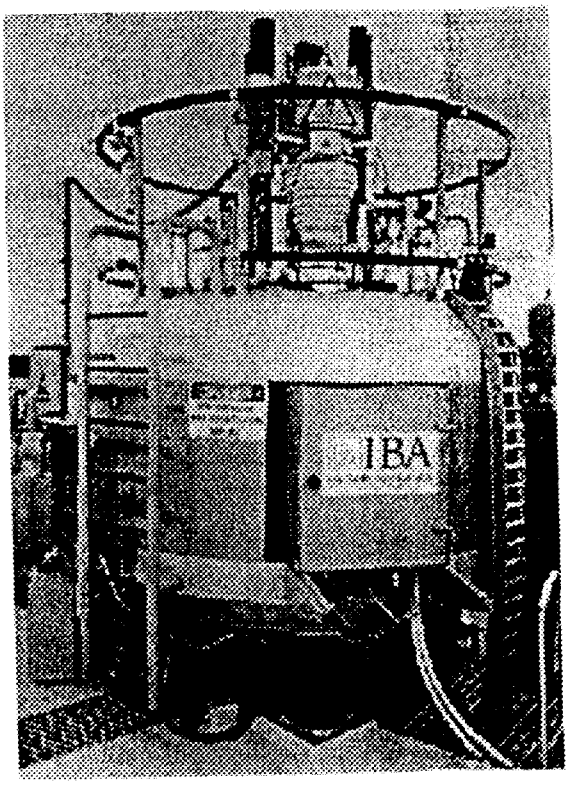
AUSTRALIAN INSTITUTE OF NUCLEAR SCIENCE & ENGINEERING

RADIATION '96

incorporating the

18th AINSE Radiation Chemistry Conference
15th AINSE Radiation Biology Conference
3rd National Workshop on Experimental Radiation Oncology

LUCAS HEIGHTS, SYDNEY
10-12 NOVEMBER 1996



CONFERENCE HANDBOOK
(PROGRAM, ABSTRACTS AND LIST OF PARTICIPANTS)

We regret that some of the pages in this report may not be up to the proper legibility standards, even though the best possible copy was used for scanning

Acknowledgements

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AINSE Theatre, Lucas Heights, Sydney
10-12 November 1996

Conference President

Dr David Hill (The University of Queensland)

Conference Committee

A/Professor Ron Cooper (The University of Melbourne)
A/Professor Jan Gebicki (Macquarie University)
Professor Barry Allen (St George Cancer Care Centre)
Dr Roger Martin (Peter MacCallum Cancer Institute)
Dr Wayne Garrett (ANSTO)
Mr David Sangster (The University of Sydney)
Dr Roger Gammon (AINSE)

Conference Manager

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PREFACE

The RADIATION '96 Conference at AINSE, Lucas Heights, Sydney, on 10-12 November 1996 is the third AINSE Radiation Science Conference. The Conference incorporates the eighteenth AINSE Radiation Chemistry Conference, the fifteenth AINSE Radiation Biology Conference and the third National Workshop on Experimental Radiation Oncology, so in many ways it is truly an interdisciplinary meeting.

The Conference Program includes eight invited lectures which cover a range of contemporary topics in Radiation Science and Technology. In addition, over the three days of the Conference, thirty-two oral papers will be presented, along with approximately forty-five poster papers. The Conference Handbook contains one-page precis of all of the papers, and is a substantial compendium of current radiation research in Australia.

RADIATION '96 is different from many other conferences because it brings together delegates with research interests drawn from widely different areas of Radiation Science and Technology. Rather than being limiting, this diversity provides the medium so often necessary for the germination and fertilisation of new ideas and the opportunity for the development of new research collaborations. I believe that the quality of the papers ensures that these outcomes will be fully realised.

One of the strong features of all AINSE conferences is the involvement of postgraduate students whose research and attendance at the meetings are supported financially by AINSE. These friendly conferences have traditionally provided a forum for many students to hone their skills at oral or poster presentation, and to develop a social network which will become the future fabric of radiation science in Australia.

Besides the substantial sponsorship provided by AINSE for RADIATION '96, the financial support provided by the Polymer Division of the RACI and the other organisations indicated in this Program, is gratefully acknowledged. In addition, I would like to especially thank our overseas and Australian invited speakers for their valued contributions to the success of the Conference.

Finally, I would like to extend my gratitude to all of the delegates for their strong support for RADIATION '96.

David Hill
Conference President

PROGRAM

SUNDAY 10 NOVEMBER 1996

TIME	PAPER	
0900		**Registration**
1020		**Welcome Address** AINSE President - Professor Bob Breakspere
SESSION 1		**GENERAL RADIATION CHEMISTRY** Chairperson: Professor G Laurence (University of Adelaide)
1030	1	**Invited talk** Professor J White, Australian National University *Australian Synchrotron Radiation Science*
1110	2	*Electron-Irradiation of Oxide Single Crystals* Caulfield K J, R Cooper and L Guy
1130	3	*The Effect of Ultrasonic Frequency on the Formation of Colloidal Gold* Caruso R and F Grieser
1150	4	*High Energy Electron Energy Degradation - Theory and Experiment* Burgers M and R Cooper
1210	5	*Radiation Chemistry and the Environment: The Radiation Degradation of Pesticides* Cornelius K and G Laurence
1230		**LUNCH** in the ANSTO canteen
SESSION 2		**RADIATION BIOLOGY** Chairperson: Dr R Martin (Peter MacCallum Cancer Institute)
1330	6	**Invited talk** Dr C Winterbourn, Christchurch School of Medicine *Glutathione as a Radical Scavenger and the Biological Consequences of Thiyl Radical Production*
1410	7	*A Mechanistic Study of the Photooxidation of L-Cystine and its Residues in Fibrous Proteins* Millington K R and J S Church
1430	8	*Oxidative Stress and Apoptosis in Intrinsic Renal Cell Populations: an in vitro Study* Gobé G C, N Hogg, D Willgoss, E Schoch, M James and Z Endre
1450	9	*The Role of Proteins in Damage Induced by Free Radicals* Gebicki J M
1510		**AFTERNOON TEA**

SESSION 3 **RADIATION SPECTROSCOPY and POSTER PRESENTATIONS**
Chairperson: Dr P J Pomery
(The University of Queensland)

1530 10 **Invited talk**
Dr G Simon, Monash University
Positron Annihiliation Lifetime Spectroscopy of Macromolecules

1610 **Poster presentations**

1710 **Poster session**

1845 **Evening BBQ**

SESSION 5 **GENERAL RADIATION CHEMISTRY**
Chairperson: Dr A K Whittaker
(The University of Queensland)

2000 11 *Protection from Solar Ultraviolet Radiation by Clothing*
Pailthorpe M

2020 12 *Preparation of Colloids by Radiation Chemistry and Radical Scavenging by Nanoparticles in Aqueous Solution*
Mulvaney P

2040 13 *Application of SIMS to the Study of Selective Deposition of Trace Amounts of Lead and Bismuth from Solution Onto the Metals Nickel and Silver*
Smith D, G Peck and K Prince

MONDAY 11 NOVEMBER

SESSION 6 **POLYMER RADIATION CHEMISTRY**
Chairperson: Professor G A George
(Queensland University of Technology)

0840 14 **Invited talk**
Dr T Seguchi, Japan Atomic Energy Research Institute
Sponsored by the Polymer Division, Royal Australian Chemical Institute
Radiation Application for Synthesis of Advanced Materials and the Related Research on Polymers

0920 15 *The Radiation Chemistry of Advanced Polymeric Materials Containing Fluorine*
Forsythe J S, D J T Hill, A L Logothetis and A K Whittaker

0940 16 *Radiation Chemistry of Halogenated Elastomers*
Perera S

1000 17 *Characterisation of Poly(methacrylates) Formed Inside Zeolites by Gamma Irradiation*
Kwiatkowski J and A K Whittaker

1020 18 *Radiation Chemistry of Biologically Compatible Polymers*
Hill D J T, P J Pomery, G Saadat and A K Whittaker

1040 **MORNING TEA**

SESSION 7 **NOVEL THERAPEUTIC APPROACHES**
Chairperson: Dr C Winterbourn
(Christchurch School of Medicine)

1100 19 *The Role of Alpha Therapy for Local and Systemic Treatment of Cancer*
Allen B J

1120 20 *Re-188 Labelling of DD-3B6/22 Fab' Monoclonal Antibody Fragment for Radio Immuno Therapy*
Schmidt P F, S V Smith and P Bundesen

1140 21 *Can Epithermal Boron Neutron Capture Therapy Treat Primary and Metastic Liver Cancer?*
Wallace S A, M C Carolan and B J Allen

1200 22 *Complementary Incorporation of Boron Compounds with Different Cellular Targets in Melanoma*
Moore D E, Y Setiawan and B J Allen

1220 23 *Pulse Radiolysis Studies on the Release of Cytotoxins from Electronic Affinic Anticancer Prodrugs Following Their One-electron Reduction*
Anderson R F, W A Denny, H Lee, M Tercel, D C Ware and W R Wilson

1240 **LUNCH** in the ANSTO canteen

SESSION 8 **RADIOSENSITIVITY IN RADIOTHERAPY**
Chairperson: Professor J S Gebicki
(Macquarie University)

1340 24 **Invited talk**
Professor L Peters, Peter MacCallum Cancer Institute
Clinical Importance of Predicting Radiosensitivity

1400 25 *Recent Studies on the ATM Gene*
Lavin M F, K K Khanna and D Watters

1440 26 *The Causes of Differences in 'Intrinsic Radiosensitivity' Between Mammalian Cell Lines*
Radford I R

1500 **AFTERNOON TEA**

SESSION 9 **POLYMER RADIATION CHEMISTRY**
Chairperson: Mr D F Sangster
(The University of Sydney)

1520 27 **Invited talk**
Professor G George, Queensland Institute of Technology
The Hidden Radiation Chemistry in Plasma Modification and XPS Analysis of Polymer Surfaces
George G A, T T Lee, F M Elms and B J Wood

1600 28 *Microemulsion Polymerisation Using Gamma-ray Initiation - the Formation of Single Chain Latex Particles*
Tan G, D H Napper and D F Sangster

1620	29	*γ-Radiolysis Investigation of the Effect of Electrosteric Stabilizers in Emulsion Polymerisation* Coen E M, R A Lyons and R G Gilbert
1640	30	*Diffusion Coefficients of Tracers in Glassy Polymer Systems Prepared by Gamma Radiolysis* Tonge M P and R G Gilbert

SESSION 10 **POSTER PRESENTATIONS**
Chairperson: A/Professor R Cooper
(The University of Melbourne)

1700 **Poster Presentations**

1800 **Poster Session**

1930 31 **CONFERENCE DINNER** - ANSTO Canteen
Guest speaker: Professor Lester Peters, Peter MacCallum Cancer Institute
Future Directions in Radiation Oncology

TUESDAY 12 NOVEMBER

SESSION 11 **DNA RADIATION CHEMISTRY AND RADIOPROTECTION**
Chairperson: Professor B J Allen
(St George Cancer Care Centre)

0900	32	**Invited talk** Dr P O'Neill, Radiation Genome Stability Unit, Medical Research Council, UK *Guanine as a Major Site of DNA Damage Involving the Direct Effects of Ionising Radiation* O'Neill P and T Melvin
0940	33	*DNA-Binding Radioprotectors - Overview* Martin, R F, P Coultas, R Budd, S Broadhurst, S D'Abrew, R Sephton, M Reum, J White, C Clarke and D P Kelly
1000	34	*Cell Survival in Irradiated Mouse Intestine is Increased by DNA-Binding Radioprotectors* Coultas P and R F Martin

1020 **MORNING TEA**

SESSION 12 **DOSIMETRY**
Chairperson: Dr W Garrett
(ANSTO)

1040	35	*Macro-Micro Dosimetry in Radiation Medicine with Semiconductor Sensors* Rosenfeld A, M Carolan, G Kaplan, B Allen and D Alexiev
1110	36	*Performance of a MOSFET Microdosimeter* Kaplan G I, A Rosenfeld and B J Allen

1130	37	*Monte Carlo Modelling of Packed Cells to Evaluate the Importance of Non-uniform ^{10}B Distribution in Tumours* D E Charlton and T D Utteridge
1150	38	*DNA Strand Breakage by ^{125}I-Decay in Oligodna* Lobachevsky P and R F Martin
1210	39	*Advances in Absorbed Dose Measurement Standards at the Australian Radiation Laboratory* Boas J F, N J Hargrave, R B Huntley, L H Kotler, D V Webb and K N Wise
1230		**CLOSING REMARKS AND PRESENTATION OF AWARDS**

*****

POSTER PAPERS

Sunday 10 November 1996

PAPER

40 *Automated Production of No Carrier Added Holmium-166*
Izard M E and E Dadachova

41 *Study of Radiation Induced Structural Changes in Nitrile Rubber*
Cardona F, D J T Hill, P J Pomery and A K Whittaker

42 *The Effect of Radiation on the Properties of Poly(Tetrafluoroethylene-Co-perfluoropropylene)*
Hill D J T, S Mohajerani and P J Pomery

43 *Surface Corrosion Analysis of Machine Elements Using Thin Layer Activation Technique with the Proton Beam from National Medical Cyclotron*
Mukherjee B

44 *The Radiation Damage in Silicon Diodes Induced by Stray Fast Neutrons from the ANSTO Cyclotron*
Mukherjee B

45 *Radiation Effects on the Liquid Crystalline Properties of Poly(Allylsulfone)s*
Choi S K, D J T Hill, P J Pomery and A K Whittaker

46 *The Radiation Chemistry of Symmetric Aliphatic Polyesters*
Babanalbandi A, D J T Hill, P J Pomery and A K Whittaker

47 *Kinetics of Radiation-Induced Apoptosis in Neonatal Urogenital Tissues With and Without Protein Synthesis Inhibition*
Gobé G C, B Harmon, F Schoch and D J Allan

48 *Tandem Accelerator Production of Tb-149 for Targeted Cancer Therapy*
Goozée G, B J Allen, S Imam, S Sarkar and J Leigh

49 *Radiochemical Separation of Tb-149 After Tandem Accelerator Production*
Sarkar S R, B J Allen, G Goozee and S Imam

50 *In Vivo Radiochemical Properties of Tb-149: A New Radiolanthanide for Targeted Cancer Therapy*
Allen B J, G J Beyer, Ch Morel, R Offord, Y Aleksandrova and S Jahn

51 *Radiolabelling of Chelators for Monoclonal Antibodies*
Imam S K, B J Allen, H K Patney and D E Moore

52 *ATM Status of the Clinically Radio-Hypersensitive*
Clarke R A, H Hasnain, A Farrell, G Birrell, P Chen, G Goozee, R Alvandi, A Miller, M Lavin and J H Kearsley

53 *In Vivo Variation of Micronuclei in BALB/c Mice After Low and High Doses of Gamma Radiation*
Strain D, D E Moore, S Prosser, B Izard and B J Allen

54 *Pulse Radiolysis Studies on the Formation and Transformation of the One-Electron Reduced Intermediate of Kalafungin and an Analogue in Aqueous Solution*
Anderson R F, M A Brimble, M R Nairn and J E Packer

55 *The Radiation Chemistry of HOECHST 33258 and its Potential Radiosensitizing Analogues*
Nel P, R Cooper and R F Martin

56 The Effects of Cosmic Radiation on Implantable Medical Devices
Bradley P

57 *Pulse Radiolysis Studies on DNA-binding Radioprotectors*
Anderson R L, R Cooper and R F Martin

58 *Radiation-Induced Crosslinking of Poly(ethylene) - Location of Crosslinks and Effects on Crystallinity*
Whittaker A K

59 *Synthesis and Characterisation of Functionalised Diamino-dithiol Ligands for Radionuclide Complexation*
Donlevy T M and S V Smith

60 *Semiconductor Dosimeters for Mixed Radiation Fields*
Carolan M G, A B Rosenfeld and B J Allen

Monday 11 November 1996

61 *Curing of Phenylethynyl Terminated Resins*
Hill D J T, P J Pomery, C M L Preston and A K Whittaker

62 *Oxygen Derived Free Radicals in Renal Injury: EPR Detection and Modulation*
Kadkhodaee M, G Hanson, B Zhang, D Willgoss, G C Gobé and Z Endre

63 *Microbeam Dosimetry Using X-Ray Film*
Allen B J and M E Barker

64 *Boron Dose Enhancement for Cf-252 Brachcytherapy*
Allen B J and A Ralston

65 *Exit in the Emulsion Polymerization of Vinyl Acetate*
De Bruyn H and R G Gilbert

66 *Radiation Stabilisation of Hyperswollen Polymer*
Hidi P, D H Napper and D F Sangster

67 *A Radical Approach to the Iodine-Thiosulfate Reaction*
Packer J E and R F Anderson

68 *Additive Effects in Radiation Grafting and Curing*
Viengkhou V, Ng L-T and J L Garnett

69 *Absorbed Dose Optimization in the Microplanar Beam Radiotherapy*
Company F Z, B J Allen and J Jaric

70 *Free Radicals in the Aqueous Environment*
Wood A and G Laurence

71 *Kinetic Studies of Ion - Recombination in Gases*
Caulfield K J, R N Bhave and R Cooper

72 *The Sonochemical Dissolution of Colloidal CdS*
Sostaric J, P Mulvaney and F Grieser

73 *Radiochemical Studies of Photopion Reactions at Intermediate Energies*
Sarkar S R, K Sakamoto, Y Oura, H Haba, S Shibata and I Fujiwara

74 *Evaluation of Di-Amino Phenol Substituted EDTA for Use in Radiolabelling Proteins with ^{64}Cu*
Schmidt P F, S V Smith and N M Di Bartolo

75 *Oxidation of Amino Acids and Proteins by Peroxynitrite*
Lacsamana M and J Gebicki

76 *Determination of Amino Acid and Protein Peroxides by the Xylenol Orange - Fe(111) Complex*
Collins J, C Gay and J M Gebicki

77 *DNA-Protein Crosslinks Induced by Protein Peroxides*
Gebicki S and J Gebicki

78 *Modification of Radiation Damage in Mouse Lung by DNA-binding Radioprotectors*
Budd R, P Coultas, S D'Abrew and R F Martin

79 *Radioprotection of Mouse CNS Endothelial Cells In Vivo*
Lyubimova N, P Coultas and R F Martin

80 *Oxidation of Urate by a Therapeutic Nitric Oxide/Air Mixture*
Hicks M, P Rogers, L Nguyen and R Day

81 *Modelling Accelerated Fractionation in Radiotherapy*
Jones L, M Carolan, P Hoban and P Metcalfe

82 *Sonoluminescence from Aqueous Solutions Containing Surface Active Solutes*
Ashokkumar M, P Mulvaney and F Grieser

ABSTRACTS

Australian Synchrotron Radiation Science

Professor J.W. White
Research School of Chemistry
Australian National University
GPO Box 414
Canberra ACT 2601
Australia

The Australian Synchrotron Radiation Program, ASRP, has been set up as a major national research facility to provide facilities for scientists and technologists in physics, chemistry, biology and materials science who need access to synchrotron radiation. Australia has a strong tradition in crystallography and structure determination covering small molecule crystallography, biological and protein crystallography, diffraction science and materials science and several strong groups are working in x-ray optics, soft x-ray and vacuum ultra-violet physics. A number of groups whose primary interest is in the structure and dynamics of surfaces, catalysts, polymer and surfactant science and colloid science are hoping to use scattering methods and, if experience in Europe, Japan and USA can be taken as a guide, many of these groups will need third generation synchrotron access.

To provide for this growing community, the Australian National Beamline at the Photon Factory, Tsukuba, Japan, has been established since 1990 through a generous collaboration with Japanese colleagues, the beamline equipment being largely produced in Australia. This will be supplemented in 1997 with access to the world's most powerful synchrotron x-ray source at the Advanced Photon Source, Argonne National Laboratory, USA.

Some recent experiments in surface science using neutrons as well as x-rays from the Australian National Beamline will be used to illustrate one of the challenges that synchrotron x-rays may meet.

REFERENCES

1. *A Strategy for Synchrotron Radiation Research in Australia,* Australian Academy of Science Report, 1994, J.W. White, Chairman.

2. Z. Barnea, R. Clapp, D. Creagh, T. Harada, H. Hashizume, Y. Kashihara, T.M. Sabine, M. Sakata, A.W. Stevenson, J.W. White, S.W. Wilkins and T. Zemb, *Design of a High Speed Powder and Small Angle X-ray Camera for Synchrotron Sources,* Proceedings Tsukuba on Synchrotron Radiation, Rev. Sci. Inst., **60**, 2537-2541 (1989).

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ELECTRON-IRRADIATION OF OXIDE SINGLE CRYSTALS

K.J. Caulfield, R. Cooper and L. Guy
School of Chemistry
University of Melbourne

Point defects created in single crystals of CaO, MgO and α–Al_2O_3 (sapphire) by electron–irradiation give rise to luminescence from colour centres.[1] The luminescence may be used to monitor the formation of point defects by elastic collision processes.

Such processes have great technological importance, in thermoluminescent dosimetry, the development of colour centre lasers, and particularly with the use of sapphire as a first-wall insulator in nuclear fusion reactors.[2] Point defect formation is the initial process which can ultimately lead to dielectric breakdown.[3]

By controlling the energy of incident electrons irradiating single crystals, thresholds may be determined for atomic displacement. The time–dependent spectroscopy and decay kinetics of luminescence may also be studied.

Displacement thresholds, luminescence spectroscopy and decay kinetics have been studied for CaO, MgO and α–Al_2O_3. Sapphire irradiated with 0.50 MeV electrons, exhibits a broad luminescence emission band around 300 nm at room temperature, which at temperatures below 60 K broadens into two distinct bands around 300 nm and 400 nm. Analysis of the logarithmic decay kinetics of the 300 nm band reveals distinctive features observed in similar oxides by other workers,[4] namely a rapid decrease in intensity punctuated by discrete plateau regions. A model comprising bimolecular electron-hole recombination, in conjunction with unimolecular electron-detrapping, is able to account for these features.

References

1. K.J. Caulfield, R. Cooper, and J.F. Boas, *J. Am. Ceram. Soc.* 78 1054 (1995).
2. E.R. Hodgson, *Cryst. Lattice Defects Amorphous Mater.* **18** 169 (1989).
3. E.R. Hodgson, *J. Nucl. Mater.* **179-181** 383 (1991).
4. See for example G.H. Rosenblatt, M.W. Rowe, G.P. Williams, Jr., R.T. Williams, and Y. Chen, *Phys. Rev. B* **39** 10309 (1989).

The Effect of Ultrasonic Frequency on the Formation of Colloidal Gold.

Rachel Caruso and Franz Grieser

Advanced Mineral Products Research Centre,
School of Chemistry, The University of Melbourne,
Parkville, Victoria 3052.

ABSTRACT

Ultrasonic irradiation of aqueous solutions is known to produce hydrogen and hydroxyl radicals due to a process called acoustic cavitation. This phenomenon involves the formation, growth and collapse of microbubbles in solution. The cavitation threshold, the resonant size of the bubble, the ratio of stable to transient cavities produced and many other bubble properties depend on the frequency of the applied sound field. A study of the reduction of Au^{III} to colloidal gold in the presence of alcohol at a number of frequencies: 20, 358, 500 and 1062 kHz has been undertaken to observe any differences in the chemical effects of the ultrasonic frequency. Alcohols are surface active molecules, therefore on bubble collapse the alcohol is present to scavenge some of the primary radicals before they recombine. The secondary radicals produced are more stable and hence can disperse into the bulk solution, where reaction with solute can occur.

HIGH ENERGY ELECTRON ENERGY DEGRADATION- THEORY AND EXPERIMENT

M Burgers, and R Cooper
School of Chemistry
University of Melbourne

The slowing down of high energy radiation is accompanied by the transfer of energy to the medium through which the particles are travelling. This energy results in physical and chemical damage which may then have biological consequences. The time taken for the initial energy losses of a high energy electron to occur to a stage where it has produced a complete secondary electron spectrum together with its accompanying population of ionised and excited partners has long been thought to be too fast to be observed. A new time dependent version of the Spencer Fano theory predicts that ions and electronic excited states of atoms should be formed over a time period as long as 10^{-7} seconds in gases at low pressures.

Pulse Radiolysis experiments using the nanosecond Febetron 706 electron pulser at Melbourne, and also the ultrafast (7×10^{-12} seconds) pulses of the Argonne National Laboratory electron LINAC have tested the predictions of this theory.

Ultra-pure low density gas samples of neon or argon were irradiated and the light emission following immediately after irradiation was observed. The technique successfully observed the formation of light emission which came from well characterised excited states of both ions and excited states of atoms.
The results may be summarised as follows;
i) The electronic excited states of neutral and singly ionised neon and argon all showed a delayed formation after the electron beam pulses.
ii) The delay became longer as the pressure was reduced.
iii) The ionised excited states were formed more rapidly than the neutral excited states which were "forbidden" states.
iv) The rate of formation was faster, for all species, closer to the surface of the electron beam entrance window than in the bulk of the gas. The effect was scanned out to about 15cm from the e-beam entrance window but seemed to be evident only in the region from 0cm to 3cm from the surface of the beam entrance window (at 1 torr gas pressure).
The conclusion here is that there is a significant flux of low energy secondary electrons created in the electron beam entrance window (~ 0.030cm thick). This flux is of different density than the one being generated in the target gas but is rapidly attenuated in the gas to below about 20 eV or less in energy.

The time scale for the production of excitation is of the order of 6 picoseconds at 1 atmosphere pressure of neon. The corresponding time scale for argon at the same pressure was shorter as may be predicted from the higher stopping power or argon.

These results agree very well with the predictions of a new time dependent version of the Spencer Fano theory. We will present both theoretical and experimental evidence to show this agreement and show how such estimates of degradation times can be found for other systems

Radiation Chemistry and the Environment: The Radiation Degradation of Pesticides

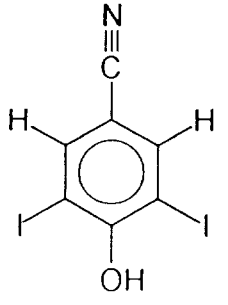
Karl Cornelius* and Gerald Laurence

Department of Chemistry, The University of Adelaide, ADELAIDE, South Australia 5005

The chemistry of the degradation of organic pesticides, herbicides and fungicides in natural systems determines operationally important parameters such as witholding times before planting or consumption. Free radicals are being increasingly recognised as important in environmental chemistry and in aqueous systems the OH, H, and O_2^- radicals are believed to be relevant to the degradation of organic molecules. Sources of these radicals in natural aqueous systems have been suggested as photochemical or transition metal reactions involving dissolved organic species such as humic acids.

We are undertaking a systematic study of the reactions of OH, H, and O_2^- radicals and halogen radical ions such as Cl_2^-, with important herbicides and fungicides in order to obtain rate constant data for modelling the possible reactions in field conditions and to establish whether the postulated reactions are capable of accounting for the disappearance of the materials in theenvironment. In addition to using gamma and pulse radiolysis to determine product yields, rate constants and the presence of reactive intermediates, we have begun to explore the stability and geometry of possible radial intermediates using Gaussian computations.

At present six pesticides in current use in Australia are being studied. Our results for one of these, Inoxyl (I) will be discussed. While electron transfer to or from the molecule is the initial reaction path for OH and H radicals, superoxide radical species are unreactive.



(I)

GLUTATHIONE AS A RADICAL SCAVENGER AND THE BIOLOGICAL CONSEQUENCES OF THIYL RADICAL PRODUCTION

Christine C Winterbourn, Department of Pathology, Christchurch School of Medicine, PO Box 4345, Christchurch, New Zealand

A large number of compounds that have toxic effects can be metabolised to free radicals and secondary reactive oxygen species. These may be directly damaging or affect cell function by altering regulatory mechanisms through changing redox status. Protection is provided by an integrated system of antioxidant defences. This includes reduced glutathione (GSH), one of the functions of which is as a free radical scavenger. Radical scavenging by GSH generates thiyl radicals (reaction 1) whose fate is dictated by equilibrium 2:

$$R^{\cdot} + GSH \Leftrightarrow RH + GS^{\cdot}$$

$$GS^{\cdot} + GS^{-} \Leftrightarrow GSSG^{\cdot -}$$

$GS^{\cdot}$ is oxidising and able to abstract hydrogen atoms from a variety of compounds including polyunsaturated fatty acids, whereas $GSSG^{\cdot -}$ is reducing. It reacts rapidly with oxygen and in aerobic solution this provides the driving force to displace equilibriums 1 and 2 and accounts for the good scavenging ability of GSH. It also generates superoxide. For GSH to be an effective radical scavenging antioxidant, therefore, it must act in concert with superoxide dismutase to remove the superoxide so generated.

Superoxide is produced in a variety of metabolic processes. It is also a secondary product of radicals reacting with oxygen either directly or through GSH. The biological reactivity of superoxide has been the subject of much debate ever since the discovery of superoxide dismutase in 1968. It has more recently become apparent that its rapid reaction with nitric oxide to give peroxynitrite, and its ability to reversibly oxidise and inactivate iron sulphur enzymes, contribute to the toxicity of superoxide. Another mechanism that could be important involves addition reactions of superoxide with other radicals to give organic peroxides. This reaction, to form a tyrosine peroxide, has come to our attention through the study of the scavenging of tyrosyl radicals by GSH. We have also shown that a tyrosine peroxide is a major product of the oxidation of tyrosine by neutrophils. Superoxide addition to phenoxyl radicals has been observed in chemical systems, but to date the biological significance of these rapid reactions has received little attention.

AU9716688

A MECHANISTIC STUDY OF THE PHOTOOXIDATION OF L-CYSTINE AND ITS RESIDUES IN FIBROUS PROTEINS

K. R. Millington and J. S. Church

CSIRO Division of Wool Technology, PO Box 21 Belmont, Victoria 3216, Australia

Extended abstract

The disulphide chromophore of the amino acid L-cystine absorbs radiation at 250 nm. The optical reflectance spectrum of crystalline L-cystine following irradiation with UVC at 254 nm shown in the Figure exhibits two absorption bands near 600 and 420 nm. The Figure also shows that a similar spectrum is obtained following UVC irradiation of dry Merino wool keratin [1], which contains high concentrations (35 mol% half-cystine) of cystine residues near the fibre surface.

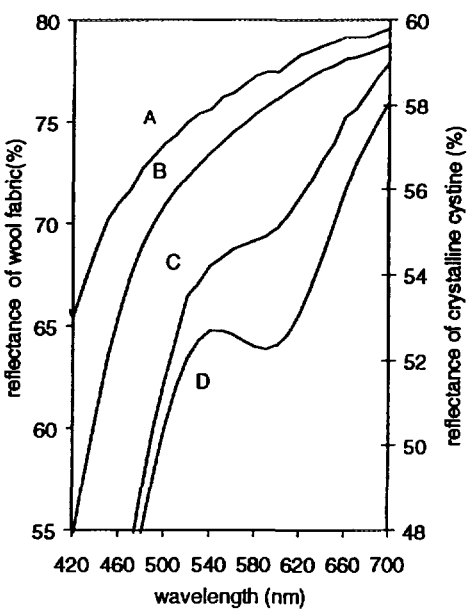


Figure Optical Reflectance Spectra of A) L-cystine, B) wool , C) cystine after UVC exposure, D) wool after UVC

In previous work on gamma-irradiated single crystals of L-cystine dihydrochloride, Akasaka [2] observed two absorption peaks in the optical spectrum at 550 and 400 nm. Akasaka found that the primary radiolytic event is removal of an electron from cystine to give the radical cation (the 550 nm absorber), followed by capture of the electron by another disulphide group to give the radical anion (the 400 nm absorber). The similarity of the positions of the absorption bands suggest that the same process occurs when L-cystine is exposed to UVC.

$$RSSR + h\nu\,(254\,nm) \rightarrow RSSR^{+\cdot} + e^{-} \qquad \text{(i)}$$

$$RSSR + e^{-} \rightarrow RSSR^{-\cdot} \qquad \text{(ii)}$$

It is interesting that cystine appears to undergo a similar ionisation process when exposed to radiation over a wide range of wavelengths which includes UVC, X- and gamma-rays. The radioprotective ability of disulphides and thiols against ionising radiation in biological systems is well known, and it appears that protection against UVC occurs via a similar mechanism.

At room temperature the disulphide radical anion exists in equilibrium with the thiyl radical $RS^{\cdot}$ and the thiyl anion. In subsequent reactions, the thiyl radical forms an adduct (Species X) with RSSR which has a characteristic esr spectrum [3]. The increased concentration of thiol groups in wool irradiated in an oxidising environment is surprising, but is supported by a growing band in the FT-Raman spectrum at 2567 cm^{-1}.

$$RSSR^{-\cdot} \rightleftharpoons RS^{\cdot} + RS^{-} \qquad \text{(iii)}$$

$$RS^{\cdot} + RSSR \rightarrow [\,RS(SR)SR\,]^{\cdot}\ (Species\ X) \qquad \text{(iv)}$$

$$RS^{-} + H^{+} \rightarrow RSH \qquad \text{(v)}$$

Oxidation of cystine residues can occur when $RSSR^{-\cdot}$ reacts with molecular oxygen to form the superoxide radical anion.

$$RSSR^{-\cdot} + O_2 \rightarrow RSSR + O_2^{-\cdot} \qquad \text{(vi)}$$

It is probable that the small, mobile superoxide anion is attracted to $RSSR^{+\cdot}$ forming partially oxidised cystine derivatives via radical intermediates. Cystine S-monoxide has been detected in UVC-irradiated wool using ATR FT-IR spectroscopy. Partially oxidised cystine derivatives can undergo further oxidation to form, ultimately, cysteic acid. However in the absence of oxygen, the $RSSR^{+\cdot}$ radical in irradiated wool keratin is stable, persisting indefinitely when kept in an inert atmosphere in the dark.

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OXIDATIVE STRESS AND APOPTOSIS IN INTRINSIC RENAL CELL POPULATIONS - AN IN VITRO STUDY

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We have been studying the interaction between incidence of apoptosis and expression of selectd oncogenes and cytokines in an *in vivo* rat model of ischaemia-reperfusion injury. The ischaemia itself, and the reperfusion, induce oxidative damage to the tissues, including damage from oxygen-derived free radicals. The scenario is therefore similar to radiation-induced injury. In the *in vivo* studies, we often observed increased expression of bcl-2, a cell survival or anti-apoptosis gene, in the distal segment of the nephron. If this occurred, not only was cell viability maintained in the distal segment of the nephron, with only very little apoptosis and no necrosis observed, but the proximal nephron segments in the vicinity of the protected distal nephron were also protected. The proximal nephron segments, especially the pars recta, are usually acutely sensitive to ischaemia-reperfusion injury, undergoing necrosis in preference to apoptosis. We have formed the hypothesis that Bcl-2 protection of the distal nephron, a segment of the nephron known as a reservoir for many growth factors or cytokines, allows increased production of growth factors during oxidative stress, which then act in a paracrine manner to protect the nearby proximal tubule.

To test this hypothesis, we have commenced using an *in vitro* model of oxidative stress on either distal (Madin Derby Canine Kidney, MDCK) or proximal (human kidney-2, HK-2) established renal cell lines. We grow the cells as "coverslip cultures" in 12-well plates in Dulbecco's Modified Eagle's Medium or serum free medium. The treatments we have used to date are either hydrogen peroxide (a gradation of concentrations from 1mM to 50mM), tumour necrosis factor-alpha (TNF-alpha) or hypoxia, as inducers of oxidative stress. The parameters analysed in the present study were (i) cell death (apoptosis or necrosis, using histology, *in situ* end labelling, and electron microscopy) (ii) cell proliferation (morphology and proliferating cell nuclear antigen (PCNA)) and (iii) Bcl-2 expression (immunohistochemistry). We have found all treatments increase levels of apoptosis in both cell lines, and TNF-alpha also causes increased cell proliferation. At the higher concentrations of hydrogen peroxide, however, the HK-2 (proximal) cells have more of a tendency to undergo necrosis than do the MDCK (distal) cells, mimicking the *in vivo* situation. Bcl-2 expression is low in both cell lines, and does not appear to be affected by the treatments in this model, and this is a divergence from the *in vivo* results.

Although results are preliminary, we have believe the model will prove to be relevant to the *in vivo* situation, and useful for analysing growth factor production from either cell line after stress, and/or improvement in pathology after oxidative stress by addition of relevant growth factors.

THE ROLE OF PROTEINS IN DAMAGE INDUCED BY FREE RADICALS

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The initial consequence of oxidative stress in living organisms is chemical modification of cell components. Recently increasing attention in this area has been paid to the modification of proteins. A form of protein modification which has been studied in some detail only recently is peroxidation. In the last 8 years, we and our collaborators have shown that a range of isolated proteins acquire hydroperoxide groups when exposed to a range of biologically plausible oxidants. These include HO· free radicals generated by radiation or in the Fenton reaction, peroxyl radicals, oxidants released by activated neutrophils, and peroxynitrite. In more complex systems, we also found protein peroxides in the apo B component of LDL treated with 20 μM Cu^{++}, and in irradiated blood serum.

These observations suggest that the formation of protein peroxides is a possible consequence of oxidative stress *in vivo*. At present this has not been demonstrated directly for a number of reasons. First, the present techniques for the peroxide assay do not yet have the required specificity and sensitivity. Second, protein peroxides are unstable. While there does not appear to be an effective ezymatic mechanism for the removal of such peroxides, they decay spontaneously in plasma with a half-life of about 1.5 days. The products of this decay are hydroxylated amino acids. Carbonyl groups are not formed, suggesting that their frequently reported appearance in aged or diseased tissues is indicative of a phenomenon different from protein peroxidation.

Perhaps the most intriguing question at present is what may be the consequences of the generation of protein peroxides. For proteins generally, it is widely believed that their main role in oxygen stress *in vivo* is benign. They are known to react rapidly with many of the biological oxidants, many are good chelators of transition metals and scavengers of free radicals, and some are effective antioxidants by virtue of their -SH groups. While the reactions with oxidizing agents may lead to loss of their normal biological function, for most proteins this may be trivial and lead only to the removal and replacement of the damaged molecules through the normal cellular processes. However, our recent findings suggest that this view may be incorrect for many proteins.

A remarkable feature of the process of protein peroxidation is its high efficiency. This is most easily measured with proteins oxidized by radiation-generated free radicals. We found that, for some proteins, peroxide yields reached 40% of the numbers of HO· radicals generated. Thus in effect, almost half of these radicals can be converted to the much more long-lived protein peroxide groups. If they, in turn, have the capacity to damage other molecules, the major oxidative pathway *in vivo* may have the sequence: free radical → protein peroxide → another oxidized molecule.

We have begun to test this hypothesis by studying the ability of protein peroxides to react with selected molecules. We found that peroxidized BSA and peroxidized valine can oxidize ascorbate and GSH, but do not react with reduced nucleotide cofactors or with ebselen. Glutathione peroxidase accelerated the decomposition of BSA peroxides, but the effect was only significant at 4^{o}. Phospholipid GSH peroxidase had no effect. Incubation of peroxidized lysozyme or insulin with glutathione reductase led to partial inactivation of this enzyme, but no inactivation was observed during incubation with peroxidized BSA or valine. Clearly, these effects are specific to individual proteins. More generally, amino acid and protein peroxides were found to be a potential source of a range of free radicals when reduced by Fe^{++}. If this turns out to be a common phenomenon, protein peroxides may prove to be a major source of oxidative damage.

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Positron Annihilation Lifetime Spectroscopy of Macromolecules

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Positron annihilation lifetime spectroscopy (PALS) is a technique which makes use of the anti-particle of the electron, the positron (e^+), first predicted by Dirac in 1931. In the technique, a radioactive nucleus such as ^{22}Na which gives off positrons is contained within a very thin titanium foil and sandwiched between the samples (such as plastic coupons) which one wishes to analyse. When the positron is ejected, it emits two gamma rays of a characteristic energy 1.21 Mev. When the positron enters the plastic it rapidly slows down (thermalises) in approximately 10-1 seconds and whilst doing so, can abstract an electron from the surroundings - becoming known as a positronium (Ps) species. The spin of the electrostatically bonded electron can be of opposite spin to the positron (known as para-positronium, p-Ps) or can be of the same, parallel spin (ortho-positronium, o-Ps), with pPs being a third likely to form as the oPs. There are thus three types of sub-atomic particle present - E+, pPs and oPs. Of the two species, the o-Ps is the longest lived with p-Ps tending to annihilate by self-destruction. The o-Ps tends to form and locate in regions of low electron density - the so-called "free volume" or "excluded volume" holes in polymers. When o-Ps is annihilated, it picks off another electron and emits a characteristic energy of 0.5 Mev - its lifetime being of the order of 1 to 5 ns in condensed polymers. The size of the free volume "holes" or "pores" in which the o-Ps localises are of the order of angstrom radii. By measuring the average time and intensity of decay of the o-Ps species, a measure of the free volume pore size and concentration can be obtained. This can - via simple models - be related to the fractional free volume of the polymer. Additional possibilities include determining distribution of free volume and even a measure of the anisotropy of free volume shape.

This talk will concentrate on the use of PALS as a technique in characterising macromolecules. Work will be presented both from the literature and from the Monash University laboratories. PALS has been used by various groups to evaluate many properties that one associates with free volume such as physical ageing, gas permeability, the glass transition, uptake of a solvent, crystallinity, crosslinking, molecular mobility.

One area of much interest for us has been the use of this technique in looking at miscibility of polymer blends. In miscible blends, the interactions of the different polymers may be expected to lead to a negative free volume of mixing because of the strong attraction between the different chains. This may influence the free volume properties. Conversely, if a material is partially miscible or totally immiscible, this should influence both the size and total content of free volume. This should be related to other properties such as mechanical properties and molecular mobility, such as measured by dielectric relaxation spectroscopy. Variations on this involve copolymerisation of crosslinked materials or linear thermoplastics (the ultimate "molecular" miscibility) and this will also be discussed. Multiphase systems such as water uptake in polymers can vary polymer properties by filling molecular voids, as well as disturbing chain conformations and, in the case of polar polymers, associating with the polymer chains.

We have also been interested in the effect of polymer molecular structure on free volume - particularly in rigid polymer chains such as substituted poly(phenylenes) and liquid crystalline polymers and results will be presented from this. Indeed, the unusual packing which arises from such anisotropic molecules leads to unusual behaviours both of the homopolymers and subsequent liquid crystal polymer - liquid crystal polymer blends.

Protection from Solar Ultraviolet Radiation by Clothing

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Textiles have been used by man since antiquity for adornment and protection from the elements. Until quite recently, and in spite of a wealth of published data, statements such as "clothing provides total reduction in UVB" were being made. In fact, subject to fabric construction, summer weight textiles can provide relatively low protection from the harmful effects of solar ultraviolet radiation, often with ultraviolet protection factors less than that of a nominal SPF 15+ suncream.

The recently published Australia/New Zealand Standard AS/NZS 4399:1996 "Sun Protective Clothing - Evaluation and Classification" specifies an in vitro spectrophotometric method for the measurement of the ultraviolet (UVR) transmission of textiles. Ultraviolet Protection Factors (UPF) are then calculated by convolving the UVR transmission data with standard CIE erythemal response data and ARL solar irradiance data. At the present time the scope of the standard is limited to loose fitting dry clothing.

Virtually every textile parameter has an influence on the UPF of the finished garment and hence on the protection afforded to skin from the harmful effects of solar UVR radiation. Textile parameters such as fibre type, the method of spinning the yarn, fabric structure, cover factor, colorant, UVR absorbers and finishing methods determine the UPF of the fabric and hence must be controlled from batch to batch.

Since garments generally shrink when washed, multiple wearing and washing cycles usually cause an increase in fabric UPF. Adventitious soiling of fabrics and the absorption of certain components of domestic laundry formulations, eg. fluorescent whitening agents, increase fabric UPF ratings. Garments with a high degree of elasticity, eg. nylon/lycra sportswear, that are stretched on to fit, will obviously have lower UPFs when stretched than when relaxed. In general fabrics worn in a wet state provide lower protection than when worn dry.

On Australia's most extreme summer day it has been estimated that there are 30 MEDs (minimal erythemal doses) in a dawn to dusk exposure. Thus outdoor workers should be provided with UPF 30 clothing, or better. Results from recent experiments using SK-II hairless mice dressed in UPF 50 "sunsuits" have shown that the mice developed no sun induced skin cancers on the skin areas protected by the UPF 50 fabric whereas multiple tumours developed on the unprotected skin.

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PREPARATION OF COLLOIDS BY RADIATION CHEMISTRY AND RADICAL SCAVENGING BY NANOPARTICLES IN AQUEOUS SOLUTION

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Over the last fifteen years, considerable work has been carried out exploring radiation induced chemical effects in microheterogeneous media such as micelles, microemulsions and colloids. Our work has focussed on redox reactions of small metal particles. Radiolytically generated reductants can not only be used to prepare nanometre sized metal particles, but may also be used to homogeneously coat them with other metals. This allows more complex nanostructures to be prepared such as bimetallic catalysts or materials with novel optical properties. In this talk, the reactions leading to radiation induced electrodeposition and the optical properties of the resultant coated metal particles will be discussed.

Metal oxide particles are formed in nuclear plant coolant waters. The particles can scavenge radiolytically generated radicals. The efficiency with which colloid particles can scavenge radical depends on the radical charge and colloid charge. Models to explain the effects of electrolyte and pH for will be presented.

Application of SIMS to the study of selective deposition of trace amounts of lead and bismuth from solution onto the metals nickel and silver.

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The natural ^{238}U decay series includes the trio ^{210}Pb, ^{210}Bi and ^{210}Po. These are useful in estimating rates of environmental processes and ^{210}Po is a major contributor to the radiation dose of marine organisms. To develop an understanding of the distribution of these closely related radionuclides in the environment it is necessary to be able to measure all three. Accurate measurements depend on preliminary separation of the nuclides. Isolation and measurement of ^{210}Bi has been a continuing problem and this has restricted the study of the role of this nuclide in environmental processes. We have developed a sample preparation that includes plating polonium from solution onto a silver disc then plating bismuth onto a nickel disc and leaving the lead in solution. The ^{210}Bi is measured by Cerenkov counting. Any ^{210}Pb plating onto nickel with the bismuth would interfere in subsequent counting as it decays rapidly to ^{210}Bi.

We have used SIMS (Secondary Ion Mass Spectrometry) to measure bismuth and lead deposited on the nickel and silver discs. This is possible because the stable isotopes of the four elements do not overlap. SIMS is especially appropriate for this study as the Bi and Pb deposited as thin films on the metal surface. Careful selection of experimental conditions allowed quantitative measurements of lead and bismuth without mutual interference. The results have been used in developing plating conditions that optimise separation of lead and bismuth.

Radiation Application for Synthesis of Advanced Materials and the Related Research on Polymers

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The characteristic of radiation effect on organic materials is the ability to produce the active species for chemical reactions at any conditions, and the species are formed uniformly in the material. The application to polymers using the characteristic has been industrialized in the past two decades such as the curing of wire and cables, processing of polyethylene foam, curing of magnetic tapes and floppy, etc.

For the radiation application to advanced materials and the needs to evaluation of the radiation resistance for space and fusion reactor materials, we have studied the irradiation effects of polymers in the wide temperature range from very low temperature to high temperature under vacuum or oxygen free atmosphere.

The chemical reactions for polymers showed a rather large difference depending on irradiation temperature in quality and/or quantity. The dependence is though to be the difference in molecular motion of polymers during irradiation. The clear difference on irradiation temperature was observed for polytetrafluoroethylene(PTFE) and polystyrene(PS). PTFE has been classified to be the typical chain scission type, but it forms crosslinking by irradiation at high temperature(about 340°C) of the molten state. The radiation crosslinked PTFE showed much improvement in the mechanical properties and also the radiation resistance. So, this processing will be transferred to an industrial plant. For the case of PS, the crosslinking is predominant below the glass transition temperature(Tg), but changes to chain scission above Tg. For other polymers, the irradiation temperature effects are observed, which may be expanding to develop new products.

The newly developed technology in radiation application is the curing of polymer fiber as ceramic fiber precursor. The silicon carbide(SiC) fiber is synthesized from silicon containing polymer of polycarbosilane(PCS) fiber by the pyrolysis at high temperature of 1200°C or more. As the melting temperature of PCS is about 230°C, the fiber must be cured to not melt down during the pyrolysis. The purpose of this work was the radiation crosslinking of PCS fiber without oxygen contamination. The key point was the irradiation technique with exclusion of oxygen to irradiate high doses, because the dose needed for the crosslinking was more than 10MGy. The basic research was carried out using gamma-rays irradiation under vacuum, where the fundamental data were obtained such as the yield of active sites and the reactivity with oxygen and the decomposed gases. For the development of the processing technology, an electron accelerator was applied. The most of work was the development of electron beams(EB) irradiation vessel to irradiate uniformly excluding oxygen. By increasing EB current to shorten the irradiation time, the PCS fiber sample was heated by EB irradiation to result melting. So, the fiber was cooled by Helium gas flow during irradiation. Finally, the 5km long PCS fiber yarn composed of 500 filaments(20μm ϕ) was cured uniformly with exclusion of oxygen. The SiC fiber obtained from the radiation cured PCS fiber has a high tensile strength of 3GPa and high heat-resistance up to 1700°C. The heat resistance of SiC fiber obtained from ordinary processing is about 1200°C. This technology was transferred to a company and the product is supplied to the market. The silicon nitride(Si_3N_4) fiber was also synthesized from radiation cured PCS fiber by the pyrolysis in ammonia gas atmosphere.

The Radiation Chemistry of Advanced Polymeric Materials Containing Fluorine

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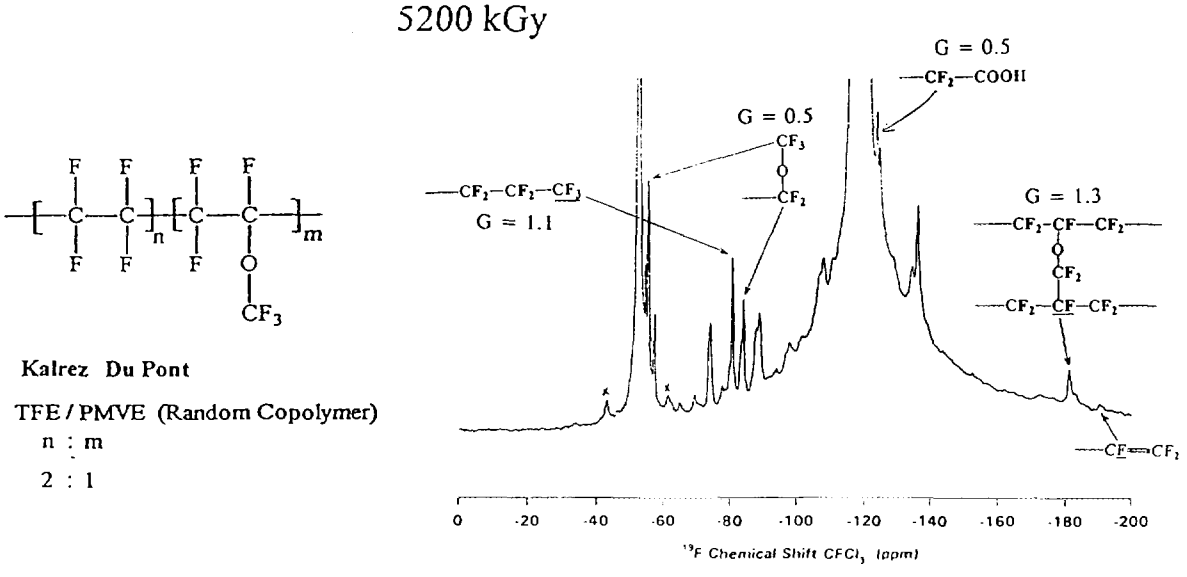
TFE/PMVE (tetrafluoroethylene/perfluoromethylvinyl ether) is a commercial perfluoroelastomer marketed by the Du Pont Company under the trade-name Kalrez. Very little is known about the radiation chemistry of this fluoropolymer which in general is consistent with all fluoropolymers. In 1984, Uschold[1],while attempting to graft vinyl monomers onto irradiated TFE/PMVE, found that the fluoroelastomer crosslinked forming and insoluble network. Unfortunately, Uschold found that the mechanical properties of irradiated TFE/PMVE were inferior when compared to the chemically crosslinked analogues because of the simultaneous radiation scissioning of the polymer chain. This chemical curing is described elsewhere[2]. The radiation crosslinking of TFE/PMVE was also briefly studied by Luo et al.[3] and later by Sun et al.[4] but they exclusively looked at the sol/gel behaviour. Recently Lyons[5] reviewed the radiation chemistry of fluoropolymers and showed that most research solely focused on the physical properties of the cured material and little attention placed on the development of mechanisms of radiation chemistry.

In this study, we have employed both physical and chemical techniques such as tensile tests and ^{19}F NMR to formulate a radiation mechanism describing both chain scission and crosslinking processes. ^{19}F NMR identified and quantified new functionalities such as carboxylic acid and saturated chain ends. The crosslinking reaction has been tentatively postulated for the first time. Factors affecting the radiation chemistry such as the presence of oxygen and irradiation temperature will be briefly discussed.



The stucture and ^{19}F NMR spectrum of TFE/PMVE γ-irradiated to 5200kGy showing new radiation induced functionalities

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High Energy Radiation Effects on Halogenated Butyl Rubbers

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Aliphatic halides, with the exception of fluorides, are among the organic compounds most sensitive to radiation. In these compounds carbon halogen bonds are weaker and the main effect of radiation is to break this bond to give halogen radicals. Due to the differences in reactivities, the final products obtained from chloro and bromo compounds are different. For example, radiolysis products from chloro compounds tend to include hydrogen chloride whereas bromides give bromine as well as hydrogen bromide.

Due to the above behaviour of low molecular weight alkyl halides when exposed to high energy radiation, it is interesting to see the behaviour of polymers which contain halogen atoms. While butyl rubber is known to undergo predominantly chain scission during exposure to high energy radiation, a drastically different response towards high energy radiation has been reported for the halogenated butyl rubbers. Rapid gelation occurs in these polymers at low doses.

No detailed study has been reported on the radiation induced reactions in halogenated butyl rubbers. We have used ESR and NMR techniques to study these reactions. Information regarding the changes in structure during exposure of butyl, chlorinated butyl and brominated butyl rubbers, to high energy radiation will be presented.

Butyl rubber is predominantly polyisobutylene with 1-2% isoprene units incorporated. The isoprene units in the halogenated butyl rubbers are of exo structure. ESR spectra indicate that during high energy irradiation, most of the radicals are generated in halogenated isoprene units. A higher radiation yield for scission was observed in chlorinated butyl rubbers than brominated butyl rubbers.

Characterisation of Poly(methacrylates) formed inside Zeolites by Gamma Irradiation

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Introduction

Inclusion polymerisation was first developed in the second half of the 50's as an alternative to Ziegler-Natta co-ordination polymerisation to obtain highly stereo-regular polymers[1]. Inclusion polymerisation was performed in organic clathrates such as thio-urea channels. However the channels are only stable when formed around the monomer[2-4]. This means there is a specific concentration of monomer, namely saturation, for which the host/channel system can exist[5]. There is also a limited number of monomers which are suitable for use with a given clathrate[3] and the channel dimension is not usually a variable parameter for a given monomer/clathrate system. One exception is Tris(o-phenolenedioxy)cycotriphosphazene[6]. Initiation of the monomer can be easliy achieved by high energy irradiation and many of the polymers obtained show considerable chemical and steric regularity. For example poly (2,3 - dimethylbutadiene) obtained by polymerisation in a thio-urea inclusion compound has only the 1,4 trans structure and is highly crystalline[3].

The restriction on the number of clathrate and monomer systems has lead us to investigate the use of zeolites as hosts for inclusion compounds. Zeolites exist independently of any included guest compound. They are aluminosilicate compounds whose structures form molecular-dimension channels and belong to a class of materials known as molecular sieves. Channel structures can be in 1,2 or 3 dimensions[7,8]. The structural aluminium in the zeolite creates a negative charge on the lattice which is balanced by cations.

In this study we have diffused methyl and ethyl methacrylate into Na-ZSM5, Beta, Y and Mordenite zeolites. The samples where irradiated under vacuum and then extracted. The structures of the exrtracted polymer have been characterized by GPC, NMR and DSC. The results will be correlated as a function of the channel sizeof the zeolite and compared to the bulk system.

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Radiation Chemistry of Biologically Compatible Polymers

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Abstract

Poly (2-hydroxy ethyl methacrylate) [PHEMA] and poly (2-ethoxy ethyl methacrylate) [PEEMA] are of biomedical and industrial interest due to their biocompatibility with living tissue. In this paper the effect of high energy radaition on these polymers is reported.

PHEMA and PEEMA have similar molecular structures to poly (methyl methacrylate) [PMMA], and the γ irradiation of this polymer is well understood. Hence the radiation chemistry of PMMA is used as model system for the the analysis of the radiation chemistry of these polymers.

The mechanism of the radiation induced chemistry of the polymers has been investigated using a range of techniques including electron spin resonance spectroscopy (ESR) to establish free radical pathways, GC to identify small molecule volatile products, NMR to identify small molecule radiation products and Gel Permeation Chromatography (GPC) to determine molecular weight changes.

Whilst much of the major part of the radiation chemistry can be attributed to similar reactions which can be observed in PMMA, there are a number of new radicals which are present as a result of the influence of the side chain interactions which reduces the mobility of the polymer chain.

THE ROLE OF ALPHA THERAPY FOR LOCAL AND SYSTEMIC TREATMENT OF CANCER

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Abstract

Major problems in the management of cancer relate to the inability to control critical primary lesions, eg glioblastoma multiforme (GBM), and the inability to deal with metastases arising from malignant cancers such as melanoma, breast and other cancers. Binary alpha therapy using neutron capture in boron-10 offers improved prognosis for high grade brain tumours such as GBM and melanoma metastases to the brain. The selective carrier of choice is BPA which gives a tumour to normal tissue ratio of 4 in melanoma. Clinical trials with an epithermal neutron beam are underway in the US and may soon commence in Europe.

Metastatic cancer proceeds through a number of quite separate stages in the development of lethal disease, ie cells in transit, preangiogenic lesions, subclinical and clinical lesions. Early stages offer the potential for control if targetted cancer therapy is applied. Prophylactic therapy requires the localisation of dose to the cancer cell and rules out radioactive beta emitting radionuclides, which are more suited for clinical lesions. Alpha emitting radionuclides are the most appropriate toxins, as their efficacy depends on the energy and range of the alpha particles. After matching the cancer stage, radiolabel and carrier, we find that Tb-149 is the radionuclide of choice for systemic therapy in all aspects except production. The production of Tb-149 in μCi quantities has been achieved using the heavy ion reaction at the ANU tandem accelerator and in multi-mCi quantities using the spallation reaction in combination with on-line isotope separation at ISOLDE. Progress in this unique R&D project will be reviewed.

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Re-188 Labelling of DD-3B6/22 Fab' Monoclonal Antibody Fragment for Radio Immuno Therapy.

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The chemical similarity of technetium and rhenium has created much interest in the nuclear medicine field to make a "matched pair" of radiopharmaceuticals for radioimmuno- diagnosis and therapy. Clinical trials with the ^{99m}Tc-DD-3B6/22 Fab' has shown promise in the diagnosis of ovarian cancer. The design of the analogous therapeutic agent with rhenium-188 (155 keV γ 15 % abundant, β^- E_{max} 2.1 MeV, $T_{1/2}$ 17 h) is under investigation. The present study describes the approach taken for direct radiolabelling of the DD-3B6/22 Fab' with carrier-free ^{188}Re and its biological evaluation in balb/c and nude mice.

It was necessary to optimise complexation conditions to maximise the availability of ^{188}Re(V) for transchelation onto the reduced antibody fragment. Rhenium-188 was eluted from a ^{188}W / ^{188}Re generator (purchased from ORNL) with 0.05 M ammonium nitrate and was evaporated to dryness. The residual $^{188}ReO_4^-$ was dissolved in a range of buffers: 0.2 M acetate (pH 4.0 - 5.5), 0.2 M phosphate (pH 5.0 - 6.0) and 0.2 M carbonate (pH 6.5 - 8.5). The $^{188}Re(VII)O_4^-$ was reduced to ^{188}Re(V) with stannous chloride (1 - 5 mg/ml) in the presence of a complexing agent (gluconate or citrate) to stabilise the reduced ^{188}Re. Complexation with citrate (0.5 M) was compared to complexation by gluconate over a range of concentrations (0.1 - 0.5 M).

Once reduced the ^{188}Re complexes were incubated with the DD-3B6/22 Fab' fragments at 37°C. Transchelation of the complexed ^{188}Re(V) from the gluconate complex was 2 times more effective than that of the citrate complex. The effect of temperature, pH and antibody concentration on the amount and rate of transchelation was also evaluated. The final product had a specific activity of 35 mCi/mg with an immunoreactive fraction of 77%. Stability of the product was assessed under various conditions: temperature, presence and absence of an inert atmosphere and presence of ascorbic acid (stabiliser). Best condition for storage were determined using an excess of ascorbic acid (40,000 fold) at 4°C in PBS pH 7.2. Under these conditions 90% of the ^{188}Re was associated with the Fab' fragment after 24 hours.

As the DD-3B6/22 antibody only recognises the cross linked fibrin of humans and primates, a pseudo animal model was established using antigen coated sepharose beads. Pharmacokinetics of the final product was evaluated in balb/c and nude mice transplanted with both D-dimer (+Ve) and Glycine (-Ve) beads. Results show that ^{188}Re DD-3B6/22 Fab' clears rapidly from the blood (α = 2.4 hr, β = 3.5 hr) and is excreted through the renal system. Localisation to subcutaneous antigen beads shows specific uptake to the D-dimer (antigen) beads was achieved within 6 h (0.23% ID) and was maintained for 24 hour post injection. Specificity to antigen implants was 5:1 ($P < 0.001$) when compared to non-specific bead implants. These results correlate well with those obtained for the ^{99m}Tc DD-3B6/22 Fab' in mice. The radiolabelling procedures are congenial for therapeutic levels and hence we believe that the ^{188}Re DD-3B6/22 Fab' has some potential for use in treatment of Ovarian cancer.

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CAN EPITHERMAL BORON NEUTRON CAPTURE THERAPY TREAT PRIMARY AND METASTATIC LIVER CANCER?

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The poor prognosis of metastatic cancer to the liver calls for the investigation of alternative treatment modalities. This paper analyses the possible use of epithermal boron neutron capture therapy for the palliative treatment of these cancers. We examine possible treatment planning scenarios for selected tumour to liver boron ratios, and specifically for the epithermal beam at the HFR, Petten. It is required that a therapeutic ratio>1 be achieved over the entire organ.

Monte Carlo calculations were performed using the radiation transport code MCNP. The geometrical model used a "variable voxel" technique to reconstruct an anthropomorphic phantom from CT scans. Regions of interest such as the liver were modelled to a resolution of a few millimetres, whereas surrounding regions were modelled with lesser detail thereby facilitating faster computation time. Three dimensional dose distributions were calculated for a frontal beam directed at the liver, and found to be in satisfactory agreement with measurements using bare and cadmium covered gold foils, PIN and MOSFET dosimeters for fast neutron and gamma measurements respectively.

Dose distributions were calculated for orthogonal epithermal neutron beams to the front and side,using the parameters of the epithermal beam at Petten, and assumed tumour and normal tissue boron-10 concentrations of 30 ppm and 7.5 ppm boron-10 respectively. The therapeutic ratio (ie the dose to the tumour relative to the maximum dose to normal tissue) was found to be about 1.8, reducing to unity for the limiting condition of a tumour in the posterior liver. This result opens up the possibility of palliative therapy for the management of primary and metastatic liver cancer.

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COMPLEMENTARY INCORPORATION OF BORON COMPOUNDS WITH DIFFERENT CELLULAR TARGETS IN MELANOMA

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The heterogeneity of malignant tumours is well known, and post-surgical control may only be achieved by the application of a number of adjuvant therapies. In boron neutron capture therapy (BNCT), a similar effect could be achieved by utilising boron compounds with quite different uptake and incorporation mechanisms. While tumour growth delay or control can be induced by BNCT in animal models, long term control in human patients may be much more difficult. Thus we have carried out experiments with two boron compounds which exhibit quite different pharmacokinetics and interact with cancer cells by quite different mechanisms. The compounds studied were p-boronophenylalanine (BPA) and boronated low density lipoprotein (B-LDL).

Non-specific boron compounds such as n-alkyl carboranes can be delivered to melanoma tumour cells when incorporated in reconstituted LDL. Biodistribution studies were performed with BALB/c mice bearing subcutaneous Harding-Passey melanoma xenografts. The mice were pretreated with a high fat diet and hydrocortisone to down regulate the non-autonomous LDL receptors. A tumour to blood boron concentration ratio of 5:1 was achieved 18 hours after administration of B-LDL. The same compound administered in a non-specific arachis oil vehicle failed to demonstrate selective uptake in the tumour. Neutron capture therapy using B-LDL as the boron delivery vehicle produced a growth delay effect on the tumours which was equivalent to that found when BPA was administered as the fructose complex to develop a similar boron concentration in the tumour.

This is indicative that the boron microdistribution across different types of tumour cells achieved by B-LDL has a similar effect to that achieved by BPA in the tumour model, even though the uptake mechanisms for BPA and B-LDL are different. BPA uptake is thought to be dependent on the amino acid transport mechanism, whereas receptor density determines LDL incorporation. Thus the combined administration of these compounds might be expected to produce enhanced control of melanoma.

Pulse Radiolysis studies on the Release of Cytotoxins from Electron Affinic Anticancer Prodrugs following their One-Electron Reduction.

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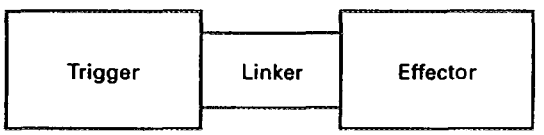
New approaches to killing chemoresistant and radioresistant hypoxic cells of solid tumours include the selective release of potent cytotoxins from relatively non-toxic prodrugs through reductive metabolism and/or radiolytic reduction[1]. Central to these studies, is an understanding of the mechanism of cytotoxin release and the basis of hypoxia-selectivity, since such information can be used to design compounds of high potency against solid tumours. Pulse radiolysis studies can offer unique insights into these underlying mechanisms in aqueous solution through the determination of (i) thermodynamic one-electron reduction potentials (E(1)) of the prodrugs, (ii) rate constants for the formation and spectral charaterization of one-electron reduced prodrugs, (iii) the kinetics release of the cytotoxins from one-electron reduced prodrugs and (iv) the influence of molecular oxygen on the obligate radical intermediates. Two main classes of prodrugs are being investigated.:-



(a) Nitroaromatic benzylquaternary compounds. These compounds consist of an electron-affinic nitroaromatic moeity (the 'trigger') linked through a benzylquaternary centre with a sidechain (the 'linker' unit) to a potent cytotoxic moeity (the 'effector').
(b) Transition metal complexes incorporating a bound ligand which is cytotoxic when released.

A series of different triggers, which are found to vary greatly in the rate constant for release of the effectors upon one-electron reduction of the prodrugs, will be discussed. Release of effector from a prodrug does not solely depend upon the type of trigger but can also be dependent on the type of linker and released effector. For example, whereas fast quantitative release of the mustard effector mechlorethamine is seen from the quaternary nitroimidazole upon one electron reduction, release of *N*-[2-(dimethylamino)ethyl] acridine-4-carboxamide (DACA), requires a higher level of reduction of the same trigger. Release of cytotoxic ligands from metal complexes requires that the metal centre is reduced. When the E(1) of the metal centre is lower than DACA bound as a ligand, reduction is seen to occur solely on the ligand without release from the metal centre.

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CLINICAL IMPORTANCE OF PREDICTING RADIOSENSITIVITY

Lester J Peters

The optimal use of radiation therapy in cancer treatment is hampered by the application of normal tissue tolerance limits that are derived from population averages. Such limits do not reflect the considerable differences in susceptibility to radiation injury that exist among individuals. Development of assays that accurately predicted normal tissue tolerance in individual patients would permit real application of the concept of treatment to tolerance. By adjusting doses upwards or downwards to achieve a uniform probability of complication in each patient, the therapeutic ratio, ie., the probability of an uncomplicated cure, would be increased for the population as a whole.

Although the pathogenesis of radiation injury is highly complex, clinical studies have demonstrated a significant correlation between the in vitro radiosensitivity of patients' fibroblasts and their risk of developing late connective tissue type complications of radiotherapy. While such assays lack the precision and practicality to be used clinically, they do establish the principle of prediction of normal tissue tolerance. Newer assays using surrogate endpoints for cell survival and incorporating insights into the effects of radiation on cellular growth, differentiation, senescence and cytokine production are being developed. Such assays may, in the future, be complemented or replaced by molecular and/or cytogenetic probes to derive robust estimates of individual tolerance. The goal of accurate prediction of individual tolerance for clinical use, while not imminent, does seem achievable.

Recent studies on the ATM gene

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Radiosensitivity is a universal characteristic of ataxia-telangiectasia (A-T), observed after exposure of patients and of cells in culture to radiation. This sensitivity is manifested as higher levels of radiation-induced chromosomal aberrations and reduced survival compared to controls. The gene for A-T was mapped to chromosome 11q 22-23 seven years ago and more recently we have been involved in the cloning of a single gene, ATM (ataxia-telangiectasia mutated), mutated in this syndrome. ATM is a large gene, approximately 150 kb in size, composed of 66 exons and codes for a major mRNA of 13 kb with a predicted open reading frame of 9.135 kb.

It is not yet known what activity the ATM gene product possesses, but the relatedness of this gene sequence to the phosphatidylinositol 3-kinase gene family supports a role for ATM in intracellular signalling. Considerable information is already available on defective signalling through the p53 damage-inducible pathway in A-T. This includes failure to arrest at either the G1/S or G2/M checkpoints as well as radioresistant DNA synthesis. A reduced and/or delayed response in the induction of p53 after exposure of A-T cells to ionizing radiation can account for the defective G1/S checkpoint. More recently we have demonstrated that the ATM gene product is involved in the control of multiple cell cycle checkpoints. Antibodies prepared against ATM peptides demonstrate the presence of a protein 350kDa in size, which is the predicted size for this protein based on open reading frame of 9 kb. This protein is present both in the nucleus and in the cytoplasm where it is present in vesicular structures. As expected from mutation data the ATM protein is absent in cells from some patients with A-T. The cloning of the ATM gene will allow for screening of radiosensitive patients for mutations in this gene and will provide a means of identifying interacting proteins and thus an understanding of how it functions.

The causes of differences in 'intrinsic radiosensitivity' between mammalian cell lines

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A central issue in radiation biology is explaining the marked differences, shown by both normal and tumour-derived cell types, in sensitivity to killing by external beam low-LET ionising radiation. A number of factors have been suggested to mediate such differences. The possible importance of differences in the efficiency of induction of DNA damage between cell lines will be examined in this paper.

In previous studies, we found that the dose-response for induction of DNA double-strand breakage (thought to be the critical lesion leading to cell death), by external beam low-LET ionising radiation, could vary markedly between cell lines and mirrored differences in the survival response. Despite such evidence, the currently prevailing view in the literature is that differences in radiosensitivity are related to differences in some aspect of enzymatic DNA repair. However, we are aware of no compelling data that supports the latter view.

A test of the importance of possible differences in enzymatic DNA repair in determining relative radiosensitivity would be to compare lethality in cells containing equivalent numbers of DNA lesions. Enzymatic DNA repair-type models would predict that cell lines of different radiosensitivity containing equivalent numbers of DNA lesions would show differences in survival that reflected their relative radiosensitivities. In contrast, our data predict that equivalent levels of DNA damage would produce equivalent killing. Such experiments were performed by measuring the sensitivity to killing by DNA-associated ^{3}H- or ^{125}I-decays of cell lines that display a wide range of radiosensitivities but which all undergo necrotic death. Consistent with the view that, in cells lacking enzymatic repair pathway defects, differences in radiosensitivity can be ascribed to differences in the efficiency of induction of DNA dsb, the D_0 values for killing by ^{3}H- or ^{125}I-decay were comparable for cell lines of similar ploidy.

The Hidden Radiation Chemistry in Plasma Modification and XPS Analysis of Polymer Surfaces.

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The surface modification of polymers using plasma treatments is being widely researched to achieve changes in the surface energetics and consequent wetting and reactivity for a range of applications.[1] These include i) adhesion for polymer bonding and composite material fabrication[2] and ii) biocompatibility of polymers when used as orthopedic implants, catheters and prosthetics.[3] A low pressure rf plasma produces a variety of species from the introduced gas which may react with the surface of a hydrocarbon polymer, such as polyethylene. In the case of O_2 and H_2O, these species include oxygen atoms, singlet molecular oxygen and hydroxyl radicals, all of which may oxidise and, depending on their energy, ablate the polymer surface. In order to better understand the reactive species formed both in and downstream from a plasma and the relative contributions of oxidation and ablation, self-assembled monolayers of n-alkane thiols on gold[4] are being used as well characterised substrates for quantiative X-ray photoelectron spectroscopy (XPS).

The identification and quantification of oxidised carbon species on plasma treated polymers from broad, asymmetric XPS signals is difficult, so derivatisation is often used to enhance sensitivity and specificity. For example, trifluoroacetic anhydride (TFAA) selectively labels hydroxyl functionality.[2] The surface analysis of a modified polymer surface may be confounded by high energy radiation chemistry which may occur during XPS analysis. Examples include scission of carbon-halogen bonds (as in TFAA adducts), decarboxylation and main-chain polyene formation. The extent of free-radical chemistry occurring in polyethylene while undergoing XPS analysis may be seen by both ESR and FT-IR analysis.

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Microemulsion Polymerisation Using γ-ray Initiation — The Formation of Single Chain Latex Particles

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Synthetic polymer chains can be prepared more or less singly by the technique of microemulsion polymersations (MEP), so that each microlatex particle formed contains only one polymer chain. Below T_g, these polymeric particles can be called single chain polymer glasses (SCPG). The conformation of a polymer in a single chain glass is in the compact form, in contrast to the expanded random coil conformation evident in conventional multichain polymer glasses (MCPG). The question is whether the physical properties of single chain glasses are identical with those of multichain glasses.

Experiments show that single chain polystyrene glasses (SCPS) display properties quite different from those of ordinary polystyrene (PS). This is apparent from measurements of their DSC, FTIR, WAXD, PALS and density. Such measurements all point to the one conclusion: that SCPS as prepared are more random than ordinary PS. Monomers other than styrene were also covered. Copolymers and crosslinked polymers were studied. The process of the particle formation was also studied. The formation of the superchain-like structure during the heating of some virgin SCPG is proposed to be responsible for the exhibition of a first-order-like DSC exotherm near T_g. It was found that there are two prerequisites for the formation of such superchain-like structure. That is, the phenyl ring in the monomer is essential and the compression factor must be more than *one*. The triad SSS is found to be the minimum length for such structure formation. It was also found that at the stage of conversion 47%, MEP starts to differ from the conventional emulsion polymerisation.

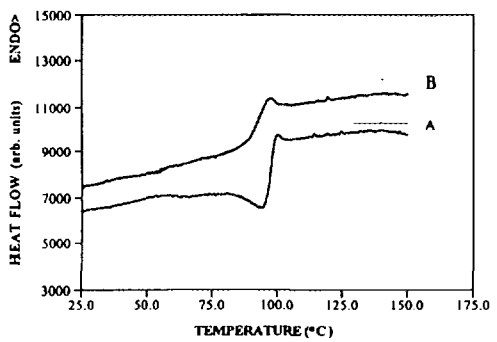

Figure 1 DSC of single chain Poly(vinyltoluene) prepared by MEP with recipe TOL/DTAB/AIBN. A. First heating; B. Second heating.

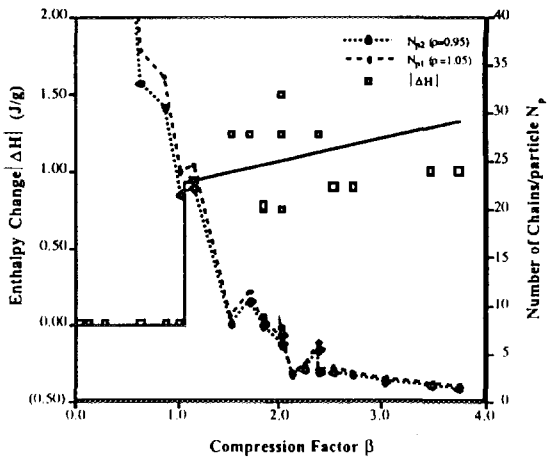

Figure 2 Enthalpy change $|\Delta H|$ versus the compression factor β and the Number of chains/particle N_p versus β. For various recipes of SCPS.

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γ-Radiolysis Investigation of the Effect of Electrosteric Stabilizers in Emulsion Polymerisation.

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INTRODUCTION

An emulsion polymerisation typically consists of two phases: the continuous aqueous phase, and the discreet organic phase, which comprises of monomer droplets and latex particles.[1] This system is stabilised by some form of surfactant. While polymerisation mainly occurs in the latex particles, the events which initiate polymerisation usually occur in the aqueous phase. Therefore, the transfer of radical activity from the aqueous phase to the organic phase (otherwise known as entry) is important in the kinetics of polymerisation. Likewise, transfer of radicals from the latex particles to the aqueous phase (exit), is important as a means whereby polymerisation in the latex particle ceases.

These entry and exit events have been studied for systems stabilised by electrostatic stabilisers (e.g. SDS, AMA80), and models for these events put forward. The current model for entry,[2] states that initiator decomposes in the aqueous phase, undergoes the initial propagation step with a monomer, and then polymerizes to a critical degree of polymerization (z) where the radical becomes surface active on the latex particle and enters the particle. It is assumed that both the initial propagation step and the entry of a radical of length z are not rate determining. The model for exit, the transfer-diffusion model[3], states that radical activity is transferred from the propagating polymeric radical to a monomer by hydrogen abstraction. This monomeric radical can either propagate in the particle or diffuse into the aqueous phase.

Experiment studies of entry and exit rate coefficients for electrostatically stabilised systems have show good agreement with these models.[4] However, studies which involved other types of surfactant, such as surface-active initiators, known as "inisurfs", have exit rate coefficients of approximately an order of magnitude below that which is expected for particles of that size.[5]

EXPERIMENTAL

This study utilises seeded emulsion polymerisations. By this method, the particle number and particle size can be chosen, and complex particle formation kinetics can be disregarded. Two electrostatically stabilised styrene latices were grown, of 24 nm and 44 nm particle radius. A portion of the these latices was reserved for kinetic studies. Poly(acrylic acid), an electrosteric stabiliser, was absorbed onto the surface of the latex particles as a second stage procedure, forming electrosterically stabilised latices.

Dilatometry was used to measure the conversion rate: the steady state rate with chemical initiator and relaxation from steady state in a system initiated by γ radiolysis, can be used to obtain the exit rate coefficient. Given the exit rate coefficient and the steady state rate of polymerisation, entry rate coefficients can be obtained.[1]

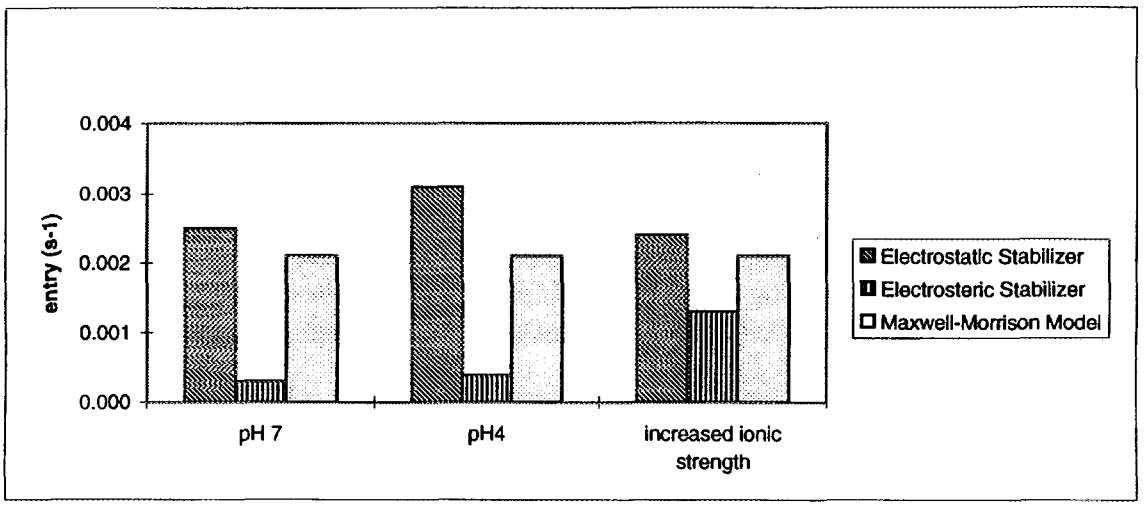
RESULTS AND CONCLUSIONS

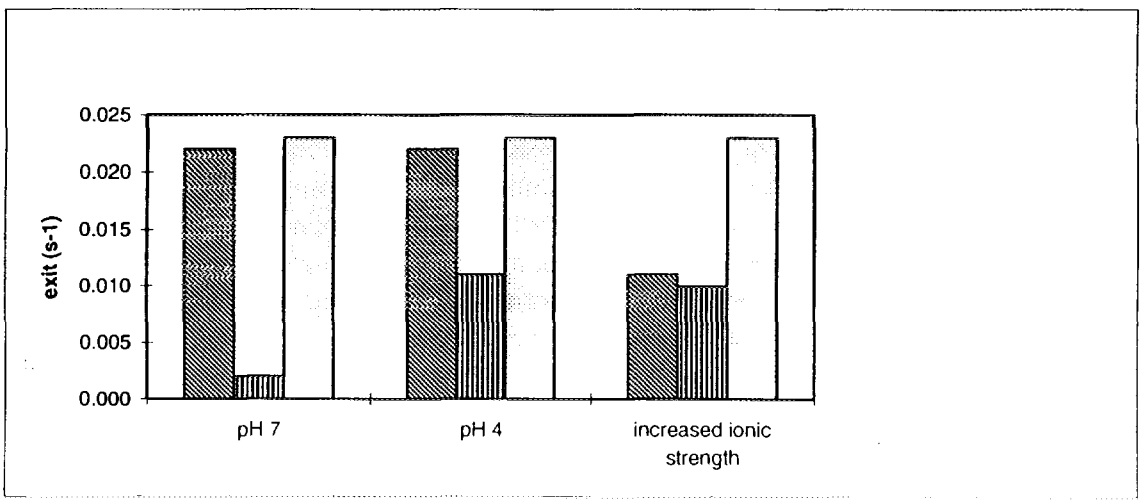
Some results are shown below for the 24 nm radius particles. Entry and exit rate coefficients were obtained for both electrostatically and electrosterically stabilised latices, for

pH 4 and pH 7, and with increased ionic concentration.

It was observed that the measured entry and exit rate coefficients electrostatically stabilised latices agreed well with the rate coefficients predicted by the models, especially at pH 4 and pH 7. However, the measured values of the entry and exit rate coefficients were significantly decreased in electrosterically stabilised systems. The largest decrease was noted at pH 7, where the electrosteric stabilized was deprotonated. As pH decreased to pH 4, the exit and exit rate coefficients increased. It was hypothesed that this increase was associated with the electrosteric stabilizer becoming more compressed. Likewise, when the electrosteric stabilizer was compressed through the addition of sodium chloride, an increase in entry and exit rate was noted.

These observations are consistent with the existance of a "hairy layer" of electrosteric stabiliser, which slows aqueous-phase diffusion. The effects of change of pH and ionic strength are consistent with this hypothesis.





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Diffusion Coefficients of Tracers in Glassy Polymer Systems Prepared by Gamma Radiolysis

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Introduction

Diffusion-controlled reactions are common in free radical polymerisation reactions, especially in glassy polymer matrices. Such reactions commonly have an important influence on the polymerisation process and final polymer properties. For example, the dominant growth-stopping event (bimolecular termination) is generally diffusion-controlled. In glassy polymer systems, where molecular mobility is very low, the chain growth mechanism (propagation) may become diffusion-controlled. At present, the mechanism for propagation in glassy polymers is poorly understood, but it is expected by the Smoluchowski expression applied to propagation to depend strongly on the diffusion coefficient of monomer. The objective of this study is to measure reliable diffusion coefficients of small tracer molecules in glassy polymers, and compare these with propagation rate coefficients (k_p) in similar systems, by the prediction above.

Experimental

Diffusion coefficients of tracer dye molecules in the glassy polymer samples (containing polymer, inert diluent, and a tracer dye) are measured by Forced Rayleigh Scattering (FRS).[1,2] Samples are required to have the following properties: must have the desired weight fraction polymer (w_p), must be homogeneous, and must be pure. Due to these constraints, gamma radiolysis of the samples is the best method for sample preparation. Samples are initially prepared in a sealed sample cell containing monomer, inert diluent, and tracer dye. After irradiation for several days, complete conversion of monomer to polymer can be obtained, even in the most glassy samples.

The FRS experiment consists of two distinct steps: the initial (writing) step induces a transient holographic grating in the sample; and the second (reading) step monitors the decay in the intensity of light diffracted through the hologram. The decay is best described by:[3]

$$I(t) = A + [B \exp(-t/\tau_1) + C \exp(-t/\tau_2) + E]^2$$

where τ_1 and τ_2 are decay constants which are dependent on the diffusion coefficients of the tracer dye and photoproduct as follows:

$$D_i = d^2 / 4\pi \tau_i$$

where D_i is the diffusion coefficient of species i, and d is the grating spacing.

A typical experimental decay is shown in figure 1.

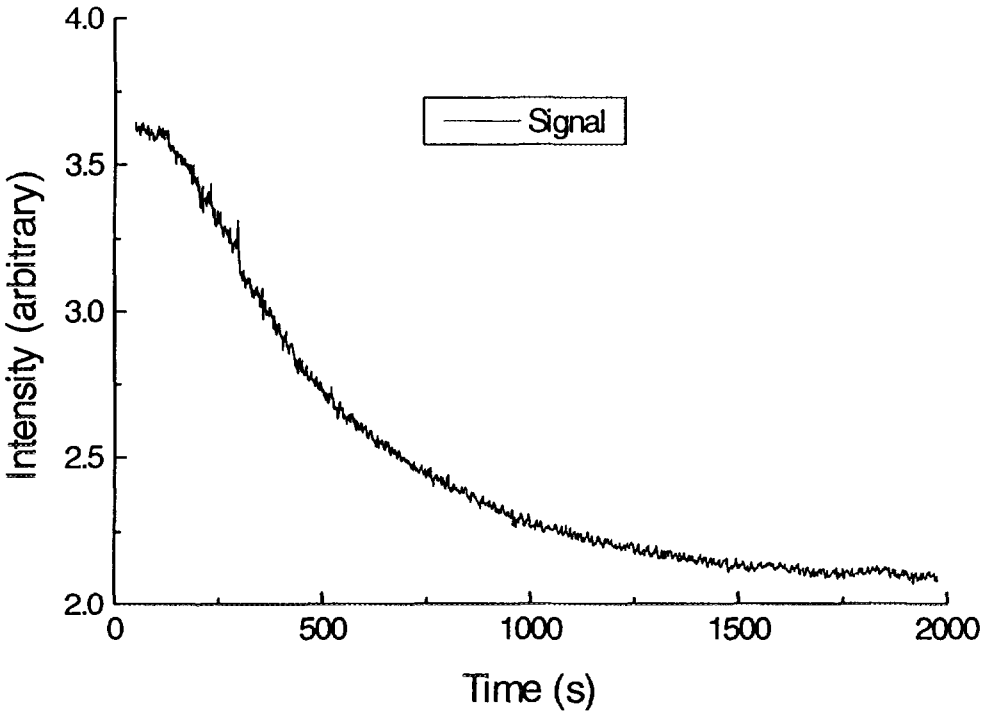

Figure 1: A typical FRS decay curve for diacetyl in pMMA, $D_{DA} = 8 \times 10^{-15}$ dm^2s^{-1}.

Conclusions

Samples with the necessary properties for FRS experiments can be prepared by gamma radiolysis of a mixture of monomer, inert diluent, and tracer dye. The diffusion coefficients for two different tracer dyes have been measured as a function of weight fraction polymer in glassy poly(methyl methacrylate) samples. The measurement of such quantities are of fundamental importance to understanding the diffusion of small molecules in glassy polymers, and to understanding diffusion-controlled reactions in glassy systems.

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FUTURE DIRECTIONS IN RADIATION ONCOLOGY

Lester J Peters

Cancer treatment has evolved progressively over the years as a joint result of improvements in technology and better understanding of the biological responses of neoplastic and normal cells to cytotoxic agents. Although major therapeutic "breakthroughs" are unlikely absent the discovery of exploitable fundamental differences between cancer cells and their normal homologs, further incremental improvements in cancer treatment results can confidently be expected as we apply existing knowledge better and take advantage of new research insights. Areas in which I can foresee significant improvements (in approximate chronological order) are as follows: better physical radiation dose distributions; more effective radiation and chemoradiation protocols based on radiobiological principles; more rational use of radiation adjuvants based on biologic criteria; use of novel targets and vectors for systemic radionuclide therapy; use of genetic markers of radiosensitivity to determine radiation dose tolerances; and use of radiation as a modulator of therapeutic gene expression. Radiation research has contributed greatly to the efficacy of radiation oncology as it is now practised but has even greater potential for the future.

Guanine as a Major Site of DNA Damage Involving the Direct Effects of Ionising Radiation

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Exposure of cells to ionising radiation results in DNA damage which is produced by either diffusible water radicals or direct effects of radiation. Although significant information is known as DNA damage by water radicals, far less is known about the chemical pathways leading to DNA damage by direct effects. Ionising radiation initially results in the formation of a radical cation and an electron in DNA. The electron is known to migrate in DNA whereas information is lacking about hole migration in DNA at ambient temperatures and its subsequent localisation.

Since 193nm light monophotonically ionises DNA at the nuclesbases, it has been possible to address the consequences of hole migration in DNA. Following photo-ionisation of DNA with 193nm light, the majority of the oxidative damage migrates and becomes localised at guanine. The resulting guanine radical results in a low yield of single strand breaks through radical transfer from the guanine moiety to produce a sugar radical. That prompt single strand breaks occur predominantly at guanine was confirmed from sequencing gel analysis. One of the major consequences of hole migration in DNA is base modification at guanine. Using an enzyme sensitive probe, 8-oxoguanine is identified as a major base modification, presumably resulting from hydration of the radical cation of guanine in double stranded DNA. In contrast, hydration of the one electron oxidised guanine radical in the mononucleoside, guanosine, does not occur. Therefore, the chemical pathways involving the guanine radical cation in DNA may differ significantly to those reported for the radical cation of guanosine.

Since the guanine radical hydrates in double stranded DNA, the question arises as to changes of the reaction pathways of the guanine radical in DNA with oxygen or other radiation modifiers, not observed with the mononucleoside radical cation of guanine.

DNA-BINDING RADIOPROTECTORS - OVERVIEW

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Abstract

The radioprotective properties of Hoechst 33342 in cultured cells were first described by Smith and Anderson (1), and later by Young and Hill (2). Hoechst 33342 binds in the minor groove of DNA, and is used extensively as a fluorescent DNA stain. The radioprotective activity of Hoechst 33342 is serendipidous, and the possibility of improving the activity has prompted mechanistic studies (3,4), and the synthesis of some new analogues. One of these new compounds - *proamine* - is both more potent as a radioprotector, and less cytotoxic, than Hoechst 33342. The radioprotective activity is further improved in another compound - *methylproamine*. The Dose Modification Factors (DMFs) obtained from survival curves of V79 cells were 1.3 (21 μM Hoechst 33342), 1.7 (84 μM *proamine*) and 2.1 (30 μM *methylproamine*). The potency of the compounds in these *in vitro* experiments has been reflected in recent *in vivo* studies, which are the subject of accompanying presentations.

The replacement of the ethoxy group of Hoechst 33342 with the more electron-donating dimethylamino group followed the hypothesis that the mechanism of radioprotection involved reduction of transient radiation-induced oxidising species (such as G+) on DNA. Previous studies (5) have demonstrated reduction of such species by tetramethylphenylenediamine (TMPD). Interestingly, proamine and TMPD are structurally related; the two secondary amino groups of proamine being connected by the extended conjugation of the phenyl-bibenzimidazole ring system. Experiments designed to investigate this mechanistic hypothesis are underway.

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CELL SURVIVAL IN IRRADIATED MOUSE INTESTINE IS INCREASED BY DNA-BINDING RADIOPROTECTORS

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Crypt survival in the mouse intestine has been used to examine effects of bisbenzimide radioprotectors. The DNA-binding ligand Hoechst 33342 was serendipitously observed to protect against radiation in cultured cells in 1984 (1) but *in vivo* radioprotective effects were not seen, possibly because insufficient concentrations of drug were delivered to the cells (2). Recently, however, *in vivo* radioprotection by Hoechst 33342 has been demonstrated both in mouse lung (3) and in brain endothelium using i.v administration.

Intravenous delivery has again been used for the present study in which the effects of methyl proamine (MP), a second generation Hoechst 33342 analogue have been examined. Recent results using the lung model suggest that MP is both more potent as a protector and less toxic than H 33342. The rapid nature of the crypt microcolony survival assay (e.g. 3) in mouse intestine provides an efficient way to examining factors which could impinge on the extent of radioprotection, for example, the interval between protector administration and radiation exposure. It is expected that once optimal timing of drug delivery and radiation exposure have been determined, topical delivery will be used to exploit fully the limited diffusion properties through cell layers of the bisbenzimides. This should permit the mitigation of normal tissue epithelial reactions without engendering unwanted concomitant protection of tumour cells

In our earlier studies on lung and vascular endothelium (see accompanying presentations) the location of the protected target cells was either in, or immediately adjacent to the vasculature through which the drug was delivered, a situation in which the limited diffusion of Hoechst 33342 through cell layers was unlikely to inhibit maximal delivery of the ligand to the target cell population. The present investigation also uses intravenous delivery but here delivery to the target crypt cell population is likely to be less efficient. The data clearly show however that for MP at 100 mg/kg, there is substantially increased crypt survival equivalent to a dose modification of about 1.33. The crypt scoring methods used indicate that protection is throughout the small intestine and preliminary data indicate that colon is also protected to a similar or slightly greater extent.

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Macro-Micro dosimetry in radiation medicine with semiconductor sensors

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This paper is a review of results obtained during the many years of research and development of semiconductor radiation dosimeters for mixed radiation fields. The last three years in Australia were devoted to development and application of such dosimeters in radiation oncology as well as development of new pioneering methods in microdosimetry.

The effect of radiation on semiconductor devices leads to defect creation in the bulk as well as to ionization. Such radiation effects selectively affect the electrical characteristics of silicon devices allowing separation of the dose components in mixed radiation fields. It is shown that most suitable silicon devices for dosimetry are P-I-N diodes and MOSFET sensors. Due to different effects of radiation on these devices the P-I-N diodes are suitable for tissue equivalent accident neutron dosimetry and insensitive to gamma radiation but MOSFET sensors are particularly sensitive to gamma radiation and are less sensitive to fast neutrons by two orders of magnitude in free air geometry. Such pairs of semiconductor sensors are uniquely suited to applications in accident and tactical dosimetry.

In medical applications they are very useful where separation of different dose components is essential. This is the case in boron neutron capture therapy (BNCT), fast neutron therapy (FNT), and Cf-252 brachytherapy. The advantages and problems of applying semiconductor integrating dosimetry have been studied.

In epithermal BNCT the dosimetric P-I-N diodes are an excellent tool for verification of Monte Carlo dose planning calculations and MOSFETs in special packages are good for gamma dose measurements.
In Cf-252 brachytherapy the P-I-N diode, being calibrated in free air geometry in terms of neutron tissue KERMA, is a good tissue equivalent dosimeter for *in vivo* applications. The experimental results have been compared with the Monte Carlo calculations and were found to agree within 2%.
In FNT with neutron energies up to 50 MeV the P-I-N diodes are useful for tissue neutron dose profile measurements in the water tank with accuracies of 3-5%. Such dosimeters could replace the time consuming method utilizing the pair TE chamber and G-M tube.

Extensive research with MOSFET dosimeters show that they are good tissue equivalent dosimeters for radiotherapy with megavoltage X-rays from a LINAC. Two main applications are i) depth dose measurements and ii) interface dosimetry in electronic disequilibrium. This type of dosimeter is uniquely suited for skin dose measurements. The results in applications of MOSFET dosimetry for BNCT and FNT in perspex and water phantoms will be presented.

The new approach for microdosimetry on a cellular level using MOS structures have been developed recently in our group. The biological cell can be modelled with micron sized silicon volumes. This method reflects real biological cell distributions and LET spectra for new radiation oncology modalities can be obtained. The theoretical basis of such an approach and promising experimental results will be presented for FNT and BNCT.

Performance of a MOSFET Microdosimeter

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Traditional applications of a MOSFET dosimeter are based on charge build up in the oxide layer. Measuring a change in MOSFET electrical characteristics which is proportional to the built up charge provides an information on the total absorbed radiation dose. However the knowledge of the total absorbed dose is not enough for estimation of the biological effect of mixed radiation fields used in modern cancer treatment modalities. High linear energy transfer (LET) particles have a high biological efficiency then low LET radiation. By measuring a LET spectrum with a microdosimeter a valuable information for calculation of the biological efficiency of a medical radiation beam can be obtained.

An optimal microdosimeter should have the sensitive volume of a cellular size and even represent a biological cell on a subcellar level for understanding deposited energy pattern in nuclear and cytoplasmic cell structures. An approach to microdosimetry, which satisfies the above criteria, models a biological cell with a silicon micro size cell. The quantitative measurement of deposited energy pattern by charge spectroscopy in a p-n junction with the size of a typical biological cell is a further step in characterisation of a mixed radiation environment. Such a dosimeter incorporates integral MOSFET dosimetry and charge collection spectroscopy in practically the same geometric volume. The integral dose has been measured using threshold voltage shift and the spectrum of deposited charge has been measured using the drain n^+-p junction as a *dE/dx* detector. These measurements were performed simultaneously on the same MOSFET detector chip.

Integral response of a MOSFET dosimeter was measured for ^{210}Po and ^{241}Am alpha particles at a range of bias voltages. It was shown that contribution of a ^{241}Am 59.9 keV x-ray to the MOSFET threshold voltage change was insignificant and decreases with the bias voltage.

The pulse height spectra were measured for ^{210}Po and ^{241}Am alpha particles, photons emitted by a ^{60}Co source and beta particles from a ^{90}Sr. For alpha particles spectra were measured for two different connection modes at different bias voltages. The changes in the spectra are discussed. It is necessary to point out that the change in threshold voltage did not affect the pulse height spectra. Low LET particles (gamma and electrons) did not contribute to a pulse height spectrum except for the few first channels while giving contribution to the threshold voltage change. This allows separation of low and high LET radiation in the medical applications. Using a MOSFET dosimeter in the single integral mode does not allow such separation.

Practical application of the MOSFET microdosimeters for separation of high and low LET radiation were done at radiation oncology facility at Brookhaven Medical Research Reactor. Some results of this study are to be discussed.

MONTE CARLO MODELLING OF PACKED CELLS TO EVALUATE THE IMPORTANCE OF NON-UNIFORM ^{10}B DISTRIBUTION IN TUMOURS

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A Monte Carlo method has been used to pack spherical cells 10 - 14 μm diameter to densities up to 51% simulating normal and tumour tissue. The average dose to the nuclei and its distribution was calculated using Monte Carlo techniques for uniform concentrations of boron (5 μg/g) and nitrogen (2 g/100 g tissue)and for non-uniform distributions. For the concentrations used here, there was a 9.5% change in nuclear dose for each 1 ppm change in ^{10}B between the average concentration and the nuclear concentration and 8% for each % of nitrogen difference. The dose was primarily deposited by ion which started and/or stopped in the nucleus, which thus experienced many passages (eg average doses of 2.9 Gy deposited by 21 passages of various ions).

Previously, Charlton (IJRB 1991, 59, 827-842) had considered dose to the nuclei of isolated cells irradiated by thermal neutrons; this method simulated the dose to nuclei of packed cells, using 200 configurations of packed cells around a target cell. Ranges and stopping power versus energy tables were produced in TRIM (Ziegler 1992) for each ion type ie Li ions (1.01 MeV, 0.87 MeV), α particles (1.78 MeV, 1.47 MeV) and protons (0.59 MeV) (the latter arising from $^{14}N(n,p)^{14}C$ in tissue nitrogen). The contribution to nuclear dose from the ^{14}C ion (40 keV) was only included if the (n,p) reaction occurred there. A cell diameter distribution of 5 - 7 μm (in 0.5 μm increments, in the ratio 1:2:4:2:1) was used and spheres were packed randomly to the desired density. The nuclear volume was set at 75% of the cell volume. The thermal cross-sections for ^{10}B and ^{14}N were used, with a neutron fluence of $5E^{15}$.

Table 1. Average doses to nuclei (Gy)

	Origin of ion			
	Nuclei	Cytoplasm	External	Sum
N (2g/100g tissue)	0.350	0.098	0.288	0.736
B (5 ppm)	1.506	0.260	0.439	2.205

While the total doses are independent of the cell packing, the contributions from the components are specific to the cell packing.

For non-uniform distributions, a variation of 1 ppm in the ^{10}B concentration in the nucleus (but for the same average concentration of 5 ppm) changes the total nuclear dose by 0.21 Gy or 9.5% per ppm. The total nitrogen dose changes at a rate of 0.06 Gy per % of ^{14}N or an 8% change in nitrogen contribution per % change in nitrogen. These figures are model-specific and illustrate the importance of knowledge of the local distribution of nitrogen and boron.

DNA STRAND BREAKAGE BY ^{125}I-DECAY IN OLIGODNA

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Abstract

A double-stranded oligodeoxynucleotide containing ^{125}I-dC in a defined location, with 5'- or 3'-^{32}P-end-labelling of either strand, was used to investigate DNA strand breakage resulting from ^{125}I decay. Samples of the ^{32}P-end-labelled and ^{125}I-dC containing oligoDNA were incubated in 20 mM phosphate buffer (PB), or PB + 2 M dimethylsulphoxide (DMSO) at 4°C during 18-20 days. The ^{32}P-end-labelled DNA fragments produced by ^{125}I decays were separated on denaturing polyacrylamide gels, and the ^{32}P activity in each fragment was determined by scintillation counting after elution from the gel. The fragment size distribution was then converted to a distribution of single stranded break probabilities at each nucleotide position. The results indicate that each ^{125}I decay event produces at least one break in the ^{125}I-dC containing strand, and causes breakage of the opposite strand in 75-80% of events. Thus, the double stranded break is produced by ^{125}I decay with probability ~0.8. Most of single stranded breaks (around 90%) occurred within 5-6 nucleotides of the ^{125}I-dC, however DNA breaks were detected up to 18-20 nucleotides from the decay site. The average numbers of single stranded breaks per decay are 3.7 (PB) and 3.3 (PB+DMSO) in ^{125}I-dC containing strand, and 1.5 (PB) and 1.3 (PB+DMSO) in the opposite strand. Deconvolution of strand break probabilities as a function of separation from the ^{125}I, in terms of both distance (to target deoxyribosyl carbon atoms, in B-DNA) and nucleotide number, show that the latter is an important parameter for the shorter-range damage. This could indicate a role for attenuation/dissipation of damage through the stacked bases. In summary, the results represent a much more extensive set of data than available from earlier experiments on DNA breakage from ^{125}I-decay, and may provide new mechanistic insights.

AU9716720

ADVANCES IN ABSORBED DOSE MEASUREMENT STANDARDS AT THE AUSTRALIAN RADIATION LABORATORY

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The applications of ionising radiation in the medical and industrial fields require both an accurate knowledge of the amount of ionising radiation absorbed by the medium in question and the capability of relating this to National and International standards. The most useful measure of the amount of radiation is the absorbed dose which is defined as the energy absorbed per unit mass. For radiotherapy, the reference medium is water, even though the measurement of the absorbed dose to water is not straighforward. The most common practice is to use ionisation chambers calibrated in terms of this quantity, where the calibration can be traced to a National primary standard of absorbed dose or of the alternative quantity, exposure. National standards are related to international standards by intercomparisons between primary standards laboratories under the umbrella of the BIPM. The responsibility for the maintenance of theAustralian primary standard of absorbed dose is in the process of being transferred from ANSTO to ARL, which already holds responsibility for the primary standard of exposure.

Two methods are commonly used to provide calibrations in absorbed dose to water. The first is the calibration of the chamber in terms of exposure in a Cobalt-60 beam, followed by the conversion by a protocol into dose to water in this and higher energy beams. The protocol recommended for use in Australia is that due to the IAEA, namely TRS-277. The other route is via the use of a graphite calorimeter as a primary standard device, where the conversion from absorbed dose to graphite to absorbed dose in water is performed either by theoretical means making use of cavity ionisation theory, or by experiment where the graphite calorimeter and secondary standard ionisation chamber are placed at scaled distances from the source of the radiation beam (known as the Dose-Ratio method).

Extensive measurements have been made at Cobalt-60 at ARL using both the exposure and absorbed dose to graphite routes. Agreement between the ARL measurements and those based on standards maintained by ANSTO and NPL is within ± 0.3%.

Absorbed dose measurements have also been performed at ARL with photon beams of nominal energy 16 and 19 MV obtained from the ARL linac. A comparison of the calibration factors for absorbed dose to graphite with those obtained by NPL for the same four secondary standard ionisation chambers gives agreement to better than ± 0.5% in these beams. The calibration factