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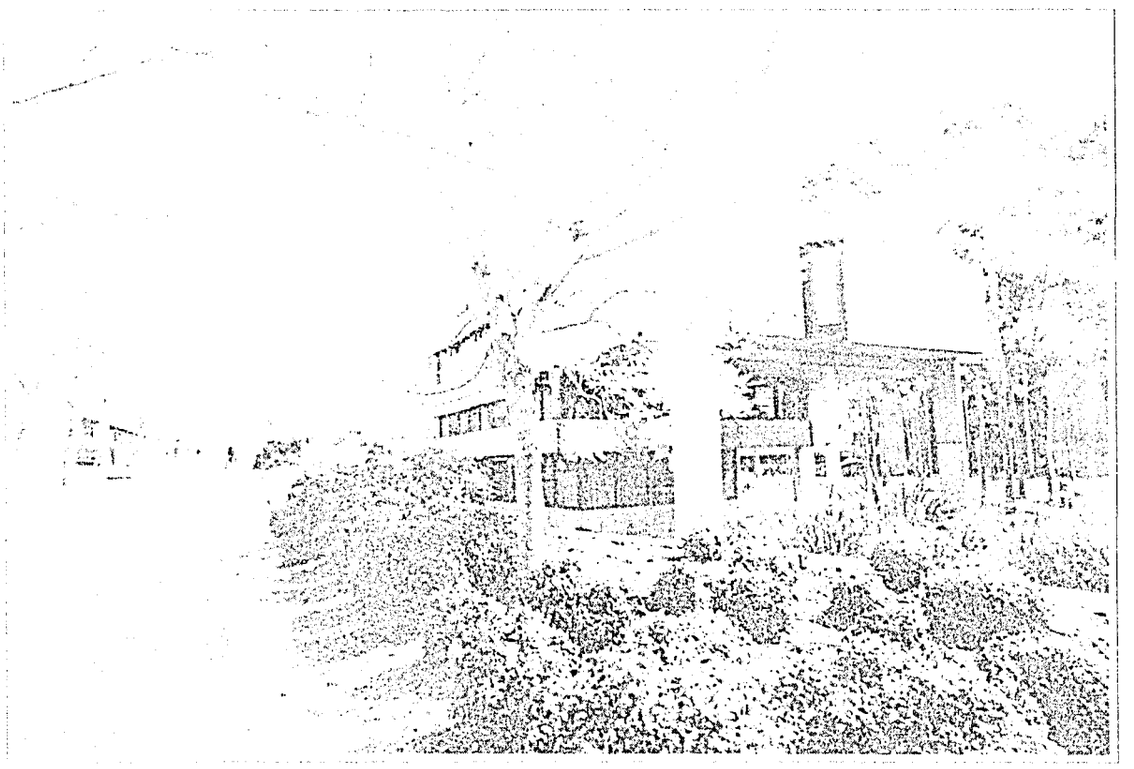
AUSTRALIAN INSTITUTE OF NUCLEAR SCIENCE AND ENGINEERING

The First Australian-Asian Conference on Radiation Science and Nuclear Medicine

17-19 FEBRUARY 1993

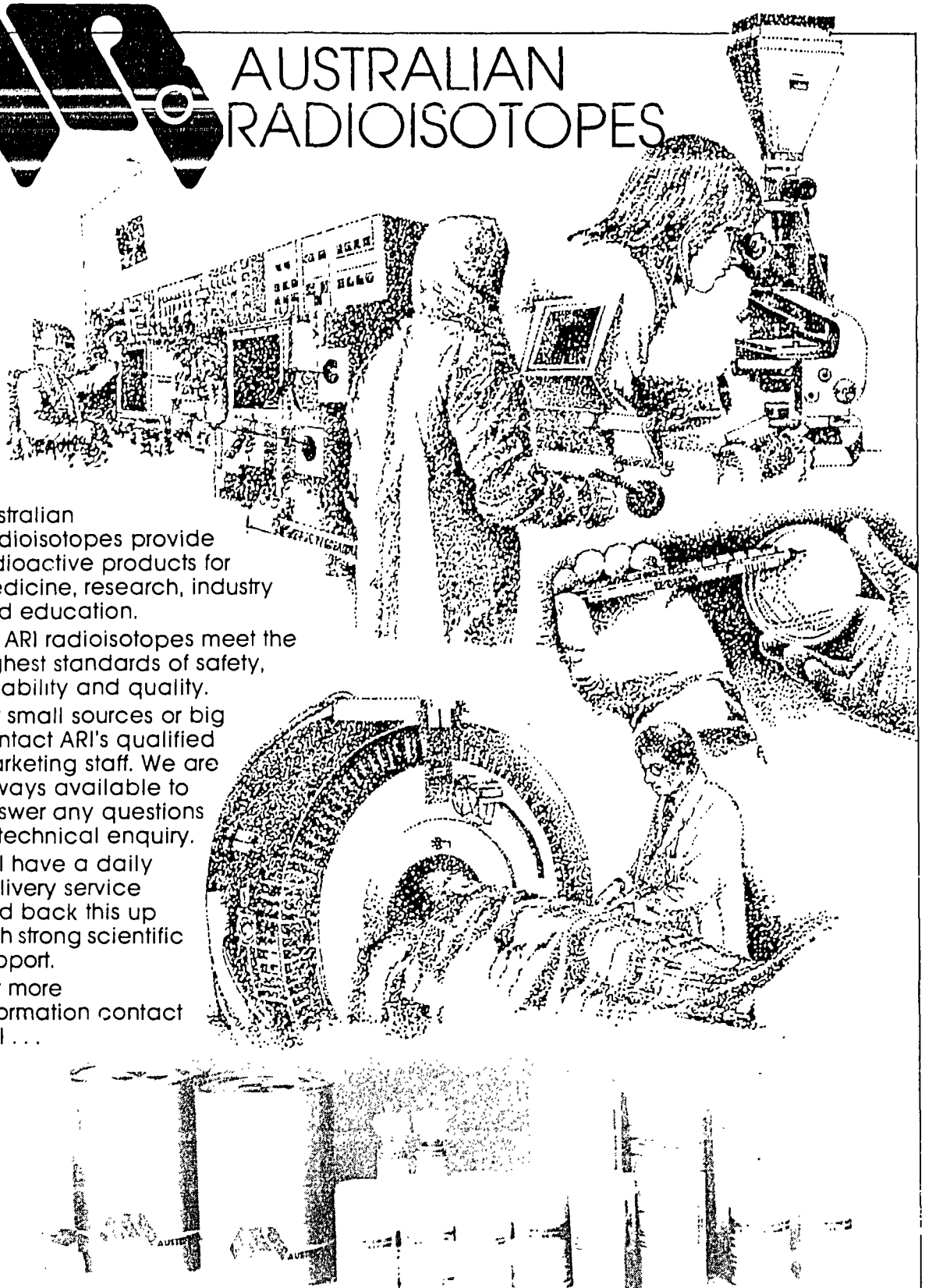
PRICE THEATRE, MACQUARIE UNIVERSITY



CONFERENCE HANDBOOK

(PROGRAM, ABSTRACTS, LIST OF PARTICIPANTS AND GENERAL INFORMATION)

AUSTRALIAN RADIOISOTOPES



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AUSTRALIAN INSTITUTE OF NUCLEAR SCIENCE AND ENGINEERING

THE FIRST AUSTRALIAN-ASIAN CONFERENCE ON

RADIATION SCIENCE AND NUCLEAR MEDICINE

PRICE THEATRE - MACQUARIE UNIVERSITY

in association with
Ansto
RACI Polymer Division
International Association for Radiation Research
Society for Free Radical Research Australasia
Radiation Protection Society
ANZ Society of Nuclear Medicine
ANZ Environmental Mutagen Society

Conference President

A/Professor Ron Cooper (University of Melbourne)

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Professor Jan Gebicki (Macquarie University)
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Professor Martin Lavin (Qld Inst of Medical Research)
Dr Roger Martin (Peter MacCallum Cancer Institute)
Dr Philip Moore (Ansto)
Professor Jim O'Donnell (University of Queensland)
Mr Des Davy (AINSE)
Mr David Sangster (AINSE)
Dr Roger Gammon (AINSE)

SUMMARY

Wednesday 17 February 1993

	Session	
10.30 - 10.40	I	Welcoming Address - Conference President A/Professor R Cooper (Uni of Melbourne)
10.40 - 12.40	II	Chairman: Dr RF Martin (Peter MacCallum Cancer Inst)
12.40 - 2.00		Conference Lunch - Dunmore Lang College
2.40 - 3.40	III	Poster Presentations Chairmen: Professor G Laurence (Uni of Adelaide) A/Professor E Senogles (James Cook Uni)
3.40 - 4.00		Afternoon Tea
4.00 - 5.00	IV	Poster Presentations Chairmen: A/Professor R Burford (Uni of Sydney) Mr D Davy (AINSE)
5.15	V	Poster Session -Dunmore Lang College
7.00		BBQ - Dunmore Lang College

Thursday 18 February 1993

9.00 - 10.40	VI	Chairman: Professor JL Garnett (Uni of NSW)
10.40 - 11.00		Morning Tea
11.00 - 1.00	VII	Chairman: Professor MF Lavin (QIMR)
1.00		Lunch - Dunmore Lang College
2.00 - 3.40	VIII	Chairman: Professor JH O'Donnell (Uni of Queensland)
3.40		Afternoon Tea
4.00 - 5.00	IX	Poster Presentations Chairmen: Professor BJ Allen (Ansto) Mr E Hetherington (Ansto)
5.15	X	Poster Session - Dunmore Lang College
6.00	XI	Rapporteur Session - Dunmore Lang College
7.00 for 7.30		Conference Dinner - Dunmore Lang College

Friday 19 February 1993

9.00 - 10.40	XII	Chairman: Dr P Moore (Ansto)
10.40 - 11.00		Morning Tea
11.00 - 1.00	XIII	Chairman: Professor JS Gebicki (Macquarie Uni)
1.00		Conference Lunch - Dunmore Lang College
2.00 - 3.20	XIV	Chairman: Professor D Napper (Uni of Sydney)
3.20 - 3.40		Closing Remarks & Presentation of Student Prize Conference President - A/Professor R Cooper

PROGRAM

WEDNESDAY 17 FEBRUARY 1993 - MACQUARIE UNIVERSITY

TIME	PAPER NO.	
10.30 - 10.40		Welcoming Address: A/Professor R Cooper (Uni of Melbourne)
Session I		**Chairman:** Dr RF Martin (Peter MacCallum Cancer Inst)
10.40 - 11.20	1 Plenary	Biologically Important Damage Caused by Ionizing Radiation JF Ward (UC San Diego, USA)
11.20 - 11.32	2	Radioprotection by DNA Ligands - Mechanistic Aspects. LS Denison, RF Martin (Peter MacCallum Cancer Inst)
11.32 - 11.44	3	Radiation and the Cell Cycle in Ataxia-Telangiectasia. MF Lavin, H Beamish (Queensland Inst of Medical Research)
11.44 - 11.56	4	Gamma Radiation: A Mechanistic Unraveller of Aqueous-Phase Kinetics in Free Radical Emulsion Polymerisations. BS Casey, BS Morrison, RG Gilbert, DF Sangster, DH Napper (Uni of Sydney), IZ Lacik (Slovak Academy of Sciences, Czechoslovakia)
11.56 - 12.08	5	Studies of the Nature and Reactions of the Transients in Certain Biologically Important Molecules. M Lal (Bhabha Atomic Research Centre, India)
12.08 - 12.20	6	Australia's Contribution to the IAEA CRP "Sources of Radioactivity in the Marine Environment and their Contributions to the Overall Dose Assessment from Marine Radioactivity (MARDOS)". RA Jeffree, JR Twining (Ansto)
12.20 - 12.40		Discussion
12.40 - 2.00		**Conference Lunch - Dunmore Lang College**
Session II		**Chairman:** Dr RM Lambrecht (Ansto)
2.00 - 2.40	7 Plenary	Radiopharmaceuticals for Understanding the Brain. Y Yonekura, H Saji, K Horiuchi (Kyoto University)
Session III		**Chairmen:** Professor G Laurence (Uni of Adelaide) A/Professor E Senogles (James Cook Uni)
Poster Presentations		
2.40 - 3.40	8	Radiopharmaceutical Labelling and Quality Control. P Schmidt, FT Lee, R Lambrecht (Ansto)
	9	Radiation Standards and Legal Measurements. H van der Gaast, S Buckman (Ansto)
	10	Structural and Electronic Aspects of Technetium Complexes. J Baldas, JF Boas, GA Williams (Aust Rad Lab)

WEDNESDAY 17 FEBRUARY 1993 - MACQUARIE UNIVERSITY

TIME	PAPER NO.	
Poster Presentations (cont)		
2.40 - 3.40	11	Automated Production of L-3-[I]Ioda-alpha-Methyltyrosine - A SPECT Imaging Agent for Diagnosis of Tumours. ME Izard, A Katsifis, N Blagojevic, H Meriaty (Ansto)
	12	The Radiation Chemistry of Poly(Acrylonitrile-Co-Styrene). DJT Hill, AP Lang, JH O'Donnell, PJ Pomery (Uni of Queensland)
	13	The Radiation Chemistry of Poly(Arylene Ether Phosphine Oxides)s. DTJ Hill, JL Hopewell, JH O'Donnell, PJ Pomery (Uni of Queensland)
	14	The Radiation Degradation of Poly(Methylmethacrylate) at Elevated Temperatures. KA Milne, JH O'Donnell (Uni of Queensland)
	15	Radiation Induced Thermal Degradation of Poly (alpha-Methyl Styrene). RW Garrett,(Ansto), DJT Hill, TT Le, JH O'Donnell, PJ Pomery (Uni of Queensland)
	16	Computer Estimation of the Lead Equivalence of Protective Barriers for Broad Beam Diagnostic X-Ray Beams. D McLean (Uni of Sydney)
	17	Environmental Radiation Protection in the Mining and Milling of Radioactive Ores at Olympic Dam Operations - A Real or Perceived Radiation Protection Concern. FF Harris (Olympic Dam Operations)
	18	Radiation Induced Apoptosis. D Findik, Q Song, G Baxter, M Lavin (Queensland Inst of Medical Research)
	19	Radioprotection by DNA-binding Bibenzimidazoles: Cell Culture Studies. S Broadhurst, RF Martin (Peter MacCallum Cancer Inst)
	20	Radioprotection by DNA-binding Bibenzimidazoles: In Vivo Studies. S De Abrew, R Sephton, R Budd, P Junor, RF Martin (Peter MacCallum Cancer Inst)
	21	Radiation Biology and the Laboratory Mouse. EM Nicholls (UNSW)
3.40 - 4.00		Afternoon Tea

WEDNESDAY 17 FEBRUARY 1993 - MACQUARIE UNIVERSITY

TIME	PAPER NO.	
Session IV		**Chairmen:** Professor R Burford (Uni of Sydney) Mr D Davy (AINSE)
Poster Presentations		
4.00 - 5.00	22	Textiles and UVR Protection. MT Pailthorpe, N Jesson (UNSW)
	23	The Effect of Antioxidants on the Photochemical Degradation of Trytophan in a Rigid Medium. PD Auer, MT Pailthorpe (UNSW)
	24	Enhancement of DNA Damage in Tumor Cells by ADPRT Inhibitor in Gamma-Irradiation, Bleomycin Treatment of Hyperthermia. T He, S-X Xia (Inst of Rad Med, China)
	25	Sensitisation of DNA by Incorporation of Iodine or Bromine. G D'Cunha, RF Martin (Peter MacCallum Cancer Inst)
	26	The Photochemistry of Some Bi-Benzimidazole Derivatives and Their Role in the UV-Sensitised Cleavage of DNA. LE Bennett, RF Martin (Peter MacCallum Cancer Inst), R Cooper (Uni of Melbourne)
	27	Boron Influence on Maximum Therapeutic Depth in Thermal Neutron Capture Therapy. SA Wallace, JN Mathur (Uni of Wollongong), BJ Allen (Ansto)
	28	Hifar Epithermal Neutron Beam for Boron Neutron Capture Therapy for Cancer. M Carolan, J Mathur (Uni of Wollongong), BJ Allen, BV Harrington, H Meriaty (Ansto)
	29	Optimisation of Neutron Capture Radiography for Analysis of Boron-10 in Tissues. HA Meriaty, BJ Allen (Ansto)
	30	Instrumental Methods for Investigating Boron Uptake in Tumour Cells in Neutron Capture Therapy. Y Setiawen, DE Moore (Uni of Sydney)
	31	Synthesis and Evaluation of 10B-labelled DNA Ligands. A Corder, RF Martin (Peter MacCallum Cancer Inst), A Whittaker, DP Kelly (Uni of Melbourne), H Meriaty, BJ Allen (Ansto)
	32	Luminescent F-type Defects in Electron Irradiated Solids. KJ Caulfield, R Cooper (Univ. of Melbourne), JF Boas (Aust Rad Lab)
	33	The Effect of Ionising Radiation on Conductivity in Low Density Polyethylene. A Markiewicz (Monash University)

WEDNESDAY 17 FEBRUARY 1993 - MACQUARIE UNIVERSITY

TIME	PAPER NO.	
Poster Presentations (cont)		
4.00 - 5.00	34	Radiation Induced Conductivity in Irradiated Solids. D Edmondson, R Cooper, R Bhave (Uni of Melbourne), MP de Haas (Delft Uni of Technology, The Netherlands)
	35	Single Molecule Glasses Prepared by Gamma-Irradiation. RA Mann, DF Sangster, DH Napper (Uni of Sydney), R Qian, D Shen (Inst of Chemistry, China), L Wu (Testing Centre of Textile Academy, China)
	36	Detection of Irradiated Spices - Enumeration of Microorganisms (DEFT/APC) and Thermoluminescence. KM Hammerton, C Banos (Ansto)
	37	Radical-Induced Chain Oxidation of Bovine Serum Albumin and its Inhibition by Chain-Breaking Antioxidants. J Neuzil, R Stocker (Heart Res Inst), JM Gebicki (Macquarie Uni)
Session V 5.15		**Poster Session - Dunmore Lang College**
7.00		**BBQ - Dunmore Lang College**

THURSDAY 18 FEBRUARY 1993 - MACQUARIE UNIVERSITY

TIME	PAPER NO.	
Session VI		**Chairman:** Professor JL Garnett (Uni of N.S.W.)
9.00 - 9.40	38 Plenary	Radical Ions in Radiation and Photchemistry. Magnetic Resonance and Other Studies. AD Trifunac (Argonne Nat Lab, USA)
9.40 - 9.52	39	Pressure and Temperature Effects on Ion-Electron Recombination Rates in Gases. RN Bhave, R Cooper, R van Sonsbeek (Uni of Melbourne)
9.52 - 10.04	40	Comparative Studies of UV-Induced DNA Cleavage by Structural Isomers of an Iodinated DNA Ligand. RF Martin, DP Kelly, M Roberts, L Denison, A Green, M Rose, M Pardee (Peter MacCallum Cancer Inst)
10.04 - 10.16	41	Evaluation of Performance of Antioxidant/Antioxidant Systems in Irradiated Natural Rubber Latex. NMV Kalyani, L Karunenayake, PHS Kumara (Rubber Res Inst, Sri Lanka)
10.16 - 10.28	42	Role of alpha Emitting Radioisotopes in Therapy of Subclinical Metastases. BJ Allen, B Blagojevic, H Meriaty (Ansto)
10.28 - 10.40		Discussion
10.40 - 11.00		**Morning Tea**
Session VII		**Chairman:** Professor MF Lavin (Queensland Inst of Medical Research)
11.00 - 11.40	43 Plenary	Radiation Sensitisers and the Radiation Chemistry of DNA. EM Fielden (MRC Radiobiology Unit, UK)
11.40 - 11.52	44	Towards Epithermal Boron Neutron Capture Therapy for Cancer. BJ Allen (Ansto)
11.52 - 12.04	45	Development of New Boron Compounds for Use in Neutron Capture Therapy of Melanoma. JK Prashar, DE Moore (Uni of Sydney), BJ Allen (Ansto)
12.04 - 12.16	46	Positron Lifetime Characterization of Polymers. AJ Hill, MD Zipper, GP Simon (Monash Uni)
12.16 - 12.28	47	Molecular Characterization of DNA-Binding Protein Abnormally Distributed within the Cells of Patients with Ataxia-Telangiectasia. KK Khanna, L Hong, MF Lavin (Queensland Inst of Med Res)
12.28 - 12.40	48	Purification, Characterisation and Separation of a Radiation-Activated DNA-Binding Complex Isolated from Human Cells. BA Teale, MF Lavin (Queensland Inst of Med Res)
12.40		Discussion
1.00		**Conference Lunch - Dunmore Lang College**

