN THE MINERAL SANDS INDUSTRY

G. S. Hewson and B.M. Hartley

Department of Mines
 100 Plain Street
 EAST PERTH WA 6004

Abstract

Potentially significant radiation hazards exist in the Mineral Sands Industry. The hazards derive from the production and handling of the "heavy" mineral sand product monazite, a rare earth phosphate, containing approximately 6% thorium by weight. External radiation levels may range from less than $1 \mu\text{Gy.h}^{-1}$ to $10 \mu\text{Gy.h}^{-1}$ in the general plant environment, to greater than $50 \mu\text{Gy.h}^{-1}$ in monazite storage areas. Internal radiation hazards may also be significant as a result of the inhalation of long lived alpha emitters associated with dust. Airborne gross alpha activity levels vary from less than 0.05 Bq.m^{-3} to about 5 Bq.m^{-3} .

Recent estimates [1] of radiation exposure, using assessment protocols and data contained within ICRP Publications 26 and 30 indicate that approximately 15% of the Mineral Sands Industry workforce exceed the formal investigation level of 15 mSv/y . A small percentage of workers are estimated to be receiving radiation doses approaching or exceeding the statutory 50 mSv/y limit. Recent reviews [2,3] of ICRP models and data reveal that the assessment protocols and default values used in the estimation of internal radiation dose may be overly conservative. It has been suggested that present internal radiation dose estimates to mineral sands workers are overstated, by possibly up to an order of magnitude or more.

In this paper, the basis for present assessment procedures is briefly reviewed, as are the major areas of uncertainty in dose estimation protocols. Regulatory and remedial actions in response to the supposedly high radiation dose estimates are described. Current approaches to risk reduction are outlined and possible future approaches are postulated. The need to adopt a flexible regulatory approach in view of the uncertainty in radiation dose estimates is highlighted.

Future priorities for radiation biology research are suggested, together with a discussion on the practicability of obtaining better estimates of internal radiation dose.

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**DAMAGE TO LYMPHOCYTES BY X-RAY AND BLEOMYCIN TREATMENT
MEASURED WITH THE CYTOKINESIS-BLOCKED MICRONUCLEUS TECHNIQUE**

by

Y. Odagiri and A.A. Morley

Department of Haematology
Flinders Medical Centre
Bedford Park, SA 5042, Australia.

Abstract

The resistance of tumour cells to radio- or chemo-therapeutic agents is a major obstacle to effective treatment of human malignancies. In contrast, high susceptibility of normal cells of bone marrow to these agents could cause marrow failure, which may complicate effective treatment. Therefore, it may be of value to determine the resistance of target cells to the agent *in vitro* before starting therapy. In the present study we are using lymphocytes from healthy individuals as model proliferating cells, and the degree of resistance to X-ray irradiation and bleomycin treatment was measured using micronucleus induction as an endpoint. Bleomycin and X-irradiation are both being studied as they act similarly in causing DNA strand breaks. The cytokinesis-blocked (CB) micronucleus technique using antikinetochore antibodies¹ is being used as it enables chromosome breakage and chromosome loss to be separately measured.

Studies were performed on cord blood from 6 newborns, and on venous blood from 8 young (mean age 34.5 ± 5.7) and 8 elderly (mean age 78.0 ± 4.2) subjects. The results showed that the effect of X-ray irradiation was not different between the three different age groups. This observation is consistent with our previous results.² In contrast, there was a significant increase in effect of bleomycin with age. The positivity rate for the antacentromere antibody reaction was clearly higher in bleomycin-induced than X-ray-induced micronuclei.

These results suggest that the type of DNA damage induced by X-irradiation is different from that induced by bleomycin, and that the increased effect of bleomycin with age is due to induction of both chromosome breaks and whole chromosome loss.

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THE EFFECTS OF CELL CYCLE ON THE MOLECULAR BASIS
OF X-RAY INDUCED MUTATIONS AT AN AUTOSOMAL LOCUS

by

J. Condon and D.R. Turner

School of Medicine, Haematology Unit
Flinders University of South Australia
Bedford Park, S.A. 5042, Australia

Abstract

Mutations at autosomal loci involving loss of heterozygosity, resulting in hemizygosity or homozygosity, have been shown to occur at critical gene loci in many human cancers. Causative genetic mechanisms include simple gene deletion, non-dysjunction events resulting in whole chromosome loss or loss and duplication of the homologous chromosome, mitotic recombination and gene conversion.

Measurement of mutation in human somatic cells has generally been conducted at the X-linked HPRT locus in human T-lymphocytes. These studies have demonstrated that the majority of mutations resulting from X-irradiation are due to gene deletion¹ and that a dose response exists between mutation frequency and X-ray dose. Also, the mutation frequency of resting (Go) cells has been shown to be higher than that for cycling cells.

HPRT is functionally hemizygous and cannot therefore be used as a model for somatic mutations at autosomal loci. As carcinogenesis is considered to occur primarily via somatic mutations mostly acting at autosomal loci, we thought it also desirable to study mutations induced by X-radiation at an autosomal locus. Such a study may permit recognition of genetic mechanisms involving homologous chromosomal interactions which lead to mutation.

Results from this department have shown that mitotic recombination, which has been observed in a substantial proportion of X-ray induced mutation, is a major mutational mechanism by which heterozygosity is lost at an autosomal locus.²

Human T-lymphocytes (Go cells or PHA-stimulated cells) from a HLA-A1, A2 heterozygous individual have been X-irradiated at 0, 50, 100, 200 and 400 cGy. The mutation frequency has been enumerated by immunoselection of cells having lost the A2 phenotype.

Following immunoselection cells mutated at the HLA-A2 locus have been clonally expanded. Southern analysis has been done using the A2 locus to determine the molecular basis of, and frequency of mutations arising from deletions, point mutations and mitotic recombination.

The extent of mitotic recombination can be mapped using other heterozygous markers on chromosome 6, the location of the HLA locus in humans.

These studies have bearing on the mechanisms of radiation induced carcinogenesis and the relative radiation sensitivities of resting and dividing cells.

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GADOLINIUM NEUTRON CAPTURE

R.F. Martin, *A. Whittaker, G. D'Cunha,
A. Haigh, M. Pardee, †B.J. Allen and †D.P. Kelly

Molecular Sciences Group, Peter MacCallum Cancer Institute,
Melbourne

*Department of Organic Chemistry, University of Melbourne

†Australian Nuclear Science and Technology Organisation,
Menai, NSW

The potential for exploitation of the ^{10}B -neutron capture (NC) reaction for cancer therapy has been recognised for some time. The thermal neutron capture cross-section for ^{10}B is much higher than that for the nuclides prevalent in biological material. Moreover the ^{10}B -NC reaction results in fission to form an alpha particle and a ^7Li atom, each with a range of the order of a cell diameter. Thus the concept of boron neutron capture therapy (BNCT) depends on the use of ^{10}B -labelled pharmaceuticals that can be delivered preferentially to tumour cells, relative to normal cells in the neutron irradiation field.

In the development of the rationale for BNCT, nuclides with higher thermal neutron capture cross sections than ^{10}B (eg. ^{157}Gd , ^{113}Cd) were considered inappropriate because the NC reactions are of the n, gamma type, rather than fission. Most of the energy released in such reactions is dissipated over relatively long distances. However we have re-examined the case of ^{157}Gd , which has the highest thermal neutron capture cross section of all naturally occurring nuclides. In particular we addressed the possibility that conversion of some of the gamma energy, might result in the emission of low energy Auger electrons. Auger electron emission is associated with the disintegration of isotopes that decay by electron capture and/or internal conversion, resulting in intense, localised radiochemical. For example decay of DNA-associated ^{125}I results in the induction of DNA double-strand (ds) breaks, and incorporation of ^{125}I into DNA, or treatment with ^{125}I -labelled DNA ligands, is cytotoxic.

Our experiments have shown that irradiation of mixtures of Gd^{3+} and plasmid DNA with thermal neutrons results in the induction of DNA ds breaks. Inclusion of EDTA markedly reduces the damage, indicating the requirement that the GdNC event must be closely associated with DNA to induce a DNA ds break. The results clearly indicate a potential for ^{157}Gd -labelled DNA ligands for NCT.

We are synthesising a number of DNA ligands conjugated to macrocyclic chelators. In the meantime, control experiments involving irradiation of V79 cells with thermal neutrons in the presence of Gd-citrate, indicate that relatively high concentrations of non-DNA-bound Gd are required to increase cell kill.

THRESHOLDS IN THE ASSESSMENT OF CHEMICAL CARCINOGENS

by

F. Paula Imray

Toxicology Evaluation Section
Environmental Health Branch
Dept of Community Services and Health
Canberra ACT 2606

ABSTRACT

Risk assessment of carcinogens is a controversial issue. Insight into the mechanisms of action enables a better assessment of risk from carcinogenic chemicals.

Long-term bioassays in rodents provide the basis for carcinogenic risk assessment for many chemicals. Other information which should be taken into account is;

- . chemical structure
- . metabolism/toxicokinetics
- . qualitative and quantitative physiological effects
- . organ specificity
- . strain or species specificity
- . dose-response relationships
- . short term genotoxicity tests
- . human data

Carcinogens may act by different mechanisms and one important distinction is whether a carcinogen is genotoxic or not. Genotoxic carcinogens interact with DNA and may induce gene mutations, alter gene expression or cause chromosome aberrations.

Genotoxic carcinogens may be effective after a single exposure and may be cumulative in effect. Chronic studies in rodents, using a limited number of animals, may demonstrate a threshold. However, theoretically, such a threshold cannot be expected for direct acting carcinogens. For regulation of such chemicals a conservative approach is needed.

Non-genotoxic carcinogens, or carcinogens which produce their effects indirectly, may show a threshold in their dose-response curve and the existence of the threshold may be used in risk assessment.

Carcinogenic chemicals must be evaluated on each individual case and all available toxicology information considered in assessment of risk to humans.

ARE OXIDISED PROTEINS DAMAGING SPECIES ?

by

J.A. Simpson and R.T. Dean

The Heart Research Institute,
145 Missenden Road, Camperdown,
Sydney, NSW 2050.

Abstract

Proteins can be oxidatively modified in a variety of ways (1,2). Protein hydroperoxides have been identified as species generated upon oxidised protein (3). We have set out to investigate whether certain oxidised proteins and their products are also reactive damaging species.

Gamma-irradiated bovine serum albumin (BSA) reduces cytochrome c as assessed by its change in absorbance at 550nm; native albumin has no effect. Part of the response with irradiated BSA was superoxide dismutase (SOD)-inhibitable and the effect with the same irradiated sample was stable for at least 14 days. The response was quenched by the addition of copper 2+ ions, was not inhibited by catalase and does not appear to correlate with the extent of detectable hydroperoxide species. The absorbance spectrum was similar after exposure to irradiated BSA, superoxide radicals or dithionite. So far we have shown that irradiated BSA can reduce cytochrome c but the nature of the active groups is still unknown; this is what we shall investigate further, as well as the possibility of any other reaction routes.

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MORPHOLOGICAL CHANGES IN MELANOMA CELLS FOLLOWING IRRADIATIOND.H. Barkla¹, B.J. Allen², J.K. Brown², S. Buck²

1 Monash University, Clayton Vic 3168

2 ANSTO, Lucas Heights NSW 2234

Abstract

Three lines of melanoma cells (two human, one murine) were propagated in tissue culture flasks and then subjected to either gamma-irradiation (using a ⁶⁰Co, source) or thermal neutron irradiation (in the MOATA reactor). Some flasks were treated with ¹⁰B boronophenylalanine (BPA) prior to neutron irradiation to simulate neutron capture therapy (NCT). Flasks of cells were then fixed at 24 hr intervals over the next 20 days and prepared for examination using light microscopy and transmission electron microscopy. Other flasks of cells were analysed for melanin content before and after irradiation.

During days 1-5 after irradiation many cells detached from the floor of the flasks and died. Changes in cell morphology after irradiation were similar for gamma-treated and ¹⁰B +ve and ¹⁰B -ve NCT-treated cells. Early changes seen during days 1-3 included abnormalities in both the plasma membrane and the nuclear membrane of melanoma cells, changes presumably leading to cell death. During days 6-12, surviving cells showed evidence of differentiation into subpopulations of cells showing increased melanin content. During days 13-20, these changes continued and, in addition, flasks were gradually repopulated with cells having a morphology similar to that of the pre-irradiated cells. The apparent increase in melanin content after irradiation was confirmed statistically using a melanin assay.

The results suggest that gamma and thermal neutron irradiation operate similarly, and disrupt the integrity of both nuclear and plasma membranes. The relationship between these changes and damage to DNA is unclear. Morphological changes distinctive of the neutron capture reaction of thermal neutrons by ¹⁰BPA were not apparent.

CLONING THE RAD4 GENE OF SCHIZOSACCHAROMYCES POMBE

Authors: M. FENECH*, A. CARR**, A.R. LEHMANN** AND F.Z. WATTS***

* CSIRO Division of Human Nutrition, Kintore Avenue, Adelaide, South Australia, Australia 5000

** MRC Cell Mutation Unit, University of Sussex, Brighton, United Kingdom

*** Microbial Genetics Unit, School of Biological Sciences, University of Sussex, Brighton, United Kingdom

The RAD4 mutant of S. pombe is temperature sensitive for cell division and hypersensitive to UV and gamma-irradiation. The RAD4 gene was cloned by transfection with a partial HIND III genomic DNA library in pDB262. Under selective culture conditions (Leu- medium, 37°C) two colonies were obtained that were apparently transfected and completely restored to the wild-type phenotype. The insert in the complementing plasmid was 2.6 Kb in size. Southern analysis of integrants and appropriate genetic crosses confirmed that the complementing DNA was in fact located at the site of the RAD4 gene. The insert has an ORF at base no 1045, is missing the 3'(C-terminal) end, probably has two introns and shows no homology to other known genes.

SENSITISATION OF PHOTO-CLEAVAGE OF DNA BY AN IODINATED
DNA LIGAND - MECHANISTIC STUDIES

L.E. Bennett, R.F. Martin and R. Cooper*

Molecular Sciences Group, Peter MacCallum Cancer Institute,
Melbourne.

*Department of Physical Chemistry, University of Melbourne

Hoechst 33258 belongs to a series of substituted bis-benzimidazoles which have been shown to bind strongly to DNA. Upon substitution of an iodine atom, this ligand sensitizes DNA to strand cleavage following irradiation with UV light. Extensive study of the site-specificity of DNA damage has given support to the proposed mechanism that photolytic de-iodination generates a carbon-centred free radical in close proximity to the DNA sugar-phosphate backbone. Abstraction of a hydrogen atom from a 5' carbon of deoxyribose in DNA is thought to occur with regeneration of the iodine-free Hoechst molecule. The carbon-centred radical on the deoxyribose then initiates a series of reactions which result in strand cleavage.

The photochemical properties of iodo-Hoechst compounds, together with their iodine-free analogues, have been investigated in order to further elucidate the proposed mechanism. Fluorescence quantum yield measurements of each species appear to support the theory that homolytic cleavage of the carbon-iodine bond proceeds via the triplet state; and that iodination decreases the fluorescence quantum yield. The greater fluorescence quantum yield of the non-iodinated Hoechst 33342 species, and its red-shifted emission maximum, provides a means to monitor the changes in the spectral characteristics of the sensitizer which result from or accompany the DNA strand cleavage event.

**DEATH (APOPTOSIS) OF CELLS IRRADIATED
IN S-PHASE IN NEONATAL TISSUES**

by

J. Allen, B.V. Harmon, D.J. Allan, and G.C. Gobé

Pathology Department
University of Queensland Medical School
Herston, Australia

Abstract

The radiosensitivity of cells is cell cycle dependent. Cells are generally considered to be more resistant to irradiation in the latter part of the DNA-synthetic phase (S phase) and more sensitive in mitosis and at the boundary between G₁ and the beginning of S phase. We have previously shown that x-irradiation causes a massive enhancement of cell death by apoptosis in a variety of neonatal tissues (Allan et al, 1988; Gobé et al, 1988). In this study, we have examined the proportion of cells, in S phase at the time of irradiation, that die by apoptosis in two neonatal tissues, the kidney and testis.

Cells were labelled with ³H-thymidine 1h prior to irradiation (to indicate cells in S phase), or 1h prior to the neonates being killed (to indicate any changes that irradiation produced on the S phase of the cell cycle). A quantitative comparison was made, from the resultant autoradiography, of the numbers of ³H-thymidine-labelled normal or apoptotic cells at 4, 8 and 24h after irradiation.

In the kidney, apoptosis peaked 4h after irradiation, and a high proportion of the apoptotic cells were labelled. This suggests that S phase cells in the neonatal kidney are, in fact, sensitive to the effects of irradiation. By contrast, very few of the apoptotic cells in the irradiated testis were labelled, suggesting that, in this tissue, S phase cells are relatively resistant to the effects of irradiation.

The marked variation shown in the radiosensitivity of S phase cells in this study suggests that the use of endpoints other than "reproductive death" should be considered when undertaking radiobiological studies.

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EXTREMELY LOW FREQUENCY ELECTROMAGNETIC
FIELDS AND CANCER

by

M.H. RepacholiChief Scientist
Royal Adelaide Hospital
Adelaide, South AustraliaAbstract

The debate on whether exposure to 50/60 Hz fields will cause cancer in humans continues in both the scientific arena and among the general public. Citizens action groups have been partly successful in many countries in halting or delaying construction of new power lines. Legal action has been taken by cancer victims living near power lines - at great expense to all concerned. The public is genuinely concerned that definitive answers are not forthcoming. However in this age of rapid communications and higher standards of education, people observe the process of scientific debate, but demand answers before the debate has run full course.

Millions of dollars are presently being spent on both laboratory and epidemiological studies to determine if a correlation exists between cancer incidence and the exposure of humans to 50/60 Hz electromagnetic fields. Findings from both of these areas of study are discussed and attention focused on their relevance to the electromagnetic field-cancer debate. So far, the conflicting results from epidemiology have succeeded only in raising the concerns of both occupationally exposed groups and the general public. Laboratory findings have suggested mechanisms by which fields could exert biological effects. However, as yet, there is insufficient evidence to indicate if these mechanisms have any relevance to human health.

The complex issues of cancer initiation and promotion, and our lack of detailed understanding of their mechanisms have added confusion. It will be at least another three to five years before there are results from large scale human studies presently being designed or undertaken. However, from an objective review of existing scientific data it can only be concluded that exposure to 50/60 Hz electric and magnetic fields at levels occurring in our environment have not been established to lead to cancer in humans. However, sufficient gaps in our knowledge exist to recommend that research continue.

REVIEW OF THE EPIDEMIOLOGICAL STUDIES LINKING ELF ELECTROMAGNETIC
RADIATION WITH CANCER

BY

A.J. CHRISTOPHERS

DEPARTMENT OF PHARMACOLOGY
UNIVERSITY OF MELBOURNE
PARKVILLE, VICTORIA

ABSTRACT

Epidemiological studies linking ELF electromagnetic radiation with cancer may be divided into two groups depending upon whether the source of the radiation was in the home or was occupational. In both groups the claimed link is with the magnetic component of the radiation, not the electric.

In the first group, there are three studies claiming a link between the home exposure to ELF radiation and childhood cancer. All of them used wiring code configurations as a surrogate for magnetic field measurement.

The first study claiming a link was made by Wertheimer and Leeper in the USA in 1979. This study breached one of the most fundamental principles of epidemiology which is that hypothesis generating data must not be included in hypothesis testing data. Another study claiming to confirm the first study was made by Tomenius in Sweden a few years later. So flawed was this study that its claims must be rejected. A well-conducted study was made by Savitz in the USA in 1988. Savitz found a very weak association between ELF exposure and childhood cancer. So weak was the association that it could be argued that it contradicted, rather than supported, the claim by Wertheimer and Leeper.

In the second group, there have been many studies all of which have relied on the occupation as recorded on the death certificate or with the cancer registry as a guide to ELF exposure. For any such study to be successful, it would need to compare the cancer record in an occupation with some outstanding exposure to ELF radiation with that of other occupations without such exposure.

Until very recently there has been very little actual measurement of magnetic field exposures associated with different occupations and only one occupation has stood out as having excessive exposure to ELF magnetic fields - the occupation of welder.

The studies in this second group have all relied on the simplistic assumption that occupations such as electricians, radio-operators, telephone lineman, etc are associated with excessive exposure to ELF radiation.

One reviewer has taken the data on welders out of these studies and done a meta-analysis of sorts and has found that the combined results show no excessive cancer in welders.

So far no study in either group has made a sufficiently good case for an association between ELF exposure and cancer for it to serve as a basis for action other than for further research.

IMPACT OF REDUCED RADIATION LIMITS ON ENVIRONMENTAL MEASUREMENTS

by

M.W. CARTER & A. JOHNSTON
OFFICE OF THE SUPERVISING SCIENTIST
BONDI JUNCTION
NSW 2022

Abstract

In recent years the radiation limit for members of the public has reduced from 5 mSv per year to 1 mSv per year (1). There have also been changes in the recommended dosimetric data for a number of radionuclides, in particular for thorium (2).

Monitoring of relevant increases in environmental air contamination resulting from technologically enhanced sources of naturally occurring radionuclides is now particularly difficult as the signal which is to be measured is within the range of the natural background noise.

For example the derived public limit for Radon 222 is now 2 mWL, but typical natural values vary with weather conditions and range from 0.1 to 5 mWL (3). Thus detection of increases above this natural level that are within the public limit requires great care in measurement and interpretation.

In the case of thorium 232, the derived air contamination limit for workers has been reduced by a factor of about 50 which has caused significant difficulties for the sand mining industry in controlling their workers' doses. An equivalent derived air contamination limit for the general public must be reduced by a further factor of over 100 giving a derived air contamination limit of only 0.002 Bq/m³. While this value is greater than the naturally occurring airborne thorium activity (4) it is within the range of natural airborne gross alpha activity and thus it is impractical to measure by conventional methods.

Adequate assessment of public doses due to increased airborne amounts of naturally occurring radionuclides is thus hampered by the background signal or the required measurement sensitivity or both. These difficulties will be discussed.

An approach being developed to measure radon-222 originating from a uranium mining operation and which may be applicable to other similar situations will be described.

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EXPERIMENTAL STUDIES OF ^{226}Ra AND RADIOCALCIUM
ACCUMULATION FROM THE AQUATIC MEDIUM BY FRESHWATER TURTLES

by

Jeffrey R.A.

Environmental Science Program, ANSTO, PMB1, Menai 2234, Australia.

Abstract

Snapping turtles (*Elseya dentata*, Fam. Chelidae) from Magela Creek, Northern Territory, were exposed under laboratory conditions for up to 30 days to waters resembling the inorganic composition of Magela Creek water during the Wet season, with background and also elevated Ca and Mg concentrations, that were labelled with ^{226}Ra and ^{45}Ca . Tissue concentrations of ^{45}Ca equilibrated by 12-18 days of exposure to these experimental conditions and were inversely related to turtle mass. An increased Ca water concentration increased the normalised tissue concentrations of ^{45}Ca concentration by factors that were greater than or proportional to the factor of increase in Ca water concentration; an increase in the Mg water concentration reduced the ^{45}Ca tissue concentrations. The ^{226}Ra tissue concentrations were positively related to their ^{45}Ca concentrations. The increased Ca water concentration did not reduce the ^{226}Ra concentration but increased its concentration in some tissues. The increased Mg water concentration reduced the ^{226}Ra concentrations in most tissues.

Studies on the anatomical sites of accumulation from the aquatic medium showed that the cloacal route was at least four times more important than the buccopharyngeal route for ^{45}Ca and ^{226}Ra accumulation. The results of histological and electron microscopic studies on the cloacal bursae were consistent with them being an important site of ^{45}Ca and ^{226}Ra uptake within the cloaca.

RADIATION BIOLOGY AND RADIOTHERAPY

by

H. Rodney Withers, MBBS, D.Sc.
Professor of Oncology
Institute of Oncology & Radiotherapy
Prince of Wales Hospital
Randwick

Abstract

The major contributions of radiation biology to the clinical practice of radiation oncology have come about during the past 30 years. Some of these have been unsuccessful but all have resulted in an increased understanding of tumour biology and radiation biology.

The most important recent contribution of radiation biology to radiation oncology is an increased understanding of the factors determining the response of normal tissues and tumours to multi-fraction irradiation. Based on such understanding it is becoming increasingly easier to individualise patient therapy. The most important area of improved understanding in recent years is in the biology of dose fractionation.

Dose per Fraction:

It was realised in about 1980 that early and late responding tissues manifest, in a systematic manner, different responses to changes in size of dose per fraction. Late responding tissues show more sparing from reducing dose per fraction than do acutely responding tissues. This has provided additional justification for the use of hyper-fractionation which was initially introduced to exploit differentials in redistribution kinetics between late responding tissues and tumours.

Accelerated Tumour Growth:

Recently it has been convincingly demonstrated that human tumours accelerate their rate of growth at some time after the initiation of radiotherapy. In head and neck cancers, such acceleration is delayed for between three and five weeks. The average time for of a clinically detectable cancer to double in volume is two months. In the latter part of a course of treatment this is shortened to an average of about four days. This has major implications for how radiotherapy should be delivered.

The maximum therapeutic differential would be achieved from delivering the maximum dose tolerated by late responding tissues in the smallest logistically feasible dose per fraction given in the shortest overall time compatible with acceptable acute morbidity.

MICRONUCLEI IN CYTOKINESIS-BLOCKED LYMPHOCYTES OF CANCER PATIENTS
FOLLOWING FRACTIONATED PARTIAL-BODY RADIOTHERAPY

Authors: M. FENECH*, J. DENHAM**, W. FRANCIS*** and A.A. MORLEY****

* CSIRO Division of Human Nutrition, Kintore Avenue, Adelaide, South Australia, Australia 5000

** Dept. of Radiation Oncology, Newcastle Mater Hospital, Waratah, New South Wales 2298, Australia

*** Dept. of Radiotherapy, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia, Australia 5000

**** Dept. of Haematology, Flinders Medical Centre, Bedford Park, South Australia, Australia 5042

We applied the cytokinesis-block micronucleus assay to measure chromosome damage in lymphocytes of eleven cancer patients undergoing fractionated partial-body irradiation. Measurements performed before, during and after cessation of radiotherapy showed a dose-related increase in micronucleus frequency in each of the patients studied. When the results for micronucleus frequency (Y) were plotted against the estimated equivalent whole body dose (X) the dose-response relationship obtained was $Y = 75.8X + 49.5$ ($R=0.783$, $p<0.0001$). A general decline in MN frequency was observed during the post-treatment period down to 57% (± 10) after twelve months but there was considerable variation between individuals. The advantages and disadvantages of the application of the cytokinesis-block micronucleus assay as a biological dosimeter for lymphocytes irradiated in vivo will be discussed.

REGRESSION OF MELANOMA XENOGRAFTS BY
NEUTRON CAPTURE THERAPY

by

S. Buck, and B.J. Allen

Australian Nuclear Science and Technology Organisation
(ANSTO)
Lucas Heights Research Laboratories
Menai, Australia

Abstract

The development of Neutron Capture Therapy (NCT) offers advantages to conventional radiation therapy which is limited by the tolerance of surrounding healthy tissues within the treatment volume. NCT also eliminates the problems associated with radioisotope labelled anti-tumour agents in that there is no initial radiation dose to whole body prior to selective tumour targeting, and no longer term background effect to normal tissues.

NCT utilizes $^{10}\text{B}(n, \alpha) ^7\text{Li}$ reaction in order to deposit short range (10-14 μm) high linear Energy Transfer (LET) radiation of an average 2.4 MeV, within a tumour mass. The efficacy of this technique relies upon an adequate ^{10}B distribution within the tumour, while maintaining pharmacologic selectivity of ^{10}B to target tissues and adequate shielding of healthy tissues using a neutron absorbing material, ^6LiF .

An in vivo irradiation facility has been installed in the thermal column of the Moata reactor. Incident neutron flux is $10^{10} \text{ n cm}^{-2} \text{ s}^{-1}$ with concomitant gamma dose of 4.8 Gy h^{-1} . Nude mice bearing human melanoma xenografts are anaesthetised and loaded into ^6LiF epoxy cylinders under Specific Pathogen Free (SPF) conditions. Melanoma xenografts are located in the thigh and protrude from the cylinders; thus being exposed to the full neutron field. Healthy tissue is shielded, reducing the neutron flux to a few percent of the incident value. We have found there to be no problem associated with the concomitant whole body gamma dose within the range of exposure used for NCT.

Irradiation follows i.p. or i.v. injection of ^{10}B enriched p-borono-L-phenylalanine. Hcl. ($^{10}\text{B}/1\text{-BPA.Hcl}$) at times when tumour/healthy tissue concentration ratios are optimal. Tumour size is monitored for volume changes following therapy; regression and growth delay indices are determined for different doses of $^{10}\text{B}/1\text{-BPA.Hcl}$ and neutron fluence. These are compared with control growth curves, ie. (1) no irradiation (2) irradiation without $^{10}\text{B}/1\text{-BPA.Hcl}$ pre-treatment.

DNA LIGANDS AS RADIOMODIFIERS

R.F. Martin, V. Murray, L. Denison, G. D'Cunha, M. Pardee,
A Haigh, *E. Kampouris, *D.P. Kelly, and G.S. Hodgson

Molecular Sciences Group, Peter MacCallum Cancer Institute
Melbourne

*Department of Organic Chemistry, University of Melbourne

*Department of Pathology, University of Melbourne

It is generally recognised that DNA is the crucial target in mediating the biological effects of ionising radiation. In particular, there is considerable evidence suggesting that DNA double-strand breaks are responsible for radiation-induced cytotoxicity. Although there is some debate as to the relative importance of direct and indirect (via water radiolysis) DNA damage, carbon-centred free radicals on deoxyribose are the likely precursors of most DNA strand breaks. DNA ligands therefore provide a means of modifying the effects of radiation, either by delivering free radical scavenging moieties to appropriate locations on DNA (protection), or by enhancing the production of free radicals on DNA (sensitisation).

We are investigating a number of DNA ligands as radiomodifiers. All are analogues of Hoechst 33258, which is a bisbenzimidazole that binds in the minor groove at sites comprising 3 or more consecutive AT base pairs. One of these analogues has been shown to protect DNA and cells against ionising radiation. The dose modifying factor for V79 cell survival is 1.7, at a DNA ligand concentration of 20 micromolar.

For radiosensitisation, our approach has been inspired by the well-known effects of incorporation of Br or I into DNA by labelling with BrUdR or IUdR. For ionising radiation the sensitisation factor for cell kill is 3-4, but for UV-B the sensitisation is much more prominent. For both UV and ionising radiation the sensitisation is thought to be mediated by the uracyl free radical formed upon photolysis of the carbon-halogen bond or by reaction with a hydrated electron. It is proposed that the uracyl radical then abstracts a H-atom from an adjacent deoxyribose moiety leaving a carbon-centred free radical, that induces a strand break. We have found that iodoHoechst 33258 sensitises UV-A induced DNA strand breakage, presumably mediated by the free radical generated on the DNA ligand in the minor groove. Analysis of the strand breaks on DNA sequencing gels indicates H atom abstraction from the 5'-deoxyribose carbon is involved. Treatment of V79 cells with 4µM iodoHoechst 33258 sensitises UV-A induced cell kill by 3-4 logs.

The potential relevance of such radiomodifiers to radiotherapy will be discussed.

ANTIMUTAGENESIS

BY

D.G. MALPHEE

MICROBIAL MUTAGENESIS LABORATORY
DEPARTMENT OF MICROBIOLOGY
LA TROBE UNIVERSITY
BUNDOORA, VICTORIA

ABSTRACT

The importance of genetic changes in cells has been recognized for many years. In most sources, the discovery of mutagenic effects in living organisms is attributed to Muller, who in 1928 reported that X-rays were mutagenic in the fruitfly *Drosophila*. An equally important and earlier (1914) report of the mutagenic effects of UV irradiation by Henri has tended to be forgotten, and the first report of a chemical mutagen (mustard gas) by Auerbach and Robson was actually suppressed until the end of World War II. It is now well established that mutations can lead to the development of cancer, of hereditary birth defects, or else alter microorganisms or tumour cells to cause drug resistance or other harmful (or in a minority of cases beneficial) changes. It is also likely that the processes of mutagenesis (which are only now beginning to be understood) and the delicate balance between mutagenesis and antimutagenesis are involved in aging, evolution and other fundamental life processes.

As clearly expressed by Garfield (1982), "Almost every aspect of modern living exposes us to health risks. The air we breathe, the food we eat, the water we drink, the drugs we take, and the places where we work may be contaminated by toxic substances or additives. This is in addition to natural carcinogens such as sunshine, and habits such as cigarette smoking or the way our food is cooked...Their effects may include cancer and organ damage... Other unfortunate effects are suffered by future generations - genetic mutations, birth defects, inherited diseases and so on."

Only recently has it become apparent that naturally occurring substances, particularly those present in the food consumed by man, are one of the most promising sources of inhibitors of mutagenesis (i.e. antimutagens). Such substances should also be a likely source of anticarcinogens, as well as inhibitors of other deleterious effects of environmental agents. Given that the mechanisms involved in the induction of mutations by radiation and chemicals are beginning to be understood in all their complexity, it is now becoming a more realistic prospect that we may shortly be able to understand at least some of the mechanisms involved in antimutagenesis. The importance of oxidative damage and the corresponding significance of antioxidants in living cells will certainly prove to be a rich source of information about the checks and balances which nature has provided for cellular organisms.

Spontaneous and Ionizing Radiation-Induced Mutagenesis In
Prokaryotes

by

D. Liaskou and D.G. MacPhee

Microbiology Department
La Trobe University
Bundoora, Victoria

Abstract

DNA damage can arise spontaneously or it can be induced by a variety of chemical and physical agents. Such damage can be lethal to a cell or it can be repaired in an error-free or error-prone manner. In the latter case mutations will result. The steps involved in the mutagenic process from initial DNA damage to the fixation of a mutation in DNA are beginning to be understood for some mutagens. However, it is surprising that at the present time very little information about the final stages of the mutagenic process has been obtained for the DNA damaging agent ionizing radiation. The type of damage caused by this agent is well documented and information about its repair is accumulating. However, very little is known about the production of mutations as a consequence of ionizing radiation-induced damage.

We will discuss the evidence for mutagenicity or lethality as a result of ionizing radiation-induced damage and its repair. Preliminary evidence that at least one class of spontaneous mutation and (ionizing) radiation-induced mutation have much in common will also be discussed.

THE EFFECT OF MISMATCH REPAIR AND GLUCOSE DEPRESSION ON
9AA-INDUCED MUTAGENESIS IN BACTERIA

by

George Kopsidas and D. G. MacPhee

Microbiology Department,
LaTrobe University, Bundoora, Victoria.

Acridines such as 9-aminoacridine (9AA) are capable of intercalating into bacterial DNA and of causing mutations. Although little is known about the precise way in which 9AA acts, the mutations it induces have been suggested to result from misrepair of DNA.

Evidence suggests that the majority of 9AA-induced lesions in actively growing cells reach the replication fork before processing. The replication fork may provide a suitable opportunity for any intermediates which are required for frameshift mutagenesis to arise. In stationary phase cells, however, it seems that the majority of 9AA lesions are repaired before replication commences.

Misrepair of 9AA-induced DNA damage seems to involve several different excision repair pathways including the *mutHLS*-dependent mismatch repair system. Mismatch repair appears to be responsible for generating the majority of 9AA-provoked mutations at non-replicated regions of the chromosome.

Interestingly, the mechanism by which 9AA induces mutations appears to be under the co-ordinate control of a general or "global" regulatory mechanism. This is best illustrated when glucose is added to the medium during 9AA treatment. The level of 9AA-induced mutagenesis is significantly depressed by comparison with that observed in cells which were treated with 9AA in a medium devoid of a carbon source.

Data which indicates a possible interaction between glucose depression and mismatch correction is presented.

THE EFFECT OF 9-AMINO ACRIDINE, ICR191 AND DEXON ON REVERSION
OF FRAMESHIFT MUTATIONS IN *SALMONELLA TYPHIMURIUM*.

by

Jenny D'Costa and Donald MacPhee.

Department of Microbiology,
Latrobe University, Bundoora, Victoria.

The effect of three chemical mutagens, 9AA, ICR191 and dexion, on reversion of three frameshift mutations was studied in *Salmonella typhimurium* LT2. Two of these mutations, *hisC3076* and *hisC3065*, are +1 frameshift mutations. The other, *hisD3052*, is a -1 frameshift mutation.

9AA-induced frameshift reversion of *hisC3076* and *hisC3065* appears to be almost wholly independent of *recA* gene product and is not greatly enhanced by the presence of plasmid pKM101. However, 9AA-induced frameshift reversion of *hisD3052* appears to be totally dependent on presence of both *recA* gene product and pKM101. In strains deficient in DNA mismatch repair only minute doses of 9AA are required to give significant reversion of *hisC3076* and *hisC3065*. 9AA does revert *hisD3052* in a mismatch repair-deficient background but only at relatively high doses.

ICR191-induced reversion of all three frameshift mutations appears to be partially dependent on RecA and is enhanced by pKM101. Relatively small doses are required to induce frameshift reversion in mismatch repair-deficient derivatives.

Dexion-induced frameshift reversion appears to be almost totally dependent on *recA* gene product and is greatly enhanced by pKM101. In mismatch repair-deficient strains there is no increase in dexion-induced mutagenesis.

The DNA mismatch repair scheme appears to be involved in correcting most frameshifts which result from treatment with 9AA and ICR191 but not in correcting frameshifts which result from treatment with dexion.

GENERAL INFORMATION

GENERAL INFORMATIONCONFERENCE VENUE

The Conference will be held in the AINSE Theatre (Institute Building), Lucas Heights see map page 48, from Friday 22nd September to Sunday 24th September 1989.

PAPERSTiming

Green light shows for presentation of paper,
Warning lights show when 5 & 2 minutes are remaining,
Red light shows when presentation time has expired,
Discussion time of 5 minutes is then allowed by the Chairman.

Slides

Authors using 35 mm slides in conjunction with their talk are requested to place their slides in the projector magazine during the break preceding the session in which the paper is scheduled.

Poster Session - Friday 22nd September - Session V

The Poster Session will be held in the AINSE Council Room, at the scheduled time (see programme). Posters should be set up before the Poster Session commences and removed before the final session. Posters should be prepared before arrival at the Conference in accordance with the guidelines previously provided.

Authors are expected to be in attendance by their posters throughout the poster session.

Materials for setting up posters will be available.

Poster Summary - Sunday 24th September - Session XI

Authors of posters will have the opportunity to summarise their posters with an oral presentation of 5 to 6 minutes.

Student Award

An award for the best paper presentation by a student, oral or poster, will be made during lunch on Sunday.

ACCOMMODATION

Accommodation has been arranged in accordance with advised requirements, at Stevens Hall, Lucas Heights (adjacent to the Institute Building, outside the Main Gate) - see map page 48, or at the Metro Motor Inn, Kingsway and Jackson Avenue, Miranda. The Institute will make payment directly to the management for room only charges at Stevens Hall or the Metro Motor Inn. Participants should make personal arrangements to pay cash for breakfast charges. Participants are requested to vacate Stevens Hall rooms by 9.00 a.m. Sunday, and to leave their luggage in the room marked 'luggage' adjacent to the Theatre Foyer. Room keys to be left in the Stevens Hall Reception Office.

MEALSBreakfast

For Stevens Hall residents, breakfast will be served in the ANSTO Canteen from 7.30 a.m.

For Metro Motor Inn residents, breakfast will be served when required, in units.

Participants should make arrangements to pay cash for breakfast charges at Lucas Heights and the Metro Motor Inn.

Lunches - Friday, Saturday & Sunday 22 -24 September

Lunch for all participants will be held in the Stevens Hall Dining Room during the scheduled lunch period (ref. programme). The cost has been included with the Conference Functions payment.

Evening Meals

Conference Dinner - Friday 22nd September

Pre-Dinner Drinks - Theatre Foyer

7.00 p.m. Buffet Dinner - ANSTO Canteen

BBQ Evening Meal - Saturday 22nd September

6.00 - 7.30 p.m. Gather by the Swimming Pool

Note: No other evening meal services will be available at Lucas Heights

Evening Meal - Thursday 21st September

Please advise the Conference Secretary prior to the Conference if you require an evening meal on this evening

TECHNICAL TOURS - Saturday 23rd September 1989

a) Technical Visit - ANSTO Laboratories 1.30 p.m.

Technical visits specifically designed for industry representatives, but open to all participants, to see ANSTO's unique national facilities and learn something of current programmes in Occupational Health and Safety, Biomedicine and Health and Environmental Science projects of particular relevance to the mining and mineral sands industry.

OR

b) Guided Tour of The Australian Museum, Sydney

"Dreamtime to Dust" - Australia's Fragile Environment

This exhibition has been sponsored by the State Bank and assisted by the Australian Museum Society and NSW Bicentennial Secretariat. It illustrates the changing environment over the last 200,000 years and two major events are highlighted, the arrival of Aborigines about 40,000 years ago and the settlement of Europeans. The aim is not just to depict the past and the factors that determined it, but also to raise questions about the future and the factors and decisions that will in turn shape it.

TOUR - Sunday 24th SeptemberRoyal National Park and Coastline South to Bulli Pass and Mt. Panorama 1.15 p.m.

A bus will depart Lucas Heights at 1.15 p.m. travelling through the very scenic Royal National Park and stopping briefly at its attractive beaches. The spectacular coastline from Stanwell Park will then be viewed and the tour will proceed to Mt. Panorama via Bulli Pass. Delegates then can take an option of being transported to either Sydney airport at approximately 5.00 p.m. or Circular Quay. From Circular Quay, the following options can be readily arranged by participants:-

A cruise on Sydney Harbour, or visits to the Opera House, the historic Rocks area or the new Darling Harbour complex.

TRANSPORTTransport from Sydney Airport - Friday 22nd September

An ANSTO bus will leave the Australian Airlines Terminal (Sydney Airport) for Lucas Heights at 9.25 a.m. Kindly give your name to the driver when entering the bus. If any difficulty is experienced in locating the bus, the Australian Airlines Commonwealth Car Desk will advise details of its precise location.

Request to Participants Arriving on ANSTO Bus from Airport

As time will be limited, participants are asked to proceed directly to the AINSE Theatre and not to Stevens Hall. Luggage may be left in a room adjoining the Theatre Foyer marked 'luggage'. Keys may be picked up from Stevens Hall Reception at any time during the day.

Transport from Sydney Airport (excluding Special Arrangements for Friday 22nd September)

Taxis are available from the airport to:-

Lucas Heights,
Sydenham Railway Station - then train to Sutherland Station,
Sutherland Railway Station - then bus to Lucas Heights(Friday only), or taxi
(ref. bus timetable below)

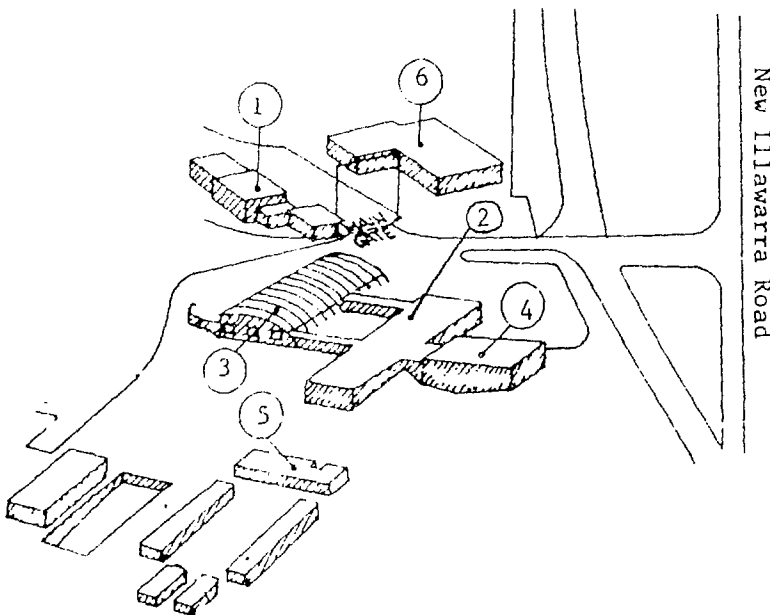
Note: Bookings must be made for all transport listed below - through AINSE, as transport is only provided if demand exists.

Monday - Friday only	
Depart Lucas Hts. for Sutherland	Depart Sutherland for Lucas Hts.
6.15 a.m.	6.50 a.m.
7.35 a.m.	7.55 a.m.
8.30 a.m.	8.15 a.m.
9.35 a.m.	9.05 a.m.
10.35 a.m.	10.05 a.m.
11.30 a.m.	11.10 a.m.
12.30 p.m.	12.00 p.m.
1.00 p.m.	1.10 p.m.
2.15 p.m.	1.30 p.m.
3.35 p.m.	2.45 p.m.
4.50 p.m.	
6.00 p.m.	
8.30 p.m..	

Buses from Lucas Heights leave from outside ANSTO Main Gate

Buses from Sutherland leave from outside Post Office, Flora Street.

LUCAS HEIGHTS N.S.W.



1. Main Gate
2. AINSE Building
3. Canteen
4. AINSE Theatre
5. Stevens Hall
6. Reception

TRANSPORT

Transport from Metro Motor Inn to Lucas Heights

Transport will be arranged for participants. Please wait outside the Motel Reception Office for pick-up at 8.20 a.m. It would be appreciated if participants with their own transport could drive to Lucas Heights and assist by transporting others if possible.

Participants are requested to vacate their rooms by 9.00 a.m. Luggage may be left in the room marked 'luggage' adjacent to the AINSE Theatre Foyer. Room keys may be left in the Stevens Hall Reception Office.

TELEPHONE MESSAGES

Telephone messages will be taken for conference participants on:-

543-3436
(AINSE)

543-3411
(AINSE)

All enquiries concerning the Conference arrangements should be directed to:-

Joan Watson,
Conference Secretary,
A.I.N.S.E.,
Private Mail Bag 1,
MENAI NSW 2234

Phone: 543-3411 or 543-3436

MOLECULAR CHANGES DURING APOPTOSIS

Glen Baxter, Peter Smith and Martin F. Lavin

Molecular Oncology, Queensland Institute of Medical Research, Herston Qld 4006

Cell death is an important component in biological processes. The most common form recognized is necrosis, however a distinct form of cell death defined by morphological and biochemical changes has been described, termed apoptosis or regulated cell death. It is observed in many normal physiological circumstances and is frequently the form of cell death associated with the immune system. Apoptosis has been demonstrated as the mechanism of cell death when lymphocytes are treated with glucocorticoids, various chemotherapeutic agents, ionizing radiation, removal of growth factor from dependent cells, as well as in target cells following attack by cytotoxic T-cells or K-cells.

Apoptosis is characterized morphologically by a series of changes, the most prominent being rapid reduction in cell volume accompanied by loss of microvilli, blebbing of the cell surface and condensation of the nuclear chromatin. DNA isolated from apoptotic cells shows extensive chromatin cleavage, giving rise to discrete fragments which are multiples of 200bp in size. This endogenous degradation of chromatin appears to be caused by activation of a $\text{Ca}^{2+}/\text{Mg}^{2+}$ dependent endonuclease. The changes occurring during apoptosis can be prevented by inhibitors of RNA and protein synthesis.

DNA fragmentation was observed in a human childhood T-cell leukaemia cell-line CEM-C7 40h after addition of dexamethasone, a glucocorticoid hormone, and 24h after γ -irradiation. A set of proteins appeared to be induced and corresponded to bands of nuclease activity on nuclease activity gels. However, sequencing of these proteins revealed that they were histones. These proteins are probably more easily extracted than normal due to the breakdown of chromatin. The apparent nuclease activity is in fact DNA-protein binding.

Protein analysis in apoptotic cells using ^{35}S -methionine labelling and 2-dimensional gel electrophoresis has revealed a number of new and upregulated proteins which are currently being purified.