THURSDAY 18 FEBRUARY 1993 - MACQUARIE UNIVERSITY

TIME	PAPER NO.	
Session VIII		**Chairman:** Professor JH O'Donnell (Uni of Queensland)
2.00 - 2.40	49 Plenary	Current Status of Radiation Processing in Maslaysia. KZH Dahlan (Nuclear Energy Unit, Malaysia)
2.40 - 2.52	50	Radiation Grafting of Ethylene-Propylene Elastomers with Hydrophilic Monomers. RP Burford, JL Garnett, V Haddadi-Asi (UNSW)
2.52 - 3.04	51	The Effect of Simulated Low Earth Orbit Radiation on Polymers. GA George, DJT Hill, JH O'Donnell, PJ Pomery, FA Rasoul (Uni of Queensland)
3.04 - 3.16	52	Generation of Hydroperoxides in Gamma-Irradiated Amino Acids and Proteins. S Gebicki, JM Gebicki (Macquarie Uni)
3.16 - 3.28	53	Protein Bound Dopa is a Reductant Formed During Gamma Radiolysis of Proteins. SP Gieseg, JA Simpson, RT Dean (Heart Res Inst), TS Charlton, MW Duncan (UNSW)
3.28 - 3.40		Discussion
3.40 - 4.00		**Afternoon Tea**
Session IX		**Chairmen:** Professor BJ Allen (Ansto) Mr E Hetherington (Ansto)
Poster Presentations		
4.00 - 5.00	54	Horizons in Radiation Polymerisation. DF Sangster (AINSE)
	55	Mechanism of the Sensitization of Radiation Vulcanisation of Natural Rubber Latex by Mono-Acrylates. DJT Hill, MCS Perera (Uni of Queensland)
	56	ESR Study of Gamma-Irradiated Polymethacrylonitrile. DJT Hill, L Dong, JH O'Donnell, PJ Pomery (Uni of Queensland)
	57	MCNP as a Tool for Calculating Neutron and Photon Doses In Tissue. BV Harrington (Ansto)
	58	In Vitro Radiosensitivity of Lymphoblastoid Cell Lines From Breast Cancer Patients. GW Birrell, JR Ramsay (Queensland Inst of Medical Research)
	59	In Vitro Radiosensitivity of Merkel Cell Carcinoma. H Leonard, G Birrell, J Ramsey, J Kearsley (Queensland Inst of Medical Research)
	60	Heterogeneity in Ataxia-Telangiectasia: Complementation Analysis of Radiation Induced Chromosome Aberrations. P Chen and MF Lavin (Queensland Inst of Medical Research)

THURSDAY 18 FEBRUARY 1993 - MACQUARIE UNIVERSITY

TIME	PAPER NO.	
Poster Presentations (cont)		
4.00 - 5.00	61	Correction of DNA Repair Gene Deficiency in Radiosensitive XP and AT Cells. S-P Ji, T He, Y-P Zhang, S-X Xia (Inst of Rad Med, China)
	62	Gene Mutation Induced by Gamma-Ray Irradiation in Mammalian Cells. S-P Ji, T He, Y-P Zhang, S-X Xia (Inst of Rad Chem China)
	63	Electron Energy Degradation in Irradiated Gases. M Burgers, R Cooper (Uni of Melbourne), M Inokuti, M Dillon, M Kimura (Argonne National Laboratory)
	64	Electron Energy Loss in Irradiated Molecular Gases. R Bhave, R Cooper (Uni of Melbourne)
	65	Redox Active Surfactants: Synthesis and Properties of a New Class of Detergent. GW Walker, AM Sargeson, RJ Geue, RM Pashley, CA Behm (ANU)
	66	Characteristics of the Radiation Fields Produced by the Australian National Medical Cyclotron. B Mukh. .jee (Nat Med Cyclotron)
	67	Application of a Whole Body Counter for Studying Pharmocokinetics in Man at Picomolar Concentrations. DL Bailey (RPAH), V Cunningham, VW Pike, CAJ Freemantle, BC Page, AKP Jones, MJ Kensett, D Bateman, SK Luthra, T Jones (Hammersmith Hospital, UK)
	68	Improved Dose Estimates Using Transmission Based SPECT Reconstructions. BF Hutton, SR Meikle, DL Bailey, S Eberl, P Farleigh, A Osiecki, R Fulton (RPAH), M Hudson, R Larkin (Macquarie University)
Session X		
5.15		**Poster Session - Dunmore Lang College**
Session XI		
6.00		**Rapporteur Session - Dunmore Lang College**
7.00 for 7.30		**Conference Dinner - Dunmore Lang College**

FRIDAY 19 FEBRUARY 1993 - MACQUARIE UNIVEPSITY

TIME	PAPER NO.	
Session XII		**Chairman:** Dr P Moore (Ansto)
9.00 - 9.40	69 Plenary	Molecular Nuclear Medicine - A New Frontier. S-H Yeh (Dept of Nuclear Med, Taiwan)
9.40 - 9.52	70	In-Vivo Dosimetry Estimation using Quantitative Whole Body Positron Emission Tomography. SR Meikle, J Towson, DL Bailey, BF Hutton (RPAH), M Dahlbom, SR Cherry (UCLA, USA)
9.52 - 10.04	71	The Radiation Monitoring and Control System for the Austin Hospital P.E.T. Centre. GF Egan, S Midgley, V Tran (Austin Hospital)
10.04 - 10.16	72	Redox Reactions of Tetraaza-Macrocyclic Complexes. GS Laurence (Uni of Adelaide)
10.16 - 10.28	73	Radiation Stability of Fullerenes: Pulse Radiolysis and Laser Flash Photolysis Studies of C_{60} and C_{70}. DK Palit, AV Sapre, JP Mittal (Bhabha Atomic Research Centre, India)
10.28 - 10.40		Discussion
10.40 - 11.00		**Morning Tea**
Session XIII		**Chairman:** Professor JS Gebicki (Macquarie Uni)
11.00 - 11.40	74 Plenary	The Use of Pre-Mix and Stopped-Flow Techniques in Combination with Pulse Radiolysis. BHJ Bielski (Brookhaven Nat Lab, USA)
11.40 -11.52	75	International Intercomparisons of TLD Based Environmental Gamma Radiation Monitors. JF Boas, JG Young (Aust Rad Lab)
11.52 - 12.04	76	The In-Service Effects of Radiation on the Graphite Moderators of UK Nuclear Reactors. KR Millington (Nuclear Electric, UK)
12.04 - 12.16	77	The Value of Dosemeter Records for Victims of Acute Radiation Doses. GJ Jenks, EJB O'Donovan (DSTO Mats Res Lab)
12.16 - 12.28	78	Studies on the Radiation Induced DNA Damage and Repair in Mammalian Cells. S-X Xia, Y-P Zhang, X-B Bai, T He, P-K Zhou, S-P Ji, T Yan (Inst of Rad Med, China)
12.28 - 12.40	79	DNA Ligands as Radiomodifiers: Molecular Evaluation in Intact Cells. J Tursi, RF Martin (Peter MacCallum Cancer Inst)
12.40 - 1.00		Discussion
1.00		**Conference Lunch - Dunmore Lang College**

FRIDAY 19 FEBRUARY 1993 - MACQUARIE UNIVERSITY

TIME	PAPER NO.	
Session XIV		**Chairman:** Professor D Napper (Uni of Sydney)
2.00 - 2.12	80	Irradiation of Poly(p-Methyl Styrene) and Acrylonitrile/p-Methyl Styrene Copolymers. RA Lyons, E Senogles (James Cook Uni), JH O'Donnell, P Pomery (Uni of Queensland)
2.12 - 2.24	81	Mechanistic Studies of Sensitization of Radiation Induced DNA Breakage of Halogenated DNA Ligands. P Nel, R Cooper (Uni of Melbourne) RF Martin (Peter MacCallum Cancer Inst)
2.25 - 3.05	82 Plenary	Molecular Mechanisms of Radiation Mutagenesis in Human Cells. JB Little (Harvard Sch of Public Health, USA)
3.05 - 3.25		**Closing Remarks and Presentation of Student Prize:** A/Professor R Cooper (Uni of Melbourne)

ABSTRACTS

BIOLOGICALLY IMPORTANT DAMAGE CAUSED BY IONIZING RADIATION

by

J.F. Ward

Div. of Radiation Biology, Dept. of Radiology, School of Medicine, U.C. San Diego, La Jolla, CA 92093, USA.

Abstract

Cellular studies indicate the DNA double strand breaks (dsb) are the biologically significant lesions induced by ionizing radiations. Question arising from this notion include: Are all dsbs alike? Can cells repair all dsbs? What causes differential cell radiosensitivity? How can the higher relative biological efficiency of high linear energy transfer radiation be explained? etc.

Studies of the chemical mechanisms by which DNA dsbs are introduced by ionizing radiation help to answer these questions. From a knowledge of these mechanisms the structures of the damages introduced by radiation can be predicted, and, thus the questions of cellular response to the damage can be considered.

The mechanistic considerations help to link the findings of microdosimetrists on radiation energy deposition with the biological consequences of the radiation. This approach linking the physics to the biology may, in the future aid in the determination the risks of exposure to radiation.

Work in the author's laboratory supported by grants from NIH CA26279 and CA46295 and from DOE DE-FG03-88ER60660.

RADIOPROTECTION BY DNA LIGANDS: MECHANISTIC ASPECTS

by

L.S. Denison and R.F. Martin

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Abstract

The bibenzimidazoles Hoechst 33258 and Hoechst 33342 bind in the minor groove of DNA at sites comprising 3 or more consecutive A-T base pairs. Experiments with purified DNA have shown that these ligands decrease the yield of radiation-induced strand breaks. DNA single strand breaks (ssb) and DNA double-strand (dsb) breaks were assayed using pBR322 DNA and agarose gel electrophoresis. Quantitation of DNA double-strand break induction has revealed preferential protection of single-hit events. DNA sequencing gel analysis has shown pronounced protection at the ligand binding sites, as well as a more generalised protection[1]. The extent of protection is influenced by pH, with pH=7 being optimal. The fact that the generalized protection persists in experiments with the inclusion of 0.5M NaCl, which prevents low affinity binding between high affinity sites, suggests that the protective effects of the bound ligand are not confined to high affinity sites in the minor groove.

In our experimental systems, namely dilute aqueous solutions of purified DNA, virtually all radiation effectes are mediated by the radiolysis products of water (principally hydroxyl radicals). These effects are described as indirect action. In a biological context however,the role of direct action is important since in cells this process accounts for approximately 50% of the radiation-induced damage. To try and elucidate whether the DNA ligands protect against DNA damage mediated by direct action , we have included high concentrations of TRIS, a known hydroxyl radical scavenger, in our systems. The results of such experiments show protection of DNA dsbs, however, in contrast there is sensitization of DNA ssbs. DNA sequencing gel analysis has revealed enhancement of damage adjacent to the binding sites of the ligand. A similar pattern of damage was observed when UVA irradiation (357nm) was used indicating the possible role of an excited state of the ligand in the observed sensitisation of DNA ssbs in the presence of the scavenger.

Possible mechanisms of the radioprotection by DNA-binding ligands will be discussed.

Reference

[1] Denison, L., Haigh, A., D'Cunha, G., and Martin, R.F., DNA-ligands as radioprotectors. Molecular studies with Hoechst 33342 and Hoechst 33258. Int. J. Rad. Biol. 61 69-81(1992).

RADIATION AND THE CELL CYCLE IN ATAXIA-TELANGIECTASIA

by

M.F. Lavin and H. Beamish

Queensland Cancer Fund Research Unit, Queensland Institute of Medical Research, Bancroft Centre, 300 Herston Road, Brisbane 4029, Australia

Abstract

Radiosensitivity is a universal characteristic of the human genetic disorder ataxia-telangiectasia (A-T). Hypersensitivity to ionizing radiation has been demonstrated in A-T patients exposed to radiotherapy and in cells in culture (Taylor et al 1975; Chen et al 1978). It appears likely that this sensitivity is not due to inability to excise radiation damage from DNA since such a defect is only apparent in a few A-T cell lines and only under certain conditions.

It is widely assumed that A-T cells undergo less radiation-induced delay in progress through the cell cycle than controls. This was thought to be due to both radioresistant DNA synthesis allowing cells to proceed through S phase unchecked and reduced mitotic delay. Zampetti-bosseler and Scott (1981) showed that suppression in mitotic index, which is normally observed in a variety of mammalian cells exposed to ionizing radiation, is less pronounced in A-T fibroblasts. The reduced effect on mitotic index was shown to be largely confined to cells which were in G2 phase at the time of irradiation. However, this result has been misinterpreted widely in the literature to mean that A-T cells in general experience less mitotic delay post-irradiation. To add to the confusion there is another body of evidence which reveals a greater and more prolonged delay of A-T cells in G2/M phase postirradiation. In addition to the anomalies displayed in G2/M phase postirradiation A-T cells also failed to show the normal delay in progression from G1 to S after irradiation of cells in G1 phase.

The present study was designed to clarify the rather confused situation concerning the effects of radiation on A-T cell cycle progression. In order to determine the source of the cells accumulating in G2 phase with time after irradiation, S phase cells were identified by labelling with 5-Bromodeoxyuridine (BrdU) and subsequently detected using a fluorescence labelled monoclonal antibody and cells were synchronized with mimosine (G1 transition point inhibition) prior to irradiation in order to follow G1 phase cells. The effects of irradiation on cells in G2 phase also employed the use of BrdU followed by synchronization in G2 phase with nocadazole prior to irradiation. Finally passage out of G1 phase was monitored by prelabelling with BrdU, synchronization with nocadazole release of the block and irradiation in the subsequent G1 phase.

γ RADIATION: A MECHANISTIC UNRAVELLER OF AQUEOUS-PHASE KINETICS IN FREE RADICAL EMULSION POLYMERISATIONS

by

Brendan S. Casey[1], Bradley S. Morrison[1], Igor Z. Lacik[2], Robert G. Gilbert[1], David F. Sangster[1,3] and Donald H. Napper[1]

[1] School of Chemistry, Sydney University, Sydney NSW 2006, Australia
[2] Polymer Institute, Slovak Academy of Sciences, Bratislava 84236, Czechoslovakia
[3] Honorary AINSE Fellow

Abstract

An emulsion polymerisation system is heterogeneous and may contain up to three separate phases: a dispersive medium, commonly water (containing a small amount of the sparingly water-soluble monomer), emulsion droplets (containing monomer) and latex particles (consisting of polymer, monomer and surfactant, which acts as a surface stabiliser). Either an oil-soluble or a water-soluble initiator is added to generate, by thermal decomposition, the free radical species which then initiate polymerisation in the latex particles.

An alternative method of free radical generation is via the application of γ radiation. γ radiation interacts with materials, like water, to cause ionisation and electronic excitation. The electrons and parent positive ions produced, their reaction products, and the radical pairs formed by homolysis of excited molecules are all free radicals which can initiate polymerisation.

The advantage of γ radiation over chemical initiators is its ability to provide a discontinuous radical flux during a polymerisation experiment. Whereas chemical initiators are present throughout polymerisation, it is a simple procedure to remove an emulsion sample from a γ-radiation source. The resulting rapid change in free radical production rate provides more kinetic information than is available from the more common steady-state experiments.

An outline of the radiation chemistry involved in emulsion systems will be presented. This will then be used to illustrate how γ-radiation experiments can be applied to elucidate mechanisms of free radical polymerisation[1], with a special emphasis on the desorption of transferred free radicals from the latex particles and subsequent aqueous-phase kinetics.[2, 3, 4]

References

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STUDIES ON THE NATURE AND REACTIONS OF THE TRANSIENTS IN CERTAIN BIOLOGICALLY IMPORTANT MOLECULES

by

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Abstract

The measurement of free radical reactivity with pertinent biological components are of great interest in view of lack of correlation between a particular free radical reaction and the specific biological effect. The pronounced toxic action of polyhalogenated molecules (e.g. CCl_4, Halothane, fluoromolecules etc) is associated with peroxyl radicals.

The rate constants of e^-_{aq} and $\dot{O}H$ radicals with halogenated organic molecules are $\sim 2.7 \times 10^9 - 3.9 \times 10^{10}$ M^{-1} s^{-1} and $9.5 \times 10^6 - 2.1 \times 10^8$ M^{-1} s^{-1} respectively. The rate constants of oxygen addition to α-halogen carbon centered radicals are in the range of $9 \times 10^8 - 3.9 \times 10^9$ M^{-1} s^{-1}, the rate increasing with increasing halogen substitution. The reactions of these peroxyl radicals with variety of antioxidants and phenothiazine drugs have been investigated. $k \sim 1.4 \times 10^8 - 2 \times 10^9$ M^{-1} s^{-1} are very high and reflect the hazardous nature of halocarbons.

The reactions of thiyl radicals (intermediates in biological systems) with promethazine, chloropromazine, prochlorperazine and trimeprazine tartrate are very fast ($2.2 \times 10^8 - 2 \times 10^9$ M^{-1} s^{-1}) and demonstrate that thiyl radicals are strong oxidising species.

The free radical induced degradation of halogenated organic molecules in γ-irradiated air saturated aqueous solutions lead to the formation of high acid yields. Peroxyl radicals have been identified as the reactive intermediates in these systems and must also be present in the metabolism of these molecules. The paper brings out the significant role of radiation chemical techniques in providing an insight into the chemistry occuring in biological systems.

Australia's Contribution to the IAEA CRP 'Sources of Radioactivity in the Marine Environment and their Contributions to the Overall Dose Assessment from Marine Radioactivity (MARDOS)'

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Abstract

The general aim of MARDOS is to estimate the radiation dose to the World's population from the consumption of artificial and naturally-occurring radionuclides that are present in the edible tissues of marine organisms. The strategy adopted to achieve this goal will be presented as well as the results of Australia's contribution, which have included (a) the measurement of the levels of caesium-137 and polonium-210 in fish, crustacea and molluscs from the three FAO Fishery regions that encompass Australia's coastal waters, (b) an estimation of the radiation doses to the average Australian consumer of seafoods from these two radionuclides, and (c) a review of the literature on the levels of Polonium-210 in edible marine organisms.

Radiopharmaceuticals for Understanding the Brain

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Abstract

Recent developments in technology have introduced various new imaging procedures in clinical medicine. Among them radionuclide methods, including both positron emission tomography (PET) and single photon emission computed tomography (SPECT), provide a unique capability to visualize regional function in living human brain by administration of small amount of radioactive tracers having specific characters.

PET detects a pair of photons radiated from positron annihilation. It utilizes short-lived positron emitting radionuclides, such as C-11, N-13, O-15 and F-18, which are produced by a compact cyclotron installed in the hospital. These radionuclides are used to label various compounds of biochemical interest. On the other hand, in the SPECT measurement, gamma rays emitted from the radionuclides with higher atomic number, such as Tc-99m and I-123, are detected.

The measurement of brain function with the radionuclide technique focuses on two major themes; measurements of neuronal activity assessed by either blood flow changes or energy metabolism, and evaluation of signal transmission between the neurons (neurotransmission). Excellent physical characteristics of PET provide better sensitivity, spatial resolution and quantification. Moreover, various labeled compounds of biochemical interest permit *in vivo* assessment of metabolism in human brain. However, PET requires a cyclotron in the hospital for production of short lived positron emitting radionuclides, which limits the wide-spread clinical use. SPECT has also shown rapid advancements to follow the successful results of PET, including both instrumentations and radiopharmaceuticals. During the past decade, extensive efforts have been made in this field to develop new radiopharmaceuticals not only for measurement of blood flow but also for assessment of metabolism and neurotransmission.

Based on these results, we are now in the entrance of new exciting field to understand how the human brain works and to clarify the underlying pathophysiology of various neurological and psychiatric diseases.

RADIOPHARMACEUTICAL LABELLING AND QUALITY CONTROL

by

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Abstract

The Biomedicine and Health program at ANSTO is actively involved in the development of radioactively labelled, molecular and monoclonal antibody based, pharmaceuticals for both diagnostic and therapeutic applications. There are many different radioisotopes which have physical properties that make them desirable as pharmaceutical agents. With the use of molecular compounds and monoclonal antibodies, it is possible to target the radioactive isotopes to particular sites in the body. When a product has been developed, it is necessary for it to proceed through quality control procedures.

Methods of labelling molecular radiopharmaceutical with radioisotopes usually involve chelation of the isotope, or incorporation of the isotope into the molecular structure[1]. Labelling of a monoclonal antibody can either be directly onto the antibody, or by binding the isotope to a bifunctional chelating agent which can be bound to the antibody[2].

When the radiopharmaceutical has been made, there are several common quality control procedures that can be applied to test the product for chemical stability.

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RADIATION STANDARDS AND LEGAL MEASUREMENTS

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ABSTRACT

The Australian Nuclear Science and Technology Organisation, acting as agent for the CSIRO Division of Applied Physics, maintains the Australian standard of measurement for activity. The standard includes all nuclear medicine gamma emitters and a new standard for pure positron emitters.

Under Section 10 of the National Measurement Act 1960, if a measurement is made for a legal purpose, or if the legality of a measurement is in dispute, it can only be confirmed if the following two conditions are fulfilled:

(a) that the measurement be in terms of the prescribed Australian legal units of measurement.

(b) that it can be proven to be traceable to an Australian primary standard of measurement.

To satisfy these requirements, radionuclide dose calibrators require a calibration report determined by Ansto. For this reason, Ansto has developed the national radionuclide dose calibrator standardisation service.

Described are the primary standard, secondary standard and standardisation procedures which establish the Australian legal units for dealing in radioactive materials.

STRUCTURAL AND ELECTRONIC ASPECTS OF TECHNETIUM COMPLEXES

by

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Abstract

Complexes of ^{99m}Tc (half life 6 hours) are the most widely used radiopharmaceuticals. We have been investigating some fundamental aspects of a variety of technetium complexes using the long-lived ^{99}Tc (half life 212,000 years), including their behaviour in aqueous and non-aqueous solutions. The techniques used have included optical, infra-red and electron spin resonance spectroscopy, electrophoresis, X-ray crystallography and EXAFS.

A recent development has been the characterisation of the technetium aquanitrido cation $[\{TcN(OH_2)_3\}_2(\mu\text{-}O)_2]^{2+}$, which is the only known transition metal aquanitrido cation.[1] This gives rise to possible new routes for the preparation of technetium based radiopharmaceuticals. The close analogy between the technetium nitrido complexes and the well-known molybdenum oxo complexes is also of current chemical interest.

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AUTOMATED PRODUCTION OF L-3-[^{123}I]-IODO-α-METHYLTYROSINE - A SPECT IMAGING AGENT FOR DIAGNOSIS OF TUMOURS.

by

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Abstract

With the commissioning of the National Medical Cyclotron and the availability of ultra-high purity I-123 a number of iodinated radiopharmaceuticals are currently under investigation as SPECT imaging agents. Of particular interest is the iodinated analogue of the α-methylated amino acid derivative tyrosine.

L-3-[^{131}I]Iodo-α-methyltyrosine (IMT) was first described in a German patent in 1971 as a possible imaging agent for neuroblastoma, ganglioneuroma and melanoma. It was not until quite recently that renewed interest arose for IMT as a potential radiotracer in nuclear medicine.

It has been reported that radioiodinated [123-I]IMT was involved in active amino acid transport across cell membranes and more significantly across the intact blood brain barrier. Preliminary reports have indicated potential use of this compound in the SPECT studies of brain and brain tumour uptake and in the delineation of malignant melanomas. IMT has been labelled with both iodine-131 and with the newer iodine-123 by electrophilic iodination in 70-90% radiochemical yield using a variety of oxidizing agents. The resultant radiopharmaceutical has been prepared in greater than 99% radiochemical and chemical purity.

Because of the production of short-lived PET and SPECT radiopharmaceuticals such as [^{123}I]IMT requires the handling of large amounts of radioactivity, rapid and remote processing is essential.

An automated radiopharmaceutical synthesis system is being developed to initially produce [^{123}I]IMT. The system will perform the complete processing from addition of reagents to final filtration and dispensing and can be modified for the production of other labelled compounds.

THE RADIATION CHEMISTRY OF POLY(ACRYLONITRILE-CO-STYRENE)

by

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Abstract

It is well known that aromatic compounds have much lower sensitivity to high energy radiation than their saturated counterparts. For example, the radiation sensitivity of benzene is much lower than that for cyclohexane, and indeed, in mixtures of these two compounds, the presence of the benzene lowers the radiation sensitivity of the cyclohexane[1]. It is also well known that aromatic polymers have a much lower radiation sensitivity than aliphatic polymers, so that polymers such as the poly(arylene sulfone)s and the poly(arylene ether ether ketone)s have been investigated for applications in high energy radiation environments.

Although this radiation protecting effect of the aromatic group is well established, relatively little attention has been given to determining the range over which protection is afforded to any other more radiation sensitive groups in polymers. For example, is protection essentially a next neighbour effect, or can any absorbed energy be channelled along a polymer chain so that groups distant from an aromatic unit may also be provided with some protection?

In this paper, the radiation sensitivity of a series of poly(acrylonitrile-co-styrene) copolymers[2,3] which have been well characterized for their compositional microstructure, will be considered in relation to the sequence distribution of aromatic units in the copolymers, and the extent of protection provided by the styrene will be assessed.

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THE RADIATION CHEMISTRY OF POLY(ARYLENE ETHER PHOSPHINE OXIDE)S

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Abstract

The poly(arylene ether phosphine oxide)s (PEPO) are a class of thermoplastics possessing desirable properties such as high glass transition temperatures (T_g), high modulus and inherent flame retardancy[1,2]. The behaviour of these materials under ionizing radiation is of interest in assessing their suitablity for use in high radiation environments.

Three PEPO polymers with different aromatic units (Figure 1) were studied. The free radicals produced by gamma radiation were observed by electron spin resonance spectroscopy (ESR). Changes in the molecular weight distributions were determined with Gel permeation chromatography (GPC). ^{31}P nuclear magnetic resonance (NMR) was used to investigate any changes in chemical environments of phosphorous.

Radiation chemical yields of radicals were used to compare radiation resistance between polymers. A mechanism for the radiation chemistry of the poly(arylene ether phosphine oxide)s is proposed.

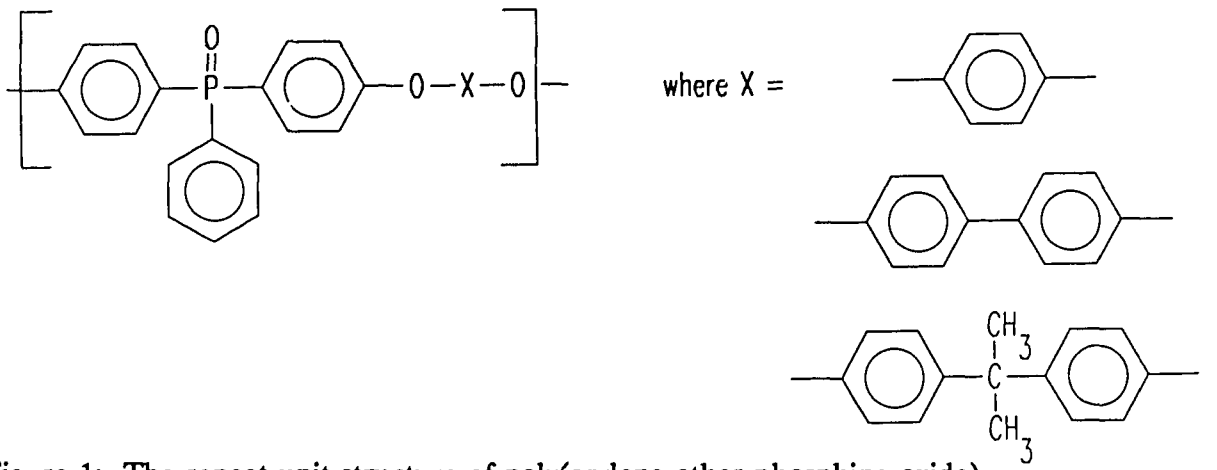

Figure 1: The repeat unit structure of poly(arylene ether phosphine oxide)

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THE RADIATION DEGRADATION OF POLY(METHYLMETHACRYLATE) AT ELEVATED TEMPERATURES

by

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Abstract

The radiation degradation of poly(methylmethacrylate) at elevated temperatures is important because depropagation leads to an underestimation of G(scission), and thus an underestimation of the degree of impairment of the physical properties in applications where poly(methylmethacrylate) is exposed to gamma radiation and high temperatures. Poly(methylmethacrylate) is studied also as a model polymer from which properties of other depropagating polymers may be extrapolated.

In the present work, poly(methylmethacrylate) samples with an initial most probable molecular weight distribution were irradiated in the GATRI facility at Lucas Heights using an aluminium block heater to provide temperatures of 125, 150, 175, and 194 ^{o}C. Experimental parameters (i.e. irradiation vessels, pumping vacuum etc.) were optimized to ensure the efficient removal of degradation products. Weight loss, the average molecular weights, $\overline{M}_n$ and $\overline{M}_w$, were measured as a function of dose and the results interpreted using the available models [1,3] to give estimates of G(scission), G(monomer loss) and depropagation zip length. One interesting result is that because the zip length is of comparable size to the chain length of the polymer for the molecular weight used, the results show a slight increase in average molecular weight of the residual sample early in the irradiation, attributable to removal of low molecular weight material of chain length equal to or smaller than the zip length.

The results are compared with previous work for poly(methylmethacrylate) [1] and other polymers [3].

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RADIATION INDUCED THERMAL DEGRADATION OF POLY (α-METHYL STYRENE)

by

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Abstract

α-Methyl styrene, αMS, has a much lower ceiling temperature (61°C) for polymerization of the pure liquid monomer at 1 atmosphere than other similar monomers, for example, isobutylene 175°C, methylmethacrylate 196°C or styrene 395°C. Therefore, Poly(α-methyl styrene), PαMS, has the potential to undergo radiation induced depolymerization at a relatively low temperature.

At temperatures below 80°C the polymer undergoes scission, but no significant depolymerization is observed. However, at 100°C radiation induced depolymerization is observed to occur at a measurable rate, with a monomer being the only product of the unzipping reaction. The rate of depolymerization increases as the temperature rises to the glass transition temperature, 180°C. At this temperature, in absence of radiation, no thermal decomposition takes places. However, if the temperature is raised to 200°C, thermal decomposition does occur spontaneously.

The loss of monomer and the resultant decrease in the weight of the polymer complicates the measurement of G(-M) and G(S), and requires that the absorbed dose be calculated with allowance for the loss in mass. If the zip length (z) is large, and comparable with the degree of polymerization, chain-end effects cannot be neglected. In these cases z and G(S) must be determined using a Monte Carlo simulation technique. In this paper we will discuss a study of the scission and depolymerization of two polymers with different initial molecular weights, and consider the implications of the results of the study.

COMPUTER ESTIMATION OF THE LEAD EQUIVALENCE OF PROTECTIVE BARRIERS FOR BROAD BEAM DIAGNOSTIC X-RAY BEAMS

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Current attenuation data for lead barriers subject to broad beam diagnostic x-ray exposure conditions is largely based on measurements made with outdated single phase x-ray equipment. The measurement of attenuation data for modern generating waveforms is non trivial and often not possible in a busy hospital medical physics department. Consequently, accurate, computer generated attenuation data, would have a significant impact on estimating the lead equivalence of protective barriers.

The scatter composition of broad beam diagnostic x-ray beams transmitted through lead has been studied and it can be shown that, for up to 150 kVp beams, the overwhelming majority of the scatter, generated in a lead protective barrier, is K-fluoroescent radiation. This process has been modelled analytically, with calculated attenuation curves showing good agreement when compared to measured data from NCRP 49[1]. The exposure ratio between broad beam and narrow beam geometries has been shown to be maximal at 150 kVp with a value of 2.7 occurring at a distance of 10 cm from the barrier. The exposure ratio is found to diminish rapidly with decreasing energy and to be unity at 80 kVp and below. The effect of voltage waveform is seen to be a major factor in determining the attenuation curve.

An iterative programme has been written which allows the lead equivalence of various materials to be calculated once the broad beam attenuation of a beam is known through any particular material. This programme has been found useful in many applications, particularly in estimating the lead equivalence of existing walls in x-ray installations.

[1] National Council on Radiation Protection and Measurement - NCRP Report No 49, Structural Shielding and Evaluation (NCRP Publications, PO Box 4867, Washington, DC 20008, USA)

ENVIRONMENTAL RADIATION PROTECTION IN THE MINING AND MILLING OF RADIOACTIVE ORES AT OLYMPIC DAM OPERATIONS - A REAL OR PERCEIVED RADIATION PROTECTION CONCERN

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Abstract

The mining and milling of radioactive ores has always been associated with providing the largest proportion of the collective dose equivalent from the nuclear fuel cycle. The public and political perception of radiation and the environment is such that elaborate and expensive monitoring programs are required to monitor extremely low levels of radioactivity. At Olympic Dam Operations, the natural exposure from ionising radiation is low by world standards and is potentially lower than exposures encountered in the primary residential regions of Australia. Above the low natural background levels, there is a small component of exposure as a result of the mining operation performed at Olympic Dam. To ensure compliance with the legislation regarding the mining and milling of radioactive ores, one of the most intensive environmental radiation monitoring programs in the world has been developed. The program is also motivated by the desire of Olympic Dam Operations to ensure the protection of the environment and remove potential concerns regarding future expansions of the project. The exposure, due to the operation, is below background and generally well within natural variation in radionuclide concentration. Expressed as a potential health risk to members of the public, operational exposure is minor and, due to the comparitively low background in the area, may actually represent a decrease in the total exposure when natural doses from other residential areas are considered. Olympic Dam Operations is committed to minimising environmental radiation concerns, but the perceived hazard of operational radiation in the environment is overrated and represents an extremely small proportion of the collective exposure from all radiation sources.

RADIATION INDUCED APOPTOSIS

by

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Abstract

Apoptosis or programmed cell death is a distinct type of cell death. It is observed in various systems under different conditions including, during morphogenesis, in hormone dependent atrophy of tissues, cytotoxic T-cell mediated killing, treatment of lymphoid cells with glucocorticoid hormone, ionizing radiation and in human B cells deprived of serum. Apoptosis is characterized by distinct morphological changes which include condensation of nuclear chromatin, blebbing of the plasma membrane with convolutions converting the cell into membrane bound apoptotic bodies in which the closely packed organelles appear intact. The only specific change known at the molecular level is the digestion of chromatin into DNA fragments of approximately 180 base pairs. Apoptosis results from the induction of active processes within the cell. In murine thymocytes there is a requirement for RNA and protein synthesis for apoptosis to occur. However, the majority of human cell types appear to undergo apoptosis independent of RNA and protein synthesis. Protein modification especially phosphorylation and dephosphorylation may play an important role in the mechanism of apoptosis in human cells. We have shown that apoptosis caused by ionizing radiation and heat treatment in lymphoma and leukemia cell lines is accompanied by the dephosphorylation of a few specific proteins. One of these proteins is common to both cell lines. Okadaic acid an inhibitor of phosphatases - 1 and 2A prevented apoptosis in all cases and inhibited the dephosphorylation of a common protein as well as several others (Baxter and Lavin, 1992; Song et al., 1992). In order to study the role of phosphatases in apoptosis we employed sense and antisense oligonucleotides for PP-1 and PP-2A. Antisense oligonucleotides for a common region of PP-1 and PP-2A protected cells from undergoing apoptosis. We have also employed H-89 and Calphostin C, specific inhibitors of cAMP dependent protein kinase (PKA) and protein kinase C (PKC) respectively to investigate the role of protein kinases in apoptosis. in apoptosis. Inhibition of PKA increased the level of apoptosis from 32% to 47% in a B cell line treated with ionizing radiation whereas inhibition of PKC did not have any effect on apoptosis.

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RADIOPROTECTION BY DNA-BINDING BIBENZIMIDAZOLES: CELL CULTURE STUDIES

by

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Abstract

Survival curve studies with cultured cells have established that the DNA binding ligand Hoechst 33342 is a potent radioprotector. Micromolar concentrations confer significant radioprotection; much higher concentrations of classical radioprotectors, -aminothiols - are required for a similar degree of protection. This potency, and the pharmaco-distribution properties of DNA binding ligands, suggests that such compounds may have applications in cancer radiotherapy. Moreover, since the radioprotective activity of Hoechst 33342 is purely fortuitous, it seems possible that even more potent analogues might be developed.

The closely related analogue of Hoechst of 33342, namely Hoechst 33258, is much less potent as a radioprotector in the cell culture system. Measurements of uptake of the ligands into V79 monolayers, suggested that part of the difference in activity could be attributed to differences in cellular uptake[1]. We have now extended these studies by using subcellular fractionation in order to estimate uptake into nuclear DNA. The results of these studies confirm that uptake into nuclei is higher for Hoechst 33342 than for its hydroxyl analogue. However, the results of a series of experiments in which the ligands were added to the culture medium at various concentrations, and then nuclear uptake and radioprotection determined, indicate that the differences in uptake do not fully account for the observed differences in radioprotection. In other words, under conditions where the nuclear concentration of the two analogues is similar, Hoechst 33342 confers greater radioprotection than Hoechst 33258.

Analysis of survival curves according to the linear-quadratic formula indicates that the radioprotectors have a more pronounced effect on the alpha component. This observation is consistent with the results of studies with purified DNA, which show preferential protection of single-hit DNA double-strand breaks.

A newly synthesised analogue has been found to be significantly more potent than Hoechst 33342 as a radioprotector, and further analogues are being synthesised. Given the limited penetration of these DNA binding ligands through cell layers, it seems possible that such compounds might be useful in the protection of critical normal tissues in radiotherapy. For example, in the protection of oral mucosa during radiotherapy of head and neck cancer.

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RADIOPROTECTION BY DNA-BINDING BIBENZIMIDAZOLES: *IN VIVO* STUDIES

by

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Abstract

Previously reported molecular and cellular studies have demonstrated the radioprotective properties of the DNA-ligand, bibenzimidazole Hoechst 33342[1]; the aim of the present study is to investigate this radioprotection *in vivo*.

The avid DNA-binding of Hoechst 33342 and its limited penetration through cell layers[2-4] suggested that the drug would be efficiently delivered to alveolar cells in lung following i.v. injection. This choice of lung as a model system was also motivated by its importance as a dose-limiting tissue in clinical radiotherapy.

Following i.v. injection of Hoechst 33342 into mice, fluorescence microscopy of frozen lung confirmed the uptake of the drug into normal lung tissue. Assays developed to determine the concentrations of the drug in mouse tissues, following i.v. administration, showed that approximately 1% of injected Hoechst 33342 had accumulated in mouse lungs, 20 minutes after injection.

The experimental system to test the efficacy of Hoechst 33342 and other analogues, as a radioprotector in mouse lung involved the irradiation of both lungs of anaesthetized $B_6D_2F_1$ mice (6-8 mice/group) with 250 keV photons, in a specially constructed jig[5,6]. Some groups received an intravenous dose of Hoechst 33342 ranging (40-80μg/gm) up to 1 hour prior to irradiation and another group received Hoechst 33342 alone. Matching sets of untreated control mice were also included.

The response of mouse lung to radiation damage (namely early pneumonitis and late fibrosis) and the potential radioprotective properties of Hoechst 33342 were assessed by measuring the lung function of each mouse. A specially constructed plethysmograph[6], interfaced to a PC with specifically developed software, was used to measure the breathing rate at weekly intervals from 12 to 52 weeks after irradiation.

Currently two experiments are in progress. In one experiment, mice received Hoechst at a dose 40μg/gm prior to 15 Gray lung irradiation and in the other mice were given Hoechst 33342 at 80μg/gm and 15 Gray to the lungs. These results and others with varying doses of Hoechst 33342 and irradiation will be presented.

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RADIATION BIOLOGY AND THE LABORATORY MOUSE

by

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Abstract

Inbred strains of mice (e.g. BALB/c) offer many advantages for controlled research in a number of fields. In radiation research we used these mice for the study of immunological factors in xenogeneic bone marrow transplantation and in pregnancies.

In each case the advantage of a small, easily maintained inbred species of short lifespan and genotypic uniformity was of significant value. The initial objection to their use was the difficulty of bleeding and intravenous injection. The first problem was solved by adopting a modified retroorbital bleeding technique using 1 cm lengths of 1 mm diameter glass capillary tubing inserted 2-3 mm through the ocular fornix of the anaesthetized mouse after gently pressing on the jugular veins to produce engorgement of the retroorbital venous plexus. This is a simple and harmless procedure which can be learned in a few minutes by a person of reasonable manual dexterity. Intraveous injection into the same venous plexus is even easier - a 26 gauge needle is inserted through the eyelid directly into the retroorbital space and as much as 1-2 ml of fluid can be injected without leakage externally or into the tissues.

In our experiments on bone marrow transplantation rat bone marrow was obtained by forcing saline through the long bones which had been prepared by removing the epiphyses. The mouse haemopoietic system was effectively destroyed by exposure to 9.0 Gy of whole body irradiation from a Cobalt-60 source. Proof of transplantation was shown by finding rat haemoglobin in the mouse after it had recovered haematologically.

The pregnancy studies involved directing a 1 cm diameter beam of γ-rays at the abdomens of 8-12 days pregnant mice. Maternal lymphocytes which were present in the embryos at a rate of 1/1000 in an unirradiated mother rose dose dependently to as much as 250/1000 36 hours after exposure to the highest dose of radiation used (5.52 Gy).

My principal collaborators in this work were D. Perkins and B. Markovic.

TEXTILES AND UVR PROTECTION

M T PAILTHORE AND N JESSEN

ABSTRACT

There is now little doubt that the incidence of skin cancer and personal UVR radiation doses are closely related. In Australia, there are 140,000 new cases of skin cancer reported each year with 1,000 deaths directly related to skin cancer.

Sun block creams with SPF (Sun Protection Factor) ratings of 15+ have been on the market in Australia for over 15 years, however recent press releases have reported that, in spite of the widespread use of sun block creams, the incidence of skin cancer has not diminished.

The obvious alternative is to "cover up" using textiles. However, do summer weight textiles provide adequate UVR protection?

This paper reports our work to date on the evaluation of the UVR protection afforded by summer weight clothing.

The matters dealt with include the use of UV spectrophotometers for the measurement of the UVR transmission of fabrics; the correlations with "on-skin" (in vivo) measurements; the effect of direct versus diffuse irradiance; the influence of wet versus dry textiles; and the impact of fabric construction, fabric finishing and additives such as dyes, fluorescent whitening agents (FWAs) and UV absorbers.

One of the most surprising outcomes of this work was that many summer weight textiles provide relatively little UVR protection and would only rate an SPF of 5+ or 10+. When wet, these same textiles generally provide even less UVR protection.

THE EFFECT OF ANTIOXIDANTS ON THE PHOTOCHEMICAL DEGRADATION OF TRYPTOPHAN IN A RIGID MEDIUM

by

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Abstract

Whitened wool, which has been treated with a fluorescent whitening agent (FWA), suffers from accelerated and photosensitised yellowing when exposed to ultra-violet (UV-R) radiation.[1] The source of the yellowness in both the cases of whitened and natural wool, is thought to be the degradation products of tryptophan (TRP), a photolabile amino acid residue present in wool keratin.[2] The photoproducts are thought to be generated by the reaction of TRP with singlet state oxygen ($^1O_2$).[3] The accelerated yellowing of whitened wool is thought to be due to the FWA acting as a photosensitiser, by generating $^1O_2$ in triplet-triplet energy transfer with molecular oxygen.[4]

The degradation of TRP to coloured photoproducts is thought to proceed via hydroperoxide intermediates.[5][6] These reactive intermediates have been successfully neutralised by the use of antioxidants, which are widely used in the plastic and food industries.[7][8][9]

Therefore, the effect of antioxidants on the photodegradation of TRP in a rigid, oxygen permeable medium, methyl cellulose (MC) was studied with the view to reduce the accelerated yellowing experienced by whitened wool. A number of problems associated with combining basically insoluble antioxidants with water soluble MC were overcome. The antioxidant effect was evaluated using TRP degradation quantum yield studies relative to the quanta absorbed by the FWA in the system.

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ENHANCEMENT OF DNA DAMAGE IN TUMOR CELLS BY ADPRT INHIBITOR IN γ-IRRADIATION, BLEOMYCIN TREATMENT OR HYPERTHERMIA

by

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Abstract

ADP-ribose transferase (ADPRT) is a chromatin-bound enzyme which catalyzes poly ADP-ribosylation in the post-translational modifications of chromosomal proteins. ADPRT was reported to be involved in the process of DNA repair. In this paper, the sensitizing effect of ADPRT inhibitor, 3-aminobenzamide (3AB), on tumor cells in case of radiation, chemical treatment and hyperthermia was studied. DNA strand breaks were measured by fluorometric assay of DNA unwinding. No DNA strand breakage and cytotoxicity were seen when HeLa S3 cells were treated with 8 mmol / L 3AB alone. It implicated that the following sensitizing effects were not due to drug toxicity.

After incubation for 30 min at 37°C, DNA strand breaks were almost completely rejoined in 2-8 Gy γ-irradiated tumor cells; if 3AB was added before irradiation, residual DNA strand breaks increased significantly, indicating 3AB could inhibit the rejoining of DNA strand breaks. The cytotoxic enhancement ratio of 4 and 8 mmol / L 3AB for γ-irradiation in HeLa S3 cells were 1.36 and 1.39 respectively.

If tumor cells were treated with definite concentration of bleomycin at 37°C, DNA strand breaks were partially rejoined; but when 3AB was added before treatment, rejoining of strand breaks was retarded. The cytotoxic enhancement ratio of 4 and 8 mmol / L 3AB were 2.1 and 2.7 respectively.

Furthermore, when the cells were treated with 3AB, and subjected to γ-irradiation (6Gy) or bleomycin treatment (40 μg / ml, 30 min), the potentially lethal damage repair (PLDR) of the cells was depressed.

3AB could also enhance the killing effect of hyperthermia to HeLa S3 cells.

This work presented some experimental evidences and theoretical background for the promising use of 3AB as a sensitizer in a variety of cases, such as radiotherapy, chemotherapy and hyperthermia in the treatment of cancer.

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SENSITISATION OF DNA BY INCORPORATION OF IODINE OR BROMINE

by

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Abstract

Incorporation of I or Br into DNA, instead of its analog thymine, results in an enhancement of the sensitivity of DNA (to strand breakage) and of cells (to cell kill) by UV irradiation[1]. There is also a modest sensitisation to ionizing radiation[2], which has lead to an interest in the use of IUdR and BrUdR as sensitisers in cancer radiotherapy.

Many of the previous mechanistic studies on sensitisation have involved bacterial systems using DNA sedimentation as the basis for assaying strand breakage, and almost all were done prior to the advent of DNA sequencing and the availability of synthetic oligonucleotides. We have therefore undertaken to study the sensitisation in oligonucleotides with Br-U incorporated at specific sites. Purified oligoDNA was ^{32}P-end labelled, photolysed with UV-B and the cleavage sites produced were compared to the Maxam-Gilbert sequencing reaction products on high resolution sequencing gels. This enables determination of sites of initial attack, in both the substituted and the opposite strands, and the nature of the terminii produced by the break.

Two types of lesions have been identified to date, both in the nucleotide immediately 5' to the site of Br-U incorporation. Both lesions are converted to breaks under mild alkali conditions, but the 5'-end labelled fragments produced have different electrophoretic mobilities. The faster fragment has a 3'-phosphoryl terminus (ie it corresponds to a Maxam-Gilbert sequencing reaction product), but the other requires more severe alkali treatment (viz hot piperidine) before it is converted to the phosphoryl-terminating species.

In addition to further characterisation of the lesions, we intend to extend these studies to intact cells, to enable investigation of their repair.

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The photochemistry of some bi-benzimidazole derivatives and their role in the UV-sensitised cleavage of DNA

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ABSTRACT

The photochemistry of an iodinated analogue of the well known DNA fluorochrome Hoechst 33258 has been studied. The substitution of an iodine atom produces a compound (Iodo-methoxy Hoechst, IMHo) capable of inducing single strand breaks in DNA. This activity is believed to be associated with the photoactivity of the carbon-iodine bond which is a consequence of the altered photophysics of the bi-benzimidazole derivative in the presence of the 'heavy' halogen atom.

The photoproducts observed following UV-irradiation of IMHo were found to be dependent on the presence of oxygen. The photolysis was monitored in a medium containing 20 % ethanol which provides a source of abstractable hydrogen atoms to mimic the DNA substrate. The results indicated the importance of competition between the reaction of molecular oxygen or hydrogen atoms with the de-iodinated radical precursor, MHo·. This effect is not observed, however, for the DNA-bound ligand in which case oxygen does not compete efficiently in the quenching of MHo·.

BORON INFLUENCE ON MAXIMUM THERAPEUTIC DEPTH IN THERMAL NEUTRON CAPTURE THERAPY

by

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Abstract

Much work has been published regarding the relationships between idealized beam energy and the NCT figures of merit of Advantage Depth, Therapeutic Depth, Modified Advantage Depth and Modified Therapeutic Depth. Little has been mentioned, however, of the functional interdependence of these figures of merit with boron-10 concentrations, ie tumour to blood ratios and absolute levels. These relationships were simulated using the Monte Carlo Neutron Photon transport code, MCNP, with an ideal 18.4cm diameter, 0.025eV thermal neutron beam incident laterally upon an ellipsoidal Neutron Photon Brain Equivalent model[1,2]. All depths used are from the brain surface

Increasing the tumour to blood boron-10 ratio predictably increases all figures of merit. Boron-10 concentration was also shown to have a strong bearing on the figures of merit when low levels were present in the system. This is the result of a non-boron-10 dependent backround dose. For a tumour to blood ratio of 4.3, characteristic of BPA[3], little advantage is gained by extending the blood boron-10 level beyond 10ppm. At this point the Advantage Depth is 3.2cm, whilst the Therapeutic Depth reaches to 1.4cm. Similar limiting values of the Modified Advantage Depth and the Modified Theraputic Depth are obtained for BSH[3] with a tumour to blood boron-10 ratio of 1.4 and a 0.3 Capillary Dose Reduction Factor.

To achieve a therapeutic depth of 6cm (brain midline from skull/brain surface), a tumour to blood ratio of 25 with 10ppm Boron-10 in the blood is required for BPA. Similarly, a tumour to blood ratio of 13 with 10ppm blood Boron-10 is required for the Modified Theraputic Depth of BSH to reach the brain midline. These requirements are an order of magnitude above current values for these compounds[3].

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HIFAR EPITHERMAL NEUTRON BEAM FOR BORON NEUTRON CAPTURE THERAPY FOR CANCER

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Abstract

An epithermal neutron beam is essential for the determination of normal tissue tolerance studies in animals, prior to the treatment of patients with local disseminating cancer by Boron Neutron Capture Therapy. An epithermal beam with the 2" collimator in the 10H hole of HIFAR has been characterised for gamma, thermal, epithermal and fast neutron flux and/or dose rate. Al, S, Cd and Pb filters are used to shape the neutron spectrum so as to maximise the epithermal component. These results are then compared with neutron transport calculations using the Monte Carlo code MCNP.

The results so obtained are extrapolated to those expected for a 10" beam, the maximum hole diameter when the 2" collimator is removed. Dose rate and spectrum shape are important characteristics of the epithermal beam in determining whether the beam is adequate for therapy. However, intensity requirements are less stringent for normal tissue studies in animals and the proposed HIFAR beam appears suitable for this purpose.

OPTIMISATION OF NEUTRON CAPTURE RADIOGRAPHY FOR ANALYSIS OF BORON-10 IN TISSUES

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Abstract

Neutron Capture Radiography utilises a Solid State Nuclear Track Detector CR-39 to register the products of the $^{10}B(n,\alpha)^{7}Li$ reaction[1]. These products cause structural damage and can be revealed as pits after chemical etching. However, the $^{14}N(n,p)^{14}C$ reaction concomitantly occurs in boron-10 loaded tissues. To discriminate the proton effect, the etching conditions are found to be 6.25 M NaOH, 70 C° and 60 minutes. The pits and their diameters can be observed and measured[2] by light microscope and photomicroscopy. Thus, the boron-10 distribution in a biological section is mapped by the location and density of pits which is of critical importance for Boron Neutron Capture Therapy.

A semi-empirical formula[3] was developed and used to calculate the etching rate ratios of the alpha, lithium and hydrogen ions. The bulk etching rate (V_B) was calculated using an empirical formula[4]. The pit diameters, the critical angles and the etching efficiencies were determined and compared with experimental results[5]. Therefore, the optimum etching conditions were determined to reveal the alpha and Li-7 pits but not the proton pits. These conditions were then applied to map the boron-10 distribution in tissue samples.

Harding Passey melanoma cells (1-2 $x10^6$ cells) were injected into the right thighs of two female nude mice. After 10 days, one mouse was injected with 5 mg BPA.HCl in 0.5 ml saline and the second mice left as a control. Microtome-sections of 8 ± 2 µm of the tumour, muscle and skin tissues were prepared and covered with CR-39 foils. The detectors were then exposed to a thermal neutron fluence of $2.49x10^{10}$ n cm^{-2} in the Moata reactor. The optimum conditions were applied to etch the CR-39 detectors of the tissue samples to reveal enhanced boron-10 uptake in the tumour relative to normal tissues and control .

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INSTRUMENTAL METHODS FOR INVESTIGATING BORON UPTAKE IN TUMOUR CELLS IN NEUTRON CAPTURE THERAPY

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Abstract

Boron labelling provides a non-toxic and non-radioactive means whereby the time course of uptake and ultimate spatial distribution of drugs and macromolecules in cells can be studied at varying degrees of resolution using the techniques of infrared and electron energy loss spectroscopy, and neutron capture radiography. This paper describes the application of these techniques to measure the uptake and distribution of several boron-labelled compounds and biological macromolecules within cultured melanoma cells and tissue sections. The sensitivity and selectivity have been determined by analysis of standard samples.

Infrared analysis has the capability to determine the boron cluster structures by virtue of their characteristic absorption around 2600 cm-1. With appropriate solvent selection, this absorption is not subject to significant interference. The application of Fourier transform infrared spectrophotometry to the determination of the concentration of polyhedral boron compounds in biological samples will be described.

Electron energy loss spectroscopy in the electron microscope is highly sensitive to elements of low atomic number, such as boron, carbon, nitrogen, etc. With a theoretical resolution of 20 nm, and a detection limit of 500 ppm boron, it is possible to generate elemental maps defining the boron distribution in relation to the intracellular structures. Progress toward this goal will be discussed in conjunction with the developed method of neutron capture (alpha-track) radiography which has a resolution of about 0.01 mm.

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SYNTHESIS AND EVALUATION OF ^{10}B-LABELLED DNA LIGANDS

by

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Abstract

It is well established that DNA is the central target for most radiobiological phenomenon and it is recognised that the optimal location for the ^{10}B for BNCT is the cell nucleus. We have therefore embarked on the synthesis of ^{10}B-labelled DNA ligands, focussing on bibenzimidazoles as the DNA binding moiety. The first of these compounds - *boroHoechst* is essentially a substituted phenylboronic acid. BoroHoechst has been shown to bind to DNA and it is freely taken up by viable V79 cells as demonstrated by both fluorescence microscopy and spectrophotometric assay of the ligand in isolated nuclei. Preliminary neutron capture experiments have demonstrated a significant enhancement of cell kill in the presence of 20 micromolar boroHoechst. The extent of the enhancement is equivalent to that reported for 4 micrograms ^{10}B-boric acid/ml, for "ambient" (unwashed) conditions[1]. Although there are difficulties in making such comparisons between experiments using different thermal neutron beams, it would appear that ^{10}B-boroHoechst is a very effective form of ^{10}B, even compared to ^{10}B- low density lipoproteins[2].

Given the potential for boronic acid to react with 1,2-diols, boroHoechst is probably not an ideal compound in terms of targeting nuclear DNA, we are therefore investigating other analogs. However, the potency of ^{10}B-boroHoechst in the NC experiments to date is very encouraging, especially in view of the possibility of incorporating multiple ^{10}B atoms per ligand molecule.

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LUMINESCENT F-TYPE DEFECTS IN ELECTRON IRRADIATED SOLIDS

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The study of luminescence from irradiated oxide single crystals is a useful means of understanding the processes involved in point defect formation. The defects in these crystals, both inherent and radiation–induced, give rise to properties with diverse applications, for example, thermoluminescence materials or new types of color center lasers. The electrical and mechanical stability of ceramics such as sapphire (α–Al_2O_3) in a radiation environment is currently under study in view of their possible use as first–wall insulators in fusion reactors. Therefore the effect of radiation and the damage produced in these materials is of fundamental importance.

Various forms of radiation may be used in order to create atomic displacement defects in ionic crystals. Electron–irradiation in particular allows a precise determination of displacement thresholds in these materials. By using electron accelerators the energy of the electron beam can be precisely monitored and controlled and the deposition of energy throughout the crystal lattice is more uniform than with irradiation by heavier particles (for example α–particles). Also, the damage produced may be analysed in terms of simple isolated point defects since the electron energies used are generally too low to produce complex damage from secondary processes such as displacement cascades, and the dose rates employed are too low to further excite these defects.

Point defects have been produced in CaO, MgO, and α–Al_2O_3 single crystals by electron–irradiation from a Febetron 706 electron accelerator and thresholds for atomic displacement have been measured using time–resolved luminescence spectroscopy. Oxygen displacement energies of approximately 50eV are found, however a temperature–dependent threshold observed for an emission band in MgO may arise from a magnesium displacement. A 300 nm emission in α–Al_2O_3 may be due to an F–center transition. Studies of electron–hole recombination kinetics are consistent with an electron–detrapping model.

THE EFFECT OF IONISING RADIATION ON CONDUCTIVITY IN LOW DENSITY POLYETHYLENE

by

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Abstract

Thermally stimulated conductivity (TSC) and thermally stimulated depolarization (TSD) currents in low density polyethylene (LDPE) samples were investigated. The samples, 100μm thick with evaporated gold electrodes, were dc-polarized at 70°C at a field strength of 100 kV/cm, cooled to -80°C with the field still applied, and then heated to 90°C at 3°C/min in short-circuit or in the presence of the field to observe TSD or TSC, respectively. These currents are shown to be very sensitive to exposure of the samples to an oxygen-ozone mixture and to X-ray irradiation.

It was found that the TSD currents in oxidized samples contain two peaks labelled D_1 and D_2, around -35 and 50°C, respectively. It is concluded that these peaks are generated by C=O dipole relaxation (reorientation) processes; D_1 peak is driven by β process (glass transition) and D_2 peak by α process. The TSD curves of samples X-irradiated at room temperature and at rotary pump pressure showed also two peaks, a small peak at -45°C due to C=O dipoles driven by glass transition, and a very large peak at 70°C due to release of trapped charge (presumably electrons injected during polarization) from traps created by X-ray irradiation. These traps are probably structural defects of various kinds in the crystalline regions of the samples, from which electrons escape by thermal excitation and/or α molecular motion. The TSC curves in the oxidized and X-irradiated samples showed that charge injection commences around 10°C and increases rapidly with increasing temperature.

Radiation Induced Conductivity in Irradiated Solids

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Pulse radiolysis studies using pulsed electron beam excitation and time resolved microwave conductivity techniques have been used to detect the production of defects within irradiated solids. This enables the observation of the decay of transient radiation induced conductivity changes from 10^{-8}s onwards.

The stability of solids under high radiation doses is being investigated. A Febetron 706 pulse electron beam generator with a 3ns, 0.6MeV electron pulse has been used together with a probing microwave system using microwaves over the frequency range 26 - 40 GHz.

Although electron beam irradiation will produce conductivity changes in some solids, the conversion of the pulse to X-rays gives a more even irradiation of the samples. The electron beam is converted to X-rays using a 0.15mm gold foil. The radiation dose is considerably reduced but signals can be observed in cadmium sulphide, titanium dioxide and polymeric materials containing CdS. Lithium fluoride thermoluminescent dosimetry has been used to monitor radiation doses from X-rays and the conductivity of CdS measured with a dose as small as 100mR.

The effects of X-ray and electron pulsed irradiation on the solid semiconductors (CdS, TiO_2) and the insulators (MgO, $MgAl_2O_4$, Al_2O_3) have been observed. Observations of the radiation induced changes in the electrical conductivity of solids have been made and an attempt to link these to the relaxation of defects from optical emissions.

SINGLE MOLECULE GLASSES PREPARED BY γ-IRRADIATION

by

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Abstract

In samples of bulk amorphous polymer, each polymer chain adopts its random coil conformation in which its entropy is maximized. As such, it occupies on average only a few percent of the available space into which it extends. The remaining space is filled by say, twenty to one hundred contiguous randomly coiled polymer chains. In this way, the occupancy of each volume element is shared by many interpenetrating and entangled chains.

It is, however, possible to prepare polymer samples composed of either single chains or several chains at most. This is accomplished by the free radical polymerization of microemulsions. If styrene is the monomer, the preferred initiating mechanism is exposure to γ-radiation. The polystyrene chains so generated have a high molecular weight (>1 x 10^6). They are contained singly or severally within microlatex particles of order 20 nm in diameter, which is only *ca.* one-third of the random coil dimensions of such high molecular weight chains. This implies that the chains of necessity adopt a compact form commonly known as 'globules'. In this compact conformation, they occupy only a few percent of the total volume that they would display if their conformation were random coil. Space filling segment-segment contacts in a globule are satisfied intramolecularly whereas those in a random coil are satisfied intermolecularly. Below the glass transition temperature, T_g, such microlatex particles are essentially single molecule glasses. Their thermal characteristics, as determined by differential scanning calorimetry, on passage through T_g appear to be unusual, even to the extent of displaying an apparent first order transition exotherm when a second order endothermic transition is both expected and observed with some conventional polystyrene samples. These observations shed light on the microstructural domains of polymers and provide evidence for the existence of localized ordered regions even in apparently amorphous polymers.

Detection of Irradiated Spices - enumeration of microorganisms (DEFT/APC) and thermoluminescence

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Absract

The development of analytical detection methods for the detection of irradiated foods is needed for enforcement of labelling regulations or import prohibitions. Irradiation processing is being used commercially in several countries for decontaminating herbs and spices. For this reason our initial work has been focussed on developing detection methods for irradiated spices. Two methods have been established: the microbiological method combining the direct epifluorescent technique and conventional aerobic plate count (DEFT/APC) and thermoluminescence (TL).

The DEFT/APC has been used for enumerating the microbial flora for over 50 irradiated spices. The DEFT is used to count live microorganisms (irrespective of viability) differentially stained with acridine orange. It has been found that for a spice sample irradiated with an absorbed dose $\geqslant$ 5 kGy the log (DEFT/APC) will be $\geqslant$ 4.5. The method has been used for identifying all samples irradiated with an absorbed dose greater than 5 kGy and 95 per cent of untreated samples. Confirmation that spice samples have been irradiated (and not treated with ethylene oxide or heat) requires another detection method such as thermoluminescence. However the combined DEFT/APC method can be used for screening purposes and also provides an indication of the microbiological quality of spices before and after irradiation processing.

Many irradiated herbs and spices exhibit strong thermoluminescence (the emission of light by release of trapped electrons on heating). It has been shown that this TL is associated with the minerals in the adhering soil and dust in the samples. Positive identification of some irradiated spices displaying weak TL signals requires separation of the minerals from the organic matter by density centrifugation using sodium polytungstate. With this method all irradiated and unirradiated spices have been identified.

Interlaboratory trials with blind samples have demonstrated the suitability of these methods for the routine identification of irradiated spices.

RADICAL-INDUCED CHAIN OXIDATION OF BOVINE SERUM ALBUMIN AND ITS INHIBITION BY CHAIN-BREAKING ANTIOXIDANTS

by

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Abstract

Free radicals (viz. radical oxygen species) have been proposed to be involved in a number of severe disorders in humans, via their action on both lipids and proteins. Exposure of proteins to oxygen-centered radicals results in dramatic changes in their structure, stability and function; these processes have been studied in many laboratories, albeit from a qualitative point of view. To allow quantitative evaluation, we exposed aerated solutions of bovine serum albumin (BSA) to hydroxyl (•OH) and superoxide anion radicals ($O_2^{\bullet-}$) generated radiolytically under conditions when all primary radicals reacted with the protein. We observed that for each •OH radical generated initially approximately 35 amino acid residues were consumed. When bilirubin or the water-soluble vitamin E analogue Trolox were added at a two-fold molar excess over BSA, the initial consumption of all measured amino acids, except tryptophan, decreased about 4-fold. The total mass of amino acids protected from radical-induced loss exceeded the amounts of antioxidants present initially. Such protective activity was not observed when BSA solutions were supplemented, prior to radiolysis, with the antioxidant inactive acetyl Trolox. Our results show that, under saturating conditions, radical-mediated oxidation of proteins can proceed via a chain reaction that may be inhibited by chain-breaking antioxidants.

RADICAL IONS IN RADIATION AND PHOTOCHEMISTRY. MAGNETIC RESONANCE AND OTHER STUDIES†

by

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Abstract

Radical ions are a ubiquitous species in radiation and in photoionization. We examine their reactions and suggest an overall framework to explain chemistry above ionization.

Time-domain studies of initial charge pair in radiolysis and in photoionization include picosecond emission study of recombination fluorescence. Nanosecond optically detected magnetic resonance studies have provided considerable detail of radical cation chemistry in both radiolysis and in photoionization. Flash photolysis and time-resolved dc-conductivity studies of photoionization were carried out to determine the energy dependence of yields of radical ions in photoionization. Product studies were carried out as well. These results led us to modify the mechanism of photoionization to include ion-molecule reactions of excited radical cations:

$$AH \xrightarrow{2h\nu} AH^{+\bullet *} + e$$

$$AH^{+\bullet *} + \underset{\text{solvent}}{RH} \longrightarrow A\bullet + RH_2^+$$

Several products from photoionization of aromatic compounds AH in hydrocarbons and in alcohols using excimer laser excitation were characterized. This chemistry is a dominant pathway for destruction of aromatic solutes in such solutions. An analogous mechanism of radiolysis can be considered, where the excited radical cation undergoes ion-molecule reaction:

$$RH^{+\bullet *} + RH \longrightarrow R\bullet + RH_2^+$$

Product yields, fast radical production and the observed difference between fluorescence and electron scavenging are all consistent with such a radiolysis scheme.

The reaction of excited radical cations is the pivot of the proposed "high-energy" chemistry. How much to we know about the occurrence of such radical cation species and how can we characterize them? We use special low temperature matrix-zeolite to stabilize the radiation created radical ions, examine their chemistry and obtain direct and indirect evidence for the role of excited radical cation states.

We conclude that radical ions are the key to a wide area of chemistry above and below the ionization threshold.

†Work performed under the auspices of the Office of Basic Energy Sciences, Division of Chemical Science, US-DOE under contract number W-31-109-ENG-38.

PRESSURE AND TEMPERATURE EFFECTS ON ION-ELECTRON RECOMBINATION RATES IN GASES

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Pulse radiolysis using a Febetron 706 accelerator coupled with an a.c. microwave conductivity technique, has been developed to measure ion-electron recombination rate constants in gaseous helium, argon and carbon dioxide. Unlike previously used glow discharge methods, the pulse radiolysis technique allows moderately high pressures (up to approximately one atmosphere) to be studied. This enables any three body effects to be detected and measured.

The total rate constants in these systems were resolved into contributions from two and three body recombination processes for the first time.

The reaction observed in all rare gas systems is

$$(He)_2^+ + e^- \longrightarrow \text{Products}$$

The particular emphasis in this current work is to study the pressure and temperature dependence of the three-body rate constant, α_3.

A temperature dependence of $T^{-2.9}$ has been determined for α_3 in helium, but since the total rate of recombination in argon shows little or no dependence on pressure, values of α_3 cannot be determined for this gas.

The results of experiments currently underway on carbon dioxide will also be presented.

COMPARATIVE STUDIES OF UV-INDUCED DNA CLEAVAGE BY STRUCTURAL ISOMERS OF AN IODINATED DNA LIGAND

by

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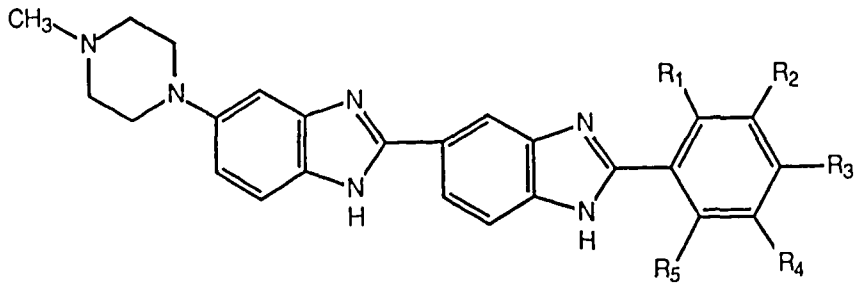
Abstract

It is well established that introduction of a halogen atom into DNA, for example by incorporation of halogenated uracil, sensitises the DNA, and cells containing such DNA, to UV and ionising radiation. The extent of sensitisation is much less pronounced for ionising radiation. In the case of UV, it seems likely that the mechanism of sensitisation involves formation of the uracilyl radical which abstracts a deoxyribosyl H-atom from a neighbouring nucleotide, thus inducing a DNA strand break.

We have extended this idea by incorporating iodine into a DNA ligand so that sensitisation is not limited to cells in the S-phase of the cell cycle. The analogue iodoHoechst 33258 (**1**: R_2 = I; R_3 = H) sensitises DNA and cells to UVA[1]. We have now synthesised analogues of iodoHoechst in which the position of substitution varies. The analogues only have an iodine substitutent, without any hydroxyl group, and the iodine is in either the *ortho* (R_1), *meta* (R_2) or *para* (R_3) position.



DNA breakage studies using plasmid DNA demonstrate a marked difference in sensitisation of UVA-induced DNA single-strand breaks by the four compounds. The order of decreasing activity is:

- *ortho* > *meta* > *para* > iodoHoechst 33258

Analysis of strand breakage on DNA sequencing gels also reveals differences in both the site of cleavage and the nature of the terminii left either side of the induced DNA strand break. For example, the cleavage site for *ortho*iodoHoechst is one nucleotide closer to the 3 or 4 consecutive AT base pairs that characterise the ligand binding site, than that for the other analogues.

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EVALUATION OF PERFORMANCE OF ANTIOXIDANT/ANTIOXIDANT SYSTEMS IN IRRADIATED NATURAL RUBBER LATEX

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Abstract

The radiation vulcanisation of natural rubber (NR) latex (RVNRL) has been investigated for many years. Commercially available centrifuged NR lattices have been used to produce RVNRL but with no satisfactory results. Recently Sri Lankan National Research Group of RVNRL developed a special NR latex concentrate which could successfully be used in radiation vulcanisation process. However, the ageing properties of the resultant latex films were poor.

This paper describes the results of an investigation conducted to improve the ageing properties of RVNRL films. It has been observed that certain antioxidants can improve ageing properties of RVNRL films and also there are optimum ratios of antioxidant concentrations at which the maximum retention of tensile properties could be observed

ROLE OF ALPHA EMITTING RADIOISOTOPES IN THERAPY OF SUBCLINICAL METASTASES

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Abstract

Subclinical cancer metastases are lesions of size such that they cannot be detected by current technology. Lesions may contain less than a few thousand cells with diameter much less than 1 mm. The use of specific cancer targeting biochemicals or monoclonal antibodies with beta emitting radioisotope labels is not indicated because of the range of the electrons, being of the order of millimetres. Thus most of the energy leaves the target cell to give a much higher dose to normal tissue. Alpha particles ranges are much shorter, 20-60 um, and as such alpha emitting radioisotopes are preferred as therapeutic labels.

These radioisotopes cannot be produced in reactors but can be formed by charged particle reactions with light or heavy ions using cyclotron or tandem accelerators. Suitable reactions are identified which produce radioisotopes with suitable properties for binding to cancer cell specific carriers. ^{211}At can be formed using the ^{209}Bi(alpha,2n) reaction, but bond strength is weak. More suitable radioisotopes can be formed from B, C, N and O beams reacting with neutron deficient rare earth nuclides.

The first experiment proposed to use this technology is the purging of leukaemia cells in autologous bone marrow transplantation, using antibodies labelled with a suitable alpha emitting radionuclide.

RADIATION SENSITISERS AND THE RADIATION CHEMISTRY OF DNA

by

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Abstract

Although a mammalian cell may typically contain 70-80% water, the aqueous component is, in effect, a highly concentrated solution of organic material so that the lifetime of a hydroxyl radical or hydrated electron will be extremely short and reaction will typically take place within 4 mm of its site of origin. Thus to all intents and purposes radiation chemically induced damage to DNA in cells arises from energy deposited within, or close to, the DNA molecule. The DNA in the cell can be regarded as a complex of DNA and water, and energy loss events from ionising radiation will, in most cases, involve deposition in both the DNA and water component, the presence of each component modifying the radiation chemistry of the other. Modification of radiation damage by radiosensitisers will also require close proximity between the DNA and the sensitiser.

Two main techniques have evolved for studying the effects of energy deposition within DNA and its associated water of solvation. Time-resolved radiation induced luminescence can measure the quantity of excited states and reveal information regarding the processes that either gave rise to the excited state or those that compete with radiative processes. Observations of steady state emission during a nanosecond electron pulse from DNA doped with a radiosensitiser led to the conclusion that the sensitiser could interfere with geminate ion recombination by electron capture and that the efficiency of this process depended on the electron affinity of the radiosensitiser. Complementary studies using diffuse reflectance spectroscopy of DNA samples doped with radiosensitisers led to the conclusion that on the microsecond timescale of these experiments, quenching of the absorption changes by the sensitiser occurred through the scavenging of electrons which had escaped their geminate partner. Luminescence quenching via geminate ion scavenging by misonidazole was 50% effective with 1 sensitiser molecule per 25 base pairs, whereas scavenging of free electrons occured with 50% probability with 1 sensitiser molecule per 90 base pairs.

Investigation of the reactions of the purine and pyrimidine nucleotides with OH radicals has led to the classification of the resulting radical intermediates into those with either oxidising or reducing properties. In addition, some primary purine radicals undergo a redox inversion reaction which can occur in competition with fixation or restitution reactions with dose modifiers, such as radiosensitisers or radioprotectors. In general the oxidising radicals of the nucleobases do not react efficiently with oxygen or oxygen mimetic radiosensitisers, whereas they will react with reducing agents, which includes most radioprotectors. Conversely the reducing radicals of the nucleobases are susceptible to reaction with oxygen and other oxidants, including radiosensitisers, but show no reactivity towards reducing agents.

In conclusion, radiosensitisers can modify the radiation chemistry of DNA by interaction at various stages from initial ionisation to secondary radical reactions.

TOWARDS EPITHERMAL BORON NEUTRON CAPTURE THERAPY FOR CANCER

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Abstract

Progress in the treatment of local disseminating cancer is poor, and the ability to kill individual cancer cells in the midst of normal cells has not yet been achieved. Binary therapies hold the most promise for this, and of these Boron Neutron Capture Therapy is the most advanced[1]. Epithermal neutron beams are essential for outpatient treatment and these are now installed in Europe and the USA, and are at the design stage in Australia[2]. These beams would allow bilateral irradiation of the entire brain, and as such are ideally suited for the prophylactic therapy of subclinical metastases. When coupled with appropriate boron compounds, therapeutic ratios of between 2 and 3 should be obtained.

However, there are serious limitations with BNCT which relate to the stochastic nature of the microscopic dose, the heterogeneous uptake of boron compounds by metastases, the positive and negative aspects of the blood brain barrier, and the possible affinity of labelled amino acids for the dopamine and noradrenalanine tracts in the brain. These disadvantages are offset by the possible dose sparing to capillaries. Recent results for normal tissue damage in rats and dogs will be reviewed. These data suggest that sparing of capillary endothelium occurs both in skin and in brain.

The application of BNCT for high grade glioma, metastatic melanoma, breast cancer and metastases to the liver will be discussed in the light of the above considerations.

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DEVELOPMENT OF NEW BORON COMPOUNDS FOR USE IN NEUTRON CAPTURE THERAPY OF MELANOMA

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Abstract

Neutron capture therapy (NCT) for cancer is based on the use of a boron-10 labelled compound which can localise preferentially in the tumour cells, there to be activated by neutron irradiation. The successful use of p-boronophenylalanine (BPA) as the agent for the delivery of boron to melanoma for NCT is based on it being incorporated with tyrosine as a precursor for melanin synthesis[1]. Ideally for the patient undergoing NCT, the boron concentration in the tumour should reach 20 to 30 ppm, and for BPA this level can be achieved by the administration of very high doses. However, the procedure would be improved by a compound with the same affinity for the tumour but with a larger boron content. Consequently a new generation of boronated amino acids are being synthesised to take advantage of the unique bonding characteristics of boron and its ability to form cluster compounds containing up to 12 boron atoms in a compact structure. Following this approach, we have synthesised a 1,2-dicarba-dodecaboranyl derivative of phenylalanine for potential use in NCT of melanoma and other cancers.

The synthesis of DBPA was initially approached by adaptation of the literature synthesis of aminoacids, using a phthalimido malonate intermediate as a means of protection of the NH2 and COOH groups. However, the product was contaminated by side products from the de-protection step, and proved difficult to purify. An alternative procedure was devised to eliminate this problem and a pure product was achieved in good yield. All the intermediates and the DBPA have been characterised by NMR, infra red and mass spectrometry.

The aqueous solubility of DBPA has been found to be lower than that of BPA, but this can be increased by the use of cosolvents. Conversion of the closo-carborane ring to the anionic nido form was successful, resulting in a product of much increased aqueous solubility. Preliminary biological testing indicates that closo-DBPA is not toxic to mice when administered to give the same boron dose as is used for BPA.

Supported by The National Health and Medical Research Council of Australia.

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POSITRON LIFETIME CHARACTERIZATION OF POLYMERS

by
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Abstract

Acquisition of a positron annihilation lifetime spectrometer (PALS) at Monash University has allowed the investigation of free volume related effects in polymer systems to be carried out in Australia. Recently long term positron experiments in some molecular solids have suggested that the irradiation of the sample with time creates radicals which accumulate and influence ortho Positronium (oPs) formation probability.[1-4] This phenomenon is very important to any long-term studies of polymers where the source is constantly in contact with the sample, as it is the oPs component of the lifetime spectra which gives information about the size and relative concentration of free volume sites. Thus this influence on oPs formation probability in some polymers must be taken into account when using PALS to examine free volume related phenomena.

For the present study, oPs annihilation data has been collected over 8 days for polycarbonate (PC) and linear low-density polyethylene (LLDPE) at room temperature. The results are presented in the figure below. The oPs lifetime τ_3 is related to the mean free volume cavity size, and τ_3 (not shown) remains constant with time for both polymers. The oPs intensity I_3, which is related to both the oPs formation probability and the number of free volume cavity sites, remains constant for the PC but decreases for the LLDPE. If one is to assume that the free volume at room temperature in LLDPE is not being affected by the radiation[4], we must conclude that the formation probability of oPs is being inhibited with irradiation time. In aqueous solutions positive ions have been shown to act as oPs formation inhibitors[5]. The oPs inhibition in solid polymers is an interesting phenomenon in itself and can hopefully give information on the species formed by this type of radiation damage. The different irradiation behaviours of these two polymers points to a link between the polymer chemistry and the oPs inhibition mechanism.

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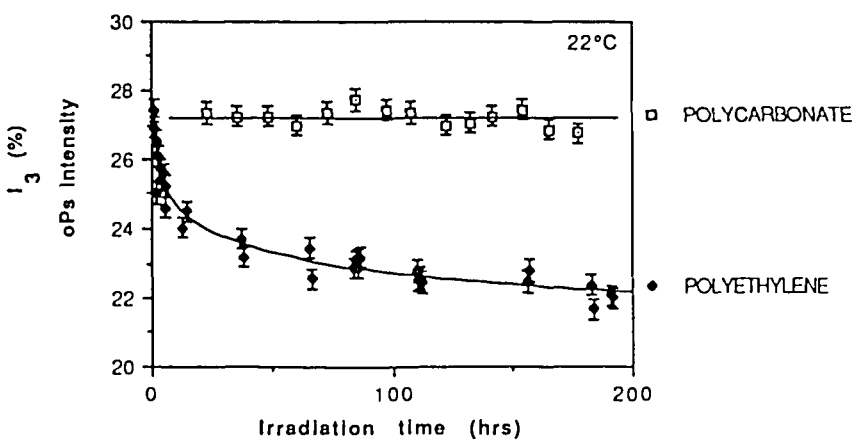

MOLECULAR CHARACTERIZATION OF DNA-BINDING PROTEIN ABNORMALLY DISTRIBUTED WITHIN THE CELLS OF PATIENTS WITH ATAXIA TELANGIECTASIA.

by

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Abstract

Ataxia-telangiectasia (A-T) is characterized by immunodeficiency, neurodegenerative changes, hypersensitivity to ionizing radiation and predisposition to cancer. We have recently described the appearance of a specific DNA-binding protein in nuclei from human cells exposed to ionizing radiation[1]. The DNA-binding protein was originally identified in the cytoplasm of the untreated cells, apparently being translocated to the nucleus in response to radiation exposure. This protein was originally identified by its ability to bind the 72bp distal respect of SV40 enhancer and the protected motif was shown to be 5′ ACCCTAACTGACA 3′. A similar activity is constitutively present in unirradiated nuclei of cells from patients with A-T. Purification of binding activity from A-T nuclei and control cytoplasm by affinity chromatography gave rise to a set of 4 similar sized bands on SDS-PAGE. Southwestern and UV crosslinking experiments revealed that a 70kDa polypeptide has the highest affinity binding for both cell types. We obtained N-terminal and internal sequence for the 70kDa protein. Oligonucleotides were synthesized based on the amino acid sequence and cDNA were generated using PCR employing gene-specific primers and an oligo-dT adaptor primer. The sequence of full length cDNA clones will be presented. It seems evident that this protein plays an important role in cellular response to radiation damage.

Reference:

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Purification, Characterisation and Separation of a Radiation-Activated DNA-Binding Complex Isolated from Human Cells

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Abstract

In 1990, the first DNA-binding protein was described which was activated by ionising radiation (1,4). This protein was found to pre-exist in human cells in an active form, was absent from the nucleus, and believed to be sequestered to the cytoplasm by an inhibitor.

This protein was purified from crude cytoplasmic extracts through the use of affinity-chromatography to a point pure enough for characterisation studies. This DNA-binding protein was shown to be phosphorylation dependant for its activity. It was heat labile, approximately 70kD in size with a K_d of $1.205 \times 10^{-6} M^{-1}$. The binding activity, *in vitro*, was also resistant to high salt (40% binding at 1M NaCl) and found to have sites upstream of the *c-myc* gene and the immunoglobulin *kappa* light chain enhancer (2). *In vivo*, the DNA-binding activity was shown to be independent of transcriptional and translational restraints, and translocated to the nucleus within 15 minutes of radiation treatment (1).

The purified extract was shown to contain four proteins, two of which show DNA-binding activity (70kD and 47kD) the others possibly protein-protein interaction (55kD and 31kD) (2). This DNA-binding activity was shown to be abnormally distributed in the radiation-sensitive Ataxia-telangiectasia (A-T) cell lines, but no distinguishable difference could be detected between the binding activities of normal and A-T cell lines (3). Thus it was necessary to separate all of the purified proteins in order to detect an abnormality in a non-DNA-binding component of the complex.

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CURRENT STATUS OF RADIATION PROCESSING IN MALAYSIA

by

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Abstract

Radiation Processing Program is being developed at the Nuclear Energy Unit (NEU). The NEU has two Co-60 facilities (160 KCi and 4000 Ci), two electron beam accelerators (3.0 MeV and 200 keV)and one Ultra Violet irradiation system. These facilities are all being used to carry out R & D in the applications of radiation and to provide irradiation services to industry. Radiation curing, radiation effects on polymer, radiation processing of rubber, radiation crosslinking of plastic and radiation processing of agro-industrial waste are the areas which have great potential to be applied in industry in Malaysia. In this research work, emphasis is given to the utilization of indigeneous materials such as natural rubber and palm oil.

RADIATION GRAFTING OF ETHYLENE-PROPYLENE ELASTOMERS WITH HYDROPHILIC MONOMERS

by

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Abstract

The grafting of hydrophilic monomers onto ethylene-propylene elastomers (EPM rubbers) has been studied using the simultaneous method initiated by ionising radiation. The monomers examined included acrylamide, vinyl pyrrolidone, hydroxyethyl methacrylate and acrylonitrile with four different EPM rubbers. The effect of solvents, particularly methanol and water on the grafting yield was evaluated. The significance of homopolymer inhibitors such as Mohr's salt, $Cu(NO_3)_2$ and $FeSO_4$ was investigated. The role of novel additives including acid, lithium nitrate and multifunctional acrylates in enhancing grafting yields was studied. A novel mechanism for the effect of these additives is proposed.

THE EFFECT OF SIMULATED LOW EARTH ORBIT RADIATION ON POLYMERS

BY

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Spacecraft in low earth orbit are subjected to significant levels of high energy radiation, including UV and VUV wavelengths. The effects of UV radiation are enhanced over those at the surface of the earth, where the only incident wavelengths are greater than 290 nm. In low earth orbit the incident UV wavelengths extended below 290 nm into the VUV region, where the Lyman-α emissions of atomic hydrogen occur at 121 nm. In addition to electromagnetic radiation, in low earth orbit polymer materials may also be subjected to atomic oxygen particle radiation, which will result indirect oxidation of the polymer.

Thus, polymeric materials for space applications must exhibit a resistance to radiation damage by VUV and atomic oxygen. One class of materials which have this characteristic are the polyimides.

Polyimides are prepared from the reaction of a tetracarboxylic acid dianhydride with a phenylene diamine, with final cure over night at 300 ° C .

As part of a materials evaluation program for space applications, we have studied the effects of UV-VUV induced degradation processes in polyimides. Thermal Gravimtric Analysis was also used to determine the weight loss due to thermal degradation in an oxidizing environment. The studies involve the photogeneration of radical species in the polymer matrices as the initial steps in the degradation process. In this paper molecular level information for the initial stages of the photodegradation processes obtained from ESR , FTIR and UV-Visible spectroscopies, will be descussed. The synergistic effect of radiation and atomic oxygen on polyimide surfaces, assessed using Scanning Electron Microscopy (SEM) and X-ray Photoelectron Spectroscopy (XPS), will be also considered.

The ESR study revealed the formation of a carbon centred radical. The radical concentration as a function of irradiation time and also the stability of this radical have been investigated under different environments.

The changes in the relative intensity of the asymmetric carbonyl stretch at 1780 cm^{-1} in the FTIR spectrum as a function of irradiation time suggests that the degradation of polyimides is by ablation from the polymer surface. Similarly, the UV absorption spectrum revealed a shift in the absorption with irradiation time. This might be related to the reduction in the electron density due to the dissociation of the imide linkage. An XPS study of the polyimide exposed to UV radiation and oxygen showed that oxidation takes place on the polymer surface.

GENERATION OF HYDROPEROXIDES IN GAMMA - IRRADIATED AMINO ACIDS AND PROTEINS

by

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Abstract

We have recently reported the results of a study (carried out in collaboration with members of The Heart Research Institute, Sydney) demonstrating the formation of reactive groups in some irradiated proteins and amino acids. When the irradiations were carried out in presence of oxygen, the molecules showed chemical reactivity characteristic of the hydroperoxide moiety. The free radicals responsible for the peroxidation were identified as the hydroxyl. The G values of the groups formed on the proteins were 1.2 -OOH moieties per 100 eV for bovine serum albumin and 0.8 for lysozyme. The protein peroxides decayed spontaneously with a half-life of 1.5 days at room temperature. They also reacted with reducing agents, of which glutathione and ascorbate were the most significant.

Of the 20 amino acids tested, only 6 showed comparable susceptibility to peroxidation : glutamic acid, isoleucine, leucine, lysine, proline and valine.

In attempting to test these findings for potential biological significance, we examined the ability of other systems generating reactive oxygen species to cause protein peroxidations. The following were effective; Fe(II)/H_2O_2, Fe(II)/ascorbate/EDTA, peroxyl free radicals, NADH/NADH oxidase/Fe or Cu, xanthine/xanthine oxidase/Fe(III) and stimulated white blood cells. It seems therefore likely that protein peroxides can form in biological systems exposed to reactive oxygen species and that their subsequent reactions can lower the antioxidant potential of the system.

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PROTEIN BOUND DOPA IS A REDUCTANT FORMED DURING GAMMA RADIOLYSIS OF PROTEINS

by

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2 Medical Mass Spectrometry Unit, Department of Medicine, University of New South Wales, Sydney 2031, Australia

Abstract

Protein damage by free radical exposure has usually been thought of as producing relatively inert chemical species, with possible pathology resulting from the loss of enzymatic activity or structural integrity. In contrast to this view, we have shown that proteins damaged by hydroxyl radicals contain a protein bound moiety which can reduce cytochrome c, free iron and copper ions[1].

Using protein acid hydrolysis/HPLC analysis and gas chromatography-mass spectrometry we have demonstrated that protein bound DOPA is a major reductant formed on radical damaged serum albumin (BSA) and bovine insulin. PB-DOPA was also generated enzymatically using mushroom tyrosinase which catalyses the hydroxylation of tyrosine residues. By comparison of the levels of DOPA measured on radical damaged or enzyme treated protein with the observed level of cytochrome c reduction, we have shown that PB-DOPA is a major source of the observed redox activity on radical damaged protein.

Protein bound DOPA may have important biochemical effects such as regeneration of reduced forms of redox active metal ions which may induce subsequent metal-dependent radical generating reactions.

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HORIZONS IN RADIATION POLYMERISATION

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Chemistry School, University of Sydney, Australia, 2006

Radiation chemistry techniques have proved to be very useful in elucidating problems in other fields of chemistry and biology including polymer research studies. Considerable use of gamma radiation has been made in investigating the mechanisms of emulsion polymerisation in developing a model to describe conventional systems initiated chemically and to predict their behaviour. The Sydney University Polymer Group, in particular, using the facilities at Lucas Heights made available through AINSE have honed a fine edge to this investigational tool. Radiation has been used to study relaxation when the system is separated from the source, approach to steady state, burning out of inhibitors and retarders and very low initiation rates. Further extensions of such studies will be considered.

Electron accelerators have been used widely in steady beam mode to bring about curing and grafting reactions but rarely to study their fundamentals except in the model-independant measurement of the absolute rate constants of radical reactions. There are comparatively few investigations using pulsed electron beams despite the great contribution this technique and other very fast time-resolved methods have made in various fields of chemistry. Some measurements have been made of rate constants for reactions between macroradicals and for determining the identity of the species formed; epr has contributed a great deal here but there have also been spectrophotometric studies. Potential research areas in this field will be described. For example, in principle it should be possible to use an repetitively pulsed electron beam to determine propagation rates in the same way as is done by the laser flash photolysis technique. Initiation could be achieved in solid state systems and in opaque systems.

MECHANISM OF THE SENSITIZATION OF RADIATION VULCANISATION OF NATURAL RUBBER LATEX BY MONO-ACRYLATES.

D.J.T.Hill, J.H.O'Donnell, M.C.S.Perera and P.J.Pomery

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Abstract

Chlorinated hydrocarbons have been used[1] as sensitizes for radiation vulcanisation of natural rubber latex. Significant quantities of these chlorinated sensitizers remain in the irradiated latex after vulcanisation and can be released into the environment during subsequent processing or use. To avoid the leaching of these hazardous materials attempts have been made to develop new sensitizers which would not be released to the environment during processing. Polyfunctional monomers, such as dimethacrylates and diacrylates, have been found[2] to sensitize the radiation vulcanisation, but they suffer from the disadvantage of being less solubile in the latex, and as a result make the latex unstable. Further, some monofunctional monomers, such as 2-ethylhexyl acrylate and n-butyl acrylate, have been found[3] to enhance the radiation vulcanisation, even though it was believed that polyfunctionality is essential for vulcanisation.

In this work the mechanism of the effect of mono acrylates on radiation vulcanisation of natural rubber latex, has been studied using Electron Spin Resonance and Infrared techniques.

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ESR STUDY OF GAMMA-IRRADIATED POLYMETHACRYLONITRILE

by

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Abstract

Polymethacrylonitrile (PMAN) has been identified as having potential industrial applications in microlithography as a photoresist. In this work, the γ-radiation of PMAN at -196° C, room temperature, 60° C, 100° C and 130° C has been investigated by ESR spectroscopy. The G-values for radical formation of PMAN have been calculated at the different temperatures; G(R·)=2.4 at -196° C, G(R·)=2.2 at room temperature and G(R·)=0.41 at 100° C.

γ-Radiation of PMAN at -196° C gave an ESR spectrum which was a poorly resolved multiplet. When the sample was photobleached by exposure to high intensity visible light having the $\lambda > 600$ nm , there was a loss of intensity in the central region which can be attributed to the loss of an anionic radical species. Then, when the sample was annealed to room temperature, the ESR spectrum had a similar structure to that for a sample irradiated at room temperature.

When PMAN was irradiated at room temperature, the ESR spectrum was assigned primary to two radicals; one being a propagation radical and the other being a polyimine radical. When the sample was warmed to 100° C, the propagation radical disappeared and the polyimine radical remained. The polyimine radical would be quenched when the sample was warmed up to 130° C, which is higher than the Tg (110° C).

When the sample was irradiated at 60° C, the content of polyimine radical increased compared with that for irradiation at room temperature. The ESR spectrum was assigned primary to polyimine radical when the sample was irradiated at 100° C. No significant stable radicals were obtained if the PMAN was irradiated at 130° C.

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MCNP AS A TOOL FOR CALCULATING NEUTRON AND PHOTON DOSES IN TISSUE

by

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Abstract

The coupled neutron-photon Monte Carlo radiation transport code, MCNP[1], developed at Los Alamos, is widely used in the research and analysis of a range of medical applications. These include Neutron Capture Therapy (NCT), californium brachytherapy, in vivo neutron activation analysis and others. At Ansto MCNP version 3A runs under the UNIX operating system on the Fujitsu VP2200 supercomputer. Since the geometry plotting module in MCNP is not portable, the module developed by M.T. Rainbow[2] has been implemented. A significant source of cross-section data for MCNP has been ENDF/B–V[3] data which are not available outside the United States but the latest cross-section data, ENDF/B-VI, are available. Eventually MCNP will be modified to use ENDF/B-VI cross-section data but in the meantime the data at Ansto are essentially from the earlier ENDF/B-IV evaluation.

The MCNP calculations for medical applications often involve neutron and photon dose distributions within tissue equivalent phantoms. MCNP is a flexible, versatile and easy to use code but the accuracy of the calculated results depends on factors such as:

- correct geometric representation, which should be checked using the plotting module,
- quality of the neutron and photon cross section data used, which may not be up-to-date for some nuclides,
- accurate representation of the spectrum, anisotropy and spatial distribution of the source,
- use of appropriate assessment volumes particularly where the spatial variation in flux is large,
- calculation of the appropriate reaction rate or 'Westcott thermal flux' (a thermal flux tally for enegies below, say, 0.4 ev is not useful since it is not a physically meaningful quantity).

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IN VITRO RADIOSENSITIVITY OF LYMPHOBLASTOID CELL LINES FROM BREAST CANCER PATIENTS.

by

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Abstract

There is considerable interest in measuring *in vitro* normal tissue radiosensitivity in individual cancer patients to see if this can predict side effects from radiotherapy. Patients with sensitive normal tissues might then be treated with lower doses to avoid severe side effects while conversely, patients with resistant normal tissues might safely be treated to higher doses with improved tumour control.

We have studied a panel of 46 lymphoblastoid cell lines (LCLs) from breast cancer patients. We have compared their radiation survival curves with those from apparently normal donors, and from patients with the radiation sensitive disease, Ataxia telangiectasia (AT).

Blood samples were obtained from breast cancer patients prior to radiotherapy from which LCLs were established. LCLs from apparently normal donors and from AT patients were used as controls. The LCLs were gamma irradiated from 0 to 2 Gray using a Caesium 137 source.

In vitro radiosensitivity of the LCLs was measured using a tetrazolium (MTT) based growth assay. This colorimetric assay was performed in microplates and measures the ability of viable cells to metabolise a water-soluble tetrazolium salt into a water insoluble formazan product. Surviving fractions from 0 to 2 Gy were calculated. The average surviving fraction at 1 Gy (SF1) for the breast cancer patients was 0.47 with a coefficient of variation (CV) of 26%. SF1 for a control LCL over 11 experiments was 0.48 with a CV of 13% while SF1 for an AT LCL over 31 experiments was 0.15 with a CV of 23%. The results were compared both with flow cytometric studies of the LCLs and the clinical records of the patients post radiotherapy.

IN VITRO RADIOSENSITIVITY OF MERKEL CELL CARCINOMA

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Merkel cell carcinoma (MCC) is a particularly aggressive form of skin cancer that arises from Merkel cells in the basal layer of the epidermis. These cells are of neuroectodermal origin, are nondendritic and contain small dense core membrane bound granules. They can be sparsely scattered but are also found in organised structures near nerves and hair follicles, suggesting a role in the touch response or in signalling the directional movement of hair.

MCC is considered to be rare but the increasing number of patients seen at QRI and their occurrence on sun exposed sites prompted a study aimed at comparing the cultured cells with other sun associated tumours. Since cultures of normal Merkel cells have not been established, these lines will also enable us to obtain a better understanding of Merkel cells and their role in the body.

MCCs are locally aggressive with 50-80% of cases having lymph node involvement at presentation. There is a high incidence of distant metastases (25-40%), a significant mortality with 25-30% of patients dying of their disease, and a high local recurrence rate (30-40%). The recommended treatment has been to give a wide local resection followed by large field radiation in cancercidal doses to the site of excision and to the regional lymph nodes.

Being a small cell carcinoma, MCC is thought to be radiosensitive. However this may not always be the case given the high local recurrence rate. To examine the *in vitro* radiosensitivity we have assayed cell lines established in our laboratory, from MCCs and from EBV transformed lymphocytes (LCLs) from MCC patients (MCLCL). Cells were irradiated using a ^{137}Cs source (dose rate 3Gy/min) at different doses and their radiosensitivity measured.

Because the MCC cell lines grow slowly and with differing growth rates, cells were plated into flasks and periodic growth measurements were made using an MTT growth assay. Growth was monitored until 7 doublings had occurred as estimated from the OD540nm in the MTT assay and then the surviving fractions plotted. Cells were split or had their media changed as required.

Data will be presented showing MCC,MCLCL and control survival curves and the change in radiosensitivity with increasing cell doublings. All lines so far tested are more sensitive than normal LCL lines but less sensitive than an Ataxia Telangiectasia LCL.

This work was supported by the Queensland Cancer Fund.

HETEROGENEITY IN ATAXIA-TELANGIECTASIA: COMPLEMENTATION ANALYSIS OF RADIATION-INDUCED CHROMOSOME ABERRATIONS

by

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Abstract

Cultured fibroblasts and Epstein-Barr virus transformed lymphoblastoid cell lines (LCLs) from patients with ataxia-telangiectasia (A-T) are hypersensitive to ionizing radiation. Both of these cell types have been used in genetic complementation studies on a series of patients. Based on abnormal DNA replication inhibition and enhanced chromosome aberration after radiation exposure, A-T fibroblasts and LCL cell fusion studies showed that there are four complementation groups for both cell types[1,2]. While complementation data is available on the two cell types no attempt has been made to cross-complement fibroblasts and LCLs. Here we present the results of complementation studies on irradiated A-T heterokaryons formed between appropriate combinations of LCLs (4 complementation groups) and fibroblasts (2 groups), using radiation induced chromosome aberrations as a marker. Discrimination between homokaryons and heterokaryons was carried out by prelabelling the DNA of one of the fusion partners with 5-bromo-deoxyuridine which causes differential chromosome staining. Radiation-induced chromosome aberrations were scored in heterokaryons and showed that complementation group 2 in LCL series is in the same group as that of the group D in fibroblast series. The experiments show the feasibility of complementation analysis between the two different cell types.

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CORRECTION OF DNA REPAIR GENE DEFICIENCY IN RADIOSENSITIVE XP AND AT CELLS

by

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Abstract

Both Xeroderma pigmentosum (XP) and Ataxia telangiectasia (AT) are genetic diseases caused by DNA repair gene deficiency. XP cells show hypersensitivity to UV light and AT cells are hypersensitive to ionizing radiation. In this paper, correction of the DNA repair gene defect by DNA mediated gene transfer was reported.

HeLa S3 genomic DNA and selective marker pSV2Neo were cotransferred into XP2OS(SV40) cells by both electroporation and calcium phosphate coprecipitation. The transfectants were selected by G418 and UV irradiation. After gene transfer the survival rates of the recipient cells markedly increased after 1-3 J / m^2UV irradiation. Meanwhile the DNA repair synthesis increased by 12%. After the primary transfectant passed for 20- 25 generations, its genomic DNA was transferred again into XP2OS(SV40) cells, the UV sensitivity of the secondary transfectant was almost the same as that of the primary transfectant. This suggested that the related repair genes from HeLaS3 DNA had stably integrated into the chromosome of the recipient cells.

In the further experiments, HeLa S3 DNA was digested by restriction enzymes, Bgl I, Xba I, Sal I, EcoR I and Xho I respectively. The DNA fragments were cotransfected again. The results suggested the gene responsible for the excision repair of UV damage might locate inside the Bgl I and Xho I digested fragments.

For AT5BIVA cells, HeLa S3 genomic DNA or its restriction enzyme digests were transfected in a similar manner as above. The radiosensitivity was studied after 1-5 Gy ^{60}Co γ-ray irradiation. But no lasting increase of radioresistance was observed in the transfected cell clones. Karyotype analysis of the AT5BIVA cells showed the number 11 chromosome lost or rearranged. Hence the chromosome mediated gene transfer was tried. Two human × mouse hybrid cell lines, FD3 and FD8 were used. The former contains human number 11 chromosome while the latter not. The micro-cells of these two cell lines were prepared and fused with AT5BIVA cells. After twice selection by 4 Gy γ rays, the preliminary results showed that the AT5BIVA × FD3 micro-cell fused clones appeared to be radioresistant, while FD8 micro-cell fused clone not. This suggested that introduction of human number 11 chromosome probably compensated the gene defect in AT5BIVA cells. Further studies are on the way.

Project supported by the National Natural Science Foundation of China.

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GENE MUTATION INDUCED BY γ-RAY IRRADIATION

In MAMMALIAN CELLS

by

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Abstract

In order to study the long-term effect of ionizing radiation and to compare mutagenicity induced by ionizing radiation between mouse and human cells, CHO-K1 and HeLa MR cells were irradiated with ^{60}Co γ-rays. The mutagenesis of one nonessential (hprt gene) and two essential genes (Na^+/K^+ ATPase gene and dhfr gene) have been observed. The mutant defective in hprt , Na^+/K^+ATPase and dhfr gene were selected by 6-TG, [^{3}H] UdR+MTX and ouabain respectively. Enzyme assay confirmed the mutation induction.

At hprt loci, the spontaneous mutation frequency was about 5.0×10^{-6}in CHO-K1 cells. After 1、 2 and 4 Gy γ-ray irradiation, the mutation frequency increased to 22.6×10^{-6}、 38.7×10^{-6} and 94.4×10^{-6} respectively. There was a linear relationship between mutation frequency and irradiation dose. In human HeLa MR cells, the spontaneous mutation frequency was about 9.9 $\times10^{-6}$ and radiation induced mutation frequency were 14.4 $\times10^{-6}$、 26.8 $\times10^{-6}$ and 66.5 $\times$ 10^{-6} after 1、 2 and 4 Gy γ-irradiation respectively. The mutagenicity of CHO-K1 cells was higher than that of HeLa MR cells. The results indicated that the hprt gene was more susceptible to mutagenesis in mouse cells than that in human cells.

At Na^+/K^+ATPase loci, the spontaneous mutation frequency were about 2.6×10^{-6} in CHO-K1 cells and 1.5×10^{-7} in HeLa MR cells. No induced point mutation was found both in CHO-K1 and in HeLa MR cells after 1 to 4 Gy γ-ray irradiation. It suggested that ionizing radiation could induce gene deletion rather than point mutation.

At dfhr loci, HeLa MR cells were irradiated by 4 Gy γ-ray and followed by three times of [^{3}H] UdR + MTX selection to get $dhfr^+/dfhr^-$heterozygous. Then, the heterozygous cells were treated by 4 Gy of γ-ray and [^{3}H]UdR + MTX selection again. We succeeded in obtaining $dhfr^-/dhfr^-$homozygous cells.

The further studies of gene structure alteration are under way by means of RFLP assay as well as by DNA sequencing.

Project supported by the National Natural Science Foundation of China.

ELECTRON ENERGY DEGRADATION IN IRRADIATED GASES

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The irradiation of a gas produces numerous excited states, ions and so-called secondary electrons with a range of energies. Secondary electrons of relatively high kinetic energy slow down by ionising and exciting the medium further, thereby producing more secondaries which may continue the process until they have insufficient energy to cause excitation or ionisation. Thus the number and energy distribution of electrons changes over time and the yields of ions and excited states grows accordingly until all electrons fall below the lowest excitation threshold energy of the gas. The spectrum of electron energies, or the electron degradation spectrum y, is described by a transport equation due to Spencer and Fano. The yield of species s can be calculated using the equation

$$N_S = n \int y(E)\, \sigma_S(E)\, dE$$

where n is the number density of the gas, E is the kinetic energy of an electron, y(E) is the degradation spectrum, and $\sigma_S(E)$ is the energy dependent cross section for excitation (or ionisation) of the gas particles from their ground state to state s.

A time - dependent version of the Spencer-Fano equation has previously been used to predict the rate of growth of ions and various excited states in argon gas. Such data may be compared to experimentally observed formation rates in gases using the technique of pulse radiolysis.

We have extended the theoretical treatment described above to electron degradation in neon gas. The theory is then tested for the first time when we compare the results for both argon and neon to experimental data obtained by irradiating samples of either gas using a Febetron 706 electron pulse radiolysis facility.

ELECTRON ENERGY LOSS IN IRRADIATED MOLECULAR GASES

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The use of ultrafast pulse radiolysis techniques has recently enabled kinetic studies of many ionic and free radical processes to be undertaken but the possibility still exists that primary radiolytic processes may interfere with such studies.

The slowest of all the primary radiolytic processes is the establishment and cooling of the secondary electron spectrum. This process may conveniently be studied in ionised gases since the conductivity depends on the number of electrons present as well as their mobility. Crucially, the mobility is dependent on the mean energy of the electrons and so provided that the loss of electrons is negligible during the experiment then the change in conductivity with time can be directly related to the rate of cooling of hot secondary electrons.

Using helium, where the thermalization time is well known, the effects of addition of small amounts of molecular gases increases the thermalization rate, and is studied using nanosecond pulse radiolysis techniques using time resolved microwave conductivity methods as detection technique. The results to date show that the distribution of electron energies is initially non thermal and also non maxwellian in distribution. This is observed in pure Helium by studying the kinetics of electron energy decay which cannot be fitted to any conventional kinetic order. However, in the case of systems with a trace of added molecular gas, e.g. CH_4, H_2, N_2 the kinetics eventually become pseudo first order. This enables a time to be measured for the attainment of a maxwellian type distribution, further, the pressure dependence of the pseudo first order rate constant will give a two body thermalization rate constant.

Redox Active Surfactants:
Synthesis and Properties of a New Class of Detergent.

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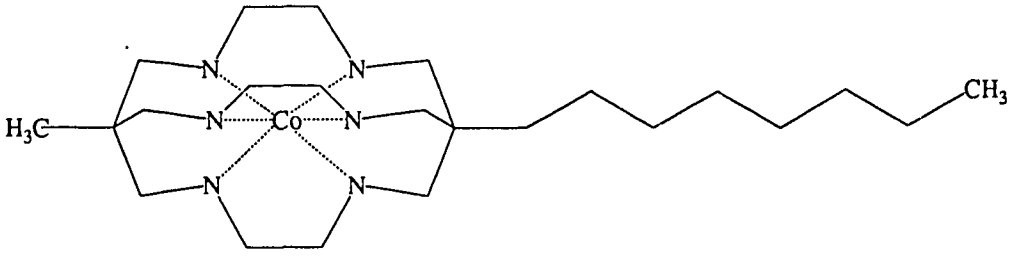
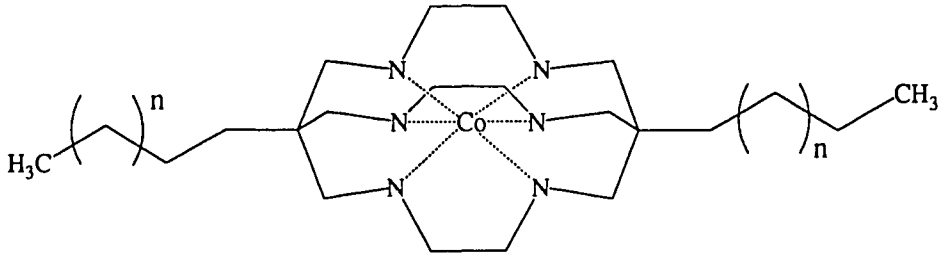
Abstract



(I)



(II); n = 5

Efficient strategies for the synthesis of aliphatically substituted sarcophagine complexes (**I-II**) have been developed. These new surfactants are antithelmetic agents capable of killing tapeworms in minutes. The development of versatile encapsulation strategies is of particular relevance to the applications of cage complexes as radio-pharmaceuticals.

CHARACTERISTICS OF THE RADIATION FIELDS PRODUCED BY THE AUSTRALIAN NATIONAL MEDICAL CYCLOTRON

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During the routine operation of the National Medical Cyclotron thick copper plates electroplated with enriched target material are bombarded with an intense beam of energetic protons and as the result strong neutron and gamma radiation fields are produced. The distribution of the prompt gamma ray dose at various locations of interest in the cyclotron beam room was measured with sensitive thermoluminescence dosimeters. Activation foils were used to estimate the neutron flux density distribution in the vicinity of the cyclotron target and compared with the calculated values. The thermal neutron activation of Ar-40 present in the air and various cyclotron parts like the target station, Faraday Cup, beam tube and the steering magnet, which play a significant role in radiation protection and maintenance work has also been highlighted.

APPLICATION OF A WHOLE BODY COUNTER FOR STUDYING PHARMOCOKINETICS IN MAN AT PICOMOLAR CONCENTRATIONS

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With the introduction of the National Medical Cyclotron at Sydney's Royal Prince Alfred Hospital, researchers in Australia will have the ability to develop a wide variety of positron emitting radiopharmaceuticals. The selection and production of specific ligands and metabolic substrates is time consuming and labour intensive. A method for evaluating these compounds in man in the early stages of development would be a great advantage. However, with a view to minimising radiation burden to volunteers, PET scans which usually require hundreds of MBq's of tracer are impractical. A need exists to study the dynamics of the compounds at much lower radiation levels. Similarly, many research questions may be answered by using positron emitting compounds and low resolution or even regional counting measurements. This would have implications as well for the pharmaceutical industry in early evaluation of new compounds.

A whole body counter has been used to evaluate a variety of ^{11}C and ^{18}F labelled compounds[1]. The counter was originally developed for whole body measurements after neutron irradiation. It consists of 5 pairs of NaI(Tl) detectors placed above and below a bed inside a suitably shielded vault. The subject is injected with around $1/1000^{th}$ of the amount of tracer required for the PET scanner outside the vault and then quickly positioned so that dynamic measurements of radiotracer uptake can be recorded. Competitive binding studies can be performed by using a remote controlled infusion pump containing unlabelled drug. Uptake is recorded over a number of sites, as either coincidences or as single photons, such as brain, heart, liver, skeletal muscle, and bladder. While the device is of obviously low resolution, its exquisite sensitivity allows measurements of drugs down to picomolar levels and represents possibly the most sensitive method for drug detection in vivo. As well, the extremely low radiation dose means that multiple measurements can be repeated in a single interview. Thus the low radiation dose and the low amount of drug mean that the compounds could be studied in man without any concern of somatic or genetic effects. Indeed, the amount of tracer employed is typically less than the amounts of impurities present in commercial drugs.

This paper will present the case for a whole body counting facility to be developed to complement the PET and cyclotron operations. It will have applications in research using currently available compounds, in the development of new compounds, and in the pharmaceutical industry in early evaluation of new compounds.

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IMPROVED DOSE ESTIMATES USING TRANSMISSION BASED SPECT RECONSTRUCTION

by

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Abstract

There is increasing interest in using single photon emission computed tomography (SPECT) to estimate absorbed radiation dose using diagnostic activity in individual patients as a guide to subsequent therapy. Such efforts require accurate correction for photon attenuation so that radionuclide uptake in the target volume can be estimated. In this paper we describe practical approaches to improving the accuracy of activity determination with SPECT.

The simplest method of attenuation correction (AC) makes the assumption of a constant attenuation coefficient (μ) within an elliptical body outline. However, there is now clear evidence that accurate SPECT requires direct measurement of μ values. Attenuation data, derived from transmission measurements, may be used in iterative post-reconstruction AC algorithms (IAC) or can be incorporated into statistically based reconstruction methods, such as estimation maximization (EM). Logistical difficulties with these methods include (a) the increased scanning time imposed by the addition of a transmission measurement and (b) the lengthy computation time of statistical reconstructions.

We have developed a collimated scanning line source which permits simultaneous measurement of emission and transmission data [1], overcoming the first of these limitations. The improvement in quantitative accuracy gained by using these data was assessed in a human lung perfusion study. A 56 year old male volunteer was administered 113MBq of ^{99m}Tc-labelled macro-aggregated albumin (MAA) which is theoretically trapped 100% in the lungs. In the case of AC, an ellipse was fitted to the body outline defined by the reconstructed μ image and a constant μ value of 0.1cm^{-1} was used. For IAC, μ values were derived from transmission data acquired simultaneously with the emission data. Total lung activity was understimated by 19% using AC and 3% using IAC.

To address the second problem, an accelerated EM algorithm has been developed [2]. The algorithm uses ordered subsets (OSEM) of the acquired data at each iteration rather than using all measured projections, typically providing an acceleration factor of 32 compared with standard EM. OSEM has been shown to provide equivalent results to EM and is currently being assessed for its quantitative potential in phantom and human studies.

We conclude that accurate estimation of activity in a target volume is possible using analytical reconstruction methods when combined with transmission measurements. OSEM may be a practical alternative to analytical methods and has the attraction that photon scattering and variable detector resolution can, in principle, be incorporated into the statistical model.

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MOLECULAR NUCLEAR MEDICINE - A NEW FRONTIER

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Abstract

Integration of individual cells is required to maintain life and make a person unique. Their disintegration results in disease or death. Health requires the proper integration of hundreds of billions of chemical reactions. Proper functions require proper chemistry, and diseases can be defined at the molecular as well as cellular level, often before structural changes have occurred. These molecular phenomena include regional blood flow, bioenergetics and intercellular communication. The cyclotron together with positron emission tomography has had a renaissance in modern medicine, based largely on the use of carbon-11 and fluorine-18. Radiotracers make it possible to detect and quantify the molecular abnormalities including intercellular communication that the genes bring about. Molecular blue prints are encoded in the inherited DNA within each cell of the body, making up the "genome", which determine cell structure and, eventually, function. It is estimated that there may be 4,000 human diseases to be genetic in origin. Gene mutation brings about biochemical abnormalities with resultant phenotype. Nuclear medicine is extending the enormous advances in molecular biology and genetics to the medical practice, going beyond the domain of regional physiology to that of in situ biochemistry. Nuclear medicine has entered into a new era of molecular medicine. Disease characterization, planning treatment and monitoring treatment will all be at molecular level. The field will continue to move science into service in a manner that not only helps the patient and the public, but also the economy.

IN-VIVO DOSIMETRY ESTIMATION USING QUANTITATIVE WHOLE BODY POSITRON EMISSION TOMOGRAPHY

by

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Abstract

By performing positron emission tomography (PET) with a scanning motion, the whole body distribution of positron-emitting tracers can be measured in-vivo [1], offering the potential for performing biodistribution studies and dosimetry calculations non-invasively in humans. However, whole body PET has two limitations which restrict its use in dosimetry: (i) the data are non-quantitative since the time necessary to acquire statistically adequate transmission data for attenuation correction (AC) is prohibitive and (ii) counting statistics in the emission study are also limited which precludes imaging at multiple time points.

A segmented AC (SAC) method has been developed which uses image segmentation to process noisy transmission data [2]. To assess the utility of the method for whole body AC, imaging was performed on a realistic phantom of a human thorax containing 0.14μCi.ml^{-1} of ^{18}F in the background. Emission data were acquired for 5 min and transmission data for 2 min. By comparison with high statistics data (3 hr acquisition), the quantitative accuracy was 98% for both AC and SAC, however signal to noise ratio (SNR) was increased from 3.0 to 3.8 in the case of SAC. This is similar to the SNR obtained using AC with 20 min transmission data (SNR=3.7). Therefore, there is no appreciable degradation in SNR using SAC with transmission data acquired for 1/10th of the time normally required.

The sensitivity of a ring tomograph can be significantly increased by removing the interplane septa and acquiring all possible lines of response (3D). The extension of the 3D method to whole body PET has been suggested [3] and studied here to assess its usefulness in human studies. Brain sized (20cm diam.) and torso sized (24cmx32cm ellipse) water-filled phantoms were imaged in 2D and 3D modes. Total activity within the field of view was 90MBq of ^{18}F in each case. Following scatter correction, a calculated (noiseless) AC was applied. The gain in SNR, calculated as the ratio of 3D to 2D SNR, was 1.8 for the brain phantom and 1.5 for the torso phantom, representing a sensitivity gain of 3.2 and 2.3 respectively. Therefore, an overall gain in sensitivity of nearly 3 times can be achieved using 3D whole body scanning.

We conclude that, using SAC and 3D acquisition, quantitative whole body PET can provide biodistribution data with sufficient accuracy and sensitivity to allow imaging at multiple time points for dosimetry calculations in humans.

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THE RADIATION MONITORING AND CONTROL SYSTEM FOR THE AUSTIN HOSPITAL P.E.T. CENTRE

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Abstract

A Positron Emission Tomography (PET) facility has been established at the Austin Hospital, Victoria. PET uses short life radioactive tracers (^{11}C, ^{13}N, ^{15}O & ^{18}F) attached to a variety of pharmaceuticals given to the patient as an intravenous injection or by gas inhalation. The PET scanner produces quantitative functional images of processes in the human body.

A 10MeV cyclotron is dedicated to PET isotope production. This is located in a shielded vault along with the radioactive gas storage and disposal system. Synthesis of radiopharmaceuticals is performed in chemistry modules located in the vault and chemistry hot lab. Stringent quality control tests must be passed before administering the dose to the patient.

The synthesising, handling and quality control testing of these radioactive labelled compounds results in radiation exposure to staff.

A radiation monitoring system and cyclotron vault access control system has been designed and installed in the Centre. These systems will be described and preliminary results discussed.

REDOX REACTIONS OF TETRAAZA-MACROCYCLIC COMPLEXES

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Abstract

Macrocyclic tetraaza and dithiadiaza ligands can stabilise unusual oxidation states of transition metals. The redox reactions of tetraaza pendant arm complexes and of sulfur-nitrogen donors which can act as models for biological electron transfer systems have been investigated using stopped flow and pulse radiolysis techniques and the effects of hydroxy-pendant arms and of ring size (12, 14 and 15 member macrocylces) suggest that ligand geometry and rigidity are the most important factors governing the rates of electron transfer reactions with copper and cobalt.

RADIATION STABILITY OF FULLERENES: PULSE RADIOLYSIS AND LASER FLASH PHOTOLYSIS STUDIES OF C_{60} AND C_{70}

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Although a number of reports are now available on various photophysical properties of C_{60} in different mediums, very little is known about its stability and properties under high energy Γ-radiations. Presence of C_{60} in the interstellar dust has also been often postulated. Hence, it is very important to study the stability of fullerenes under high energy photons and Γ-radiations. Our recent results on the time resolved study of the laser flash photolysis and pulse radiolysis of fullerenes in hydrocarbon solvents will be presented. The transient optical absorption spectra obtained on electron pulse radiolysis of deaerated solutions of C_{60} and C_{70} in benzene is assigned to the triplet state of C_{60} and C_{70}. $G(^{T}C_{60}) = 0.52$ and $G(^{T}C_{70}) = 0.48$ were estimated. However, very low $G(-C_{60})$ and $G(-C_{70})$ in the steady state Γ-radiolysis in benzene and hexane suggest their stability towards Γ-radiation.

THE USE OF PRE-MIX AND STOPPED-FLOW TECHNIQUES IN COMBINATION WITH PULSE RADIOLYSIS

by

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Abstract

Pulse radiolysis is a powerful technique for generating and studying free radicals. The advantage of this technique lies in its capability of producing a large variety of free radicals within less than one microsecond and in observable concentrations (> 1 μmol dm^{-3}). The formation and disappearance of the primary radicals is usually followed by measuring their light absorption. Studies in our laboratory of certain free radicals and metal species have led to the development of methods that combine the stopped-flow and pulse radiolysis techniques, that is, stopped-flow mixing is implemented either immediately before or immediately after pulse irradiation. The first method is used in studies of free radicals with relatively long half-lives ($t_{1/2}$ > 5 ms), which are formed in a solution that passes through a 2 MeV electron beam, prior to mixing with a solution containing the reactant. In the second method, solutions containing compounds that normally react with each other, are rapidly mixed in a jet-mixer, transported to the pulsing cell, and pulse irradiated before the reactants can disappear.
Experiments utilizing conventional pulse radiolysis as well as the pre-mix and stopped-flow methods will be discussed and illustrated with a number of typical examples.

This research was supported by National Institute of Health Grant RO1 GM23656-15 and was carried out at Brookhaven National Laboratory under contract DE-AC02-76CH00016 with the United State Department of Energy and supported by its Division of Chemical Sciences, Office of Basic Energy Sciences.

INTERNATIONAL INTERCOMPARISONS OF TLD BASED ENVIRONMENTAL GAMMA RADIATION MONITORS

by

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Abstract

Thermoluminescent dosimetry is a convenient technique for the measurement of environmental background gamma radiation levels. A relatively simple monitor, using dysprosium doped calcium sulphate impregnated teflon discs as the thermoluminescent material, is capable of giving reliable results given adequate control monitors and some care in the analysis of the results.

We have participated in a number of international intercomparisons of environmental radiation monitors in recent years.[1] These intercomparisons have been conducted by the U.S. Department of Energy and have attracted up to 130 participating organisations from over 30 countries. The environmental exposure sites have ranged from a disused nuclear weapons test site (mainly man-made radionuclides) to a sandy beach site (mainly cosmic radiation). The main precautions required are to allow for extraneous exposures during transit and storage of the dosemeters and to account for fading of the TLD signal. With appropriate analysis, we have achieved results which are within 5% of the actual exposures. This performance is within the top 10% of all participants.

Reference

(1) Young, J.G., Boas, J.F. and Hargrave, N.J., "Participation of the Australian Radiation Laboratory in International Intercomparisons of the Measurement of External Environmental Radiation Using Thermoluminescent Dosemeters", ARL/TR091, 1990.

THE IN-SERVICE EFFECTS OF RADIATION ON THE GRAPHITE MODERATORS OF UK NUCLEAR REACTORS

by

Keith R Millington

Formerly of Nuclear Electric, Technology Division, Berkeley Nuclear Laboratories, Berkeley, Gloucestershire, GL13 9PB, UK. Now at CSIRO Division of Wool Technology, Geelong, VIC 3216.

Abstract

The physics and chemistry of nuclear graphite in commercial UK gas-cooled reactors (Magnox and AGR) are profoundly affected by both neutron and gamma irradiation, and it is therefore essential for safe operation of the plant to monitor and understand the changes which occur through life and to be able to predict graphite properties after further periods of operation. By monitoring the changes which occur in the properties of graphite samples withdrawn and trepanned from various positions within reactor cores throughout the life of the plant, it is possible to refine the predictive models to give a more accurate assessment of the future condition of the moderators.

The most important radiation-induced effects in nuclear graphite are dimensional changes, build up of Wigner energy, radiolytic oxidation, reduced thermal conductivity and the formation of carbonaceous deposits on exposed graphite surfaces. Also important are changes in the graphite / air reactivity and the activation energy for the graphite / oxygen reaction, and changes in the gas transport properties diffusivity and permeability. The mechanical properties of irradiated graphite, of which compressive strength is particularly important since it is a measure of the moderator's load-bearing capability, tend to be somewhat improved, provided that radiolytic oxidation is controlled.

Dimensional changes and Wigner energies at any point in the core, caused by fast neutron damage, are affected by local moderator temperatures and neutron fluxes. By maintaining moderator temperatures sufficiently high, the build up of Wigner energy can be controlled. Measurements of the rate of release of Wigner energy using differential scanning calorimetry suggest that after prolonged exposure the rate of release saturates for a given moderator temperature.

Optimisation of the coolant composition by adding small amounts of CO and methane (or hydrogen) to the CO_2 limits the rate of the radiolytic oxidation reaction:-

$$C + CO_2 \rightarrow 2CO \qquad G(-C) \approx 3$$

by reducing G(-C) from 3 to ~1. Care has to be exercised however to avoid the formation of carbonaceous deposit on fuel, and also unacceptable levels of moisture in the coolant which may lead to condensation and corrosion of steel components. Radiolytic oxidation can be monitored by measuring the weight loss of installed graphite specimens, or by measuring the bulk densities or open-pore volumes of specimens trepanned from the wall of fuel or interstitial channels. Recent studies have confirmed that radiolytic oxidation within a 5mm thick annulus near the fuel channel walls in Magnox reactors is significantly lower than predicted. This is a beneficial effect suggesting that friability at the most heavily irradiated graphite surfaces is unlikely. Several possible theories have been proposed for the mechanism of surface protection.

THE VALUE OF DOSEMETER RECORDS FOR VICTIMS OF ACUTE RADIATION DOSES

by

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Abstract

In the remote possibility of an individual receiving a large acute dose of ionising radiation, the usual physical manifestations (for example, nausea, degradation in behaviour) may not become apparent for some time (typically hours) after exposure. In this period, when advice may be sought from medical triage personnel, the reading on an externally-worn dosemeter is the only indication of the degree of injury suffered.

This presentation addresses the utility of these dosemeter records. These readings are at best a first approximation of the dose received by critical body organs; in particular, they may be very dependent on the posture, orientation and shielding of the individual at time of exposure and the type of radiation received. They provide no indication of the personal radiation sensitivity, and, unless records have been maintained, cannot reflect any history of exposure.

The authors propose that the urgency and nature of medical care should not be based on the measured dose directly, but rather indirectly on the relationship between the measured dose and dose categories defined by dose "benchmarks". Values of these "benchmarks" are nominated following analyses of radiation casualty statistics, of the implications of uncertainties in physical dosimetry data, and of progress in available medical treatment.

STUDIES ON THE RADIATION INDUCED DNA DAMAGE AND REPAIR IN MAMMALIAN CELLS

by

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P-K Zhou, S-P Ji, T. Yan

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Abstract

Under the topic several aspects of experimental studies have been carried out in our laboratory:

(1) Correction of DNA repair deficiency by gene transfer was tried. The UV-sensitive XP (Xeroderma pigmentosum) cells and γ-ray sensitive AT (Ataxia telangiectasia) cells were chosen as recipient cells. After DNA mediated gene transfer the UV- resistance and DNA repair synthesis increased markedly and stably in XP cells and the responsible repair genes were roughly located. After chromosome mediated gene transfer, the preliminary results showed the introduction of human number 11 chromosome appeared to be able to increase the γ-resistance.

(2) The radiation induced mutation frequencies of essential and non-essential genes, such as dhfr gene, Na^+ / K^+ATPase gene and hprt gene, were studied at different radiation doses. The mutation frequencies of these two kinds of genes between human HeLa MR cell and mouse CHO-K1 cell were compared. The mutation was further studied by RFLP analysis.

(3) By means of pulse field gel electrophoresis, the stimulating effect of low doe γ-irradiation on the rejoining of DNA double strand breaks was observed. Under similar condition the mutation frequency of hprt gene decreased also. These results provided clue to further elucidation of the mechanism of radiation hormesis at the molecular level.

(4) The inhibition of DNA repair related enzymes leads to the increase of DNA strand breaks caused by harmful factors in tumor cell. With this idea, the possible use of ADP-ribose transferase inhibitor, 3-aminobenzamide, in radiotherapy, chemotherapy and hyperthermia were explored.

(5) The removal of UV-induced TT dimer from the active c-myc gene in human HL-60 leukemia cells was found much more efficient than that from the inactive β-globin gene or the overall genome. This result verified the popularity of heterogeneous DNA repair in the genome, as proposed by Prof. Hanawalt et al. Furthermore, using DMSO induced transcription negative-regulatory system for c-myc gene, the correlation between transcription activity and repair efficiency was further proved.

Part of this project was supported by the National Natural Science Foundation of China and the International Atomic Energy Agency.

DNA LIGANDS AS RADIOMODIFIERS: MOLECULAR EVALUATION IN INTACT CELLS

by

J. Tursi and R.F. Martin

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Abstract

DNA-binding bibenzimidazoles are being investigated as radiomodifiers potential use in with in cancer radiotherapy. For example Hoechst 33342 is a radioprotector[1], and an iodinated analogue of Hoechst 33258 sensitises DNA and cells to UVA[2]. In attempting to design improved radiomodifiers, new analogues are being synthesised and evaluated.

The evaluation of the new compounds involves two distinct experimental systems:

(i) Analysis of DNA strand breakage following irradiation of dilute solutions of purified DNA. Plasmid DNA is used for quantitative studies, and DNA sequencing gel analysis for the study of the sites of DNA strand breakage. The bibenzimidazoles bind at discrete sites in the minor groove; the binding sites are characterised by 3-4 consecutive AT base pairs.

(ii) Survival curve studies using cultured cells.

In many cases the two systems yield conflicting results, and the aim of the present project is to try to "bridge" the gap between the two systems, by adapting DNA sequencing techniques to enable analysis of DNA damage in intact cells. Such a method has now been successfully developed.

The method exploits the sequence homogeneity of alpha DNA[3], a repetitive sequence of approximately 100,000 copies in the diploid human genome. We have synthesised an oligodeoxynucleotide, comprising of 33 nucleotides complimentary to alpha DNA with an oligo $(A)_{20}$ "tail". The hybridization of the oligomer and alpha DNA from human cells is monitored by native polyacrylamide gel electrophoresis. Hybrid purification has also been achieved on an affinity chromatography support namely (magnetic beads) containing oligodT. Hybrids generated in this fashion have been sequenced by the Maxam-Gilbert method, and the sequence obtained directly compares with the hybrid sequence obtained after native gel purification. Thus the oligoDNA essentially "fishes-out" the alpha DNA (damaged and undamaged) from total human genomic DNA.

The new method, which is a substantial improvement on an earlier approach[3], is now being applied to investigation of UVA/*ortho*iodoHoechst-induced damage in K562 cells (a human CML cell line).

References

[1] Denison, L., Haigh, A., D'Cunha, G., and Martin, R.F., DNA ligands as radioprotectors: molecular studies with Hoechst 33342 and Hoechst 33258. Int. J. Radiat. Biol. 61: 69-81 1992

[2] Martin, R.F., Murray, V., D'Cunha, V., Pardee, M., Kampouris, E., Haigh, A., Kelly, D.P., and Hodgson, G.S., Radiation sensitization by an iodine-labelled DNA ligand. Int. J. Radiat. Biol. 57: 939-946, 1990.

[3] Murray, V., and Martin, R.F., The sequence specificity of Bleomycin-induced DNA damage in Intact cells. J. Biol. Chem. 19: 10389-10391, 1985.

IRRADIATION OF POLY(P-METHYL STYRENE) AND ACRYLONITRILE/P-METHYL STYRENE COPOLYMERS

by

R.A. Lyons[2], J.H. O'Donnell[1], P.Pomery[1], and E.Senogles[2]

1 Department of Chemistry, University of Queensland
2 Department of Chemistry and Biochemistry, James Cook University

Abstract

At the last AINSE radiation conference we reported on E.S.R studies with the above polymers. These showed evidence for a protective effect of p-methyl styrene units on the acrylonitrile units of the copolymers.. Studies since then have concentrated on the measurement of gel fractions present in the polymers as a function of radiation dose.

Polymer samples were prepared by polymerisation of the monomers in methyl ethyl ketone at 60°C with benzoyl peroxide as initiator. Conversions were restricted to less than 4%. Polymers were recovered by precipitation in methanol and purified by further precipitations and freeze-drying. Copolymer compositions were determined by ^{1}H-NMR.

Samples were irradiated in the absence of air to various doses and weighed amounts then subjected to prolonged extraction with THF, followed by filtration to remove residual gel. Aliquots of the resulting solutions were passed through a ultrastyragel GPC column and the area under the molecular weight distribution curve evaluated and compared with those of standard solutions of the unirradiated polymer, so enabling the soluble and gel fractions of the irradiated samples to be determined.

The results obtained from these studies will be reported and discussed.

MECHANISTIC STUDIES OF SENSITIZATION OF RADIATION INDUCED DNA BREAKAGE BY HALOGENATED DNA LIGANDS

by

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#Molecular Sciences Group, Peter MacCallum Cancer Institute
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Abstract

It is well established, that the incorporation of iodouracil sensitizes DNA to cleavage by UV light and to a lesser extent by ionizing radiation. A mechanism for photosensitization has been proposed. it involves photo-dissociation of the carbon-halogen bond, generating a carbon-centered radical on the uracil. This radical abstracts an H-atom from a 2'-deoxyribosyl carbon on a neighbouring nucleotide. In a series of non-enzymatic free radical reactions the deoxyribose is degraded, generating a DNA strand break.

We have extended this concept in the design of radiosensitizers. In this instance the halogen substituent is incorporated to a DNA binding ligand. It is a requirement that the carbon-centered radical generated on the ligand be appropriately located to induce a DNA strand break in a similar fashion to the halogenated DNA system previously described. This idea is being pursued in a collaborative effort between Peter MacCallum Cancer Institute and The University of Melbourne. Halogenated analogues of the commercially available dye Hoechst 33258 have been synthesized as potential sensitizers.

Previous work shows that treatment of cultured cells with a halogenated ligand, markedly sensitizes cell-killing by UVA. Strand breakage is observed with purified DNA experiments. However, sensitization was not observed in cell culture or purified DNA experiments with ionizing radiation. When these experiments were repeated with the uniodinated compounds they were found to be protectors of ionizing radiation. This radioprotective activity may explain the lack of sensitization observed to ionizing radiation by the halogenated ligand in contrast to the marked sensitization observed for UV. Another explanation for this difference, between UV and ionizing radiation, may reside in the respective yields of free radical species generated.

As part of our attempt to design halogenated ligands that are radiosensitizers it is clearly important to investigate the mechanism of sensitization. Previous spectroscopic studies of the photophysical and photochemical properties of a halogenated analogue provided evidence for UV-induced dehalogenation when the ligand was free in solution and also when the ligand was bound to DNA. Current work aims to continue spectroscopic characterisation of halogenated analogues and to quantitate relative yields of dehalogenation and DNA strand breakage when irradiating with UV or ionizing radiation. A method has been developed to separate reaction products from DNA after irradiation so that dehalogenation can then be quantitated by HPLC after irradiation. DNA damage is assayed by agarose gel electrophoresis. UV-induced dehalogenation has now been demonstrated for an iodinated analogue when free in solution and when bound to DNA. Preliminary spectroscopic results, suggest that dehalogenation occurs at high doses of ionizing radiation.

MOLECULAR MECHANISMS OF RADIATION MUTAGENESIS IN HUMAN CELLS

by

J.B. Little

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Boston, Massachusetts 02115

Abstract

Mutation at autosomal loci in human cells can result from either small or large scale structural changes in DNA. Small scale events include single base changes (transitions, transversions, frameshifts, etc.) as well as small intragenic deletions. Large scale changes can involve loss of the entire gene often extending to other loci in the chromosome; they result from large deletions or tracks of mitotic recombination. The spectrum of DNA structural changes associated with radiation-induced mutations at the thymidine kinase locus will be described, and evidence presented for the involvement of homologous recombination. Finally, these data will be discussed in light of the hypothesis that DNA double strand breaks are important mutagenic lesions in human cells.

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GENERAL INFORMATION

GENERAL INFORMATION

CONFERENCE VENUE

The conference will be held at Macquarie University in the Price Theatre on campus (see map at last page of book) from Wednesday 17 February to Friday 19 February 1993.

PAPERS

The co-operation of session chairmen and speakers is sought in keeping presentation strictly to the scheduled times.

Timing

Green light shows for presentation of paper,
Warning lights show when 5 & 2 minutes are remaining,
Red light shows when presentation time has expired,

Video projection with computer interface is available, if required.

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 Sessions

The oral poster presentations will be in the Price Theatre and the poster sessions themselves will be held at Dunmore Lang College, Macquarie University at the scheduled time (see program). Posters should be set up early in the day before the first poster session commences and removed immediately after the poster session concludes. Posters should be prepared before arrival at the conference in accordance with the guidelines previously provided. Oral poster presentations will be at the Price Theatre and not at Dunmore Lang College. Authors are expected to be in attendance by their posters throughout the sessions.

ACCOMMODATION

For participants distant from Sydney, accommodation has been arranged at Dunmore Lang College as requested on the registration forms. The Institute will make payment directly to the management for all accommodation and seek reimbursement from delegates where necessary.

MEALS

Lunches

Lunch for all participants will be held in the Dunmore Lang dining room during the scheduled lunch period on each day of the conference.

BBQ Evening Meal - Wednesday 17 February
At Dunmore Lang College

Conference Dinner - Thursday 18 February
At Dunmore Lang College

TRANSPORT
Transport from and to Sydney Airport at beginning and conclusion of conference will be arranged. Please book with AINSE for this service.

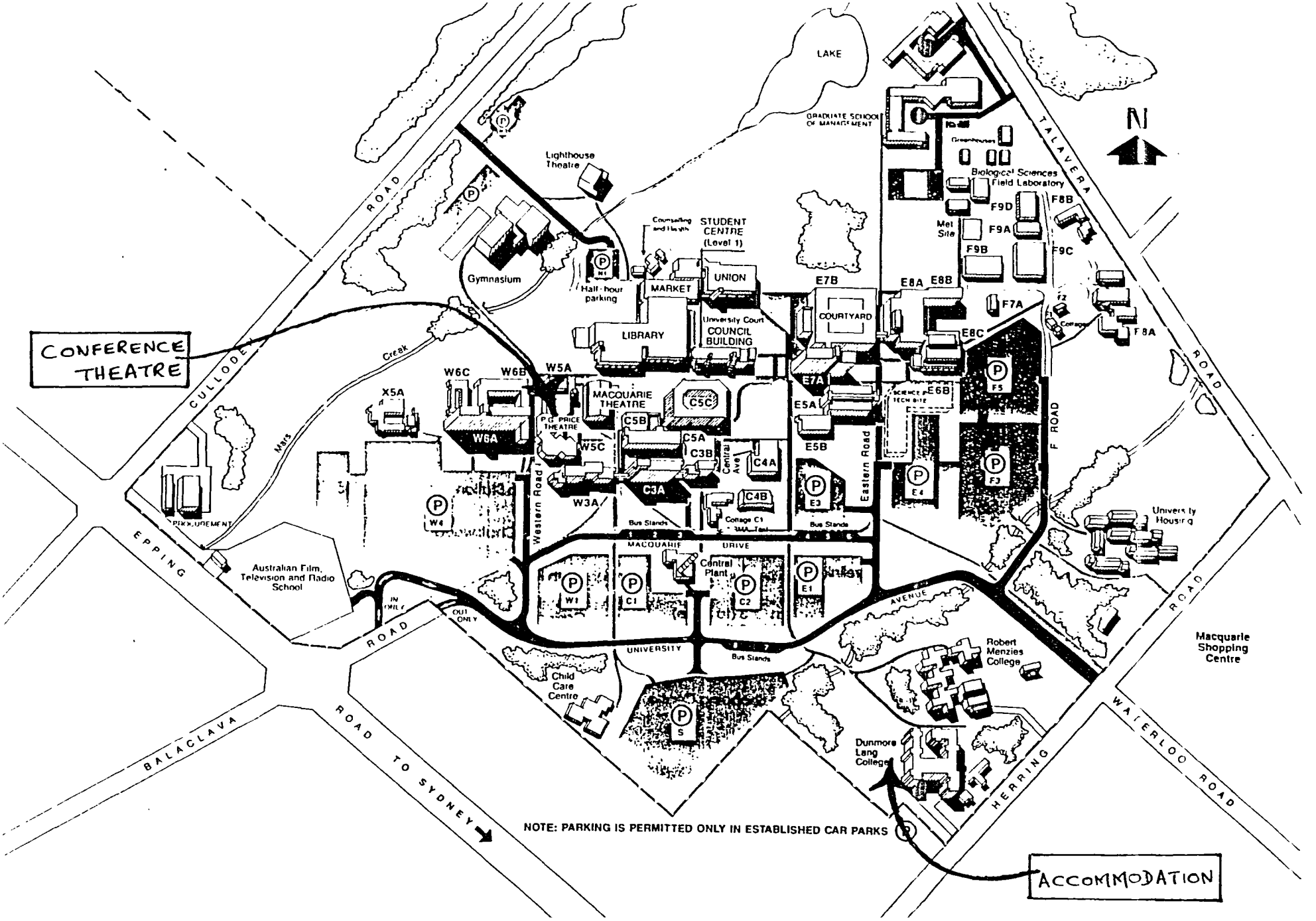
TELEPHONE MESSAGES
Telephone messages will be taken for conference participants on:-

888-1122 (Dunmore Lang College)

ALL ENQUIRIES concerning the conference arrangements should be directed to:-

Dr Roger Gammon
Executive Officer
AINSE
Private Mail Bag 1
MENAI NSW 2234

Phone: 717 3376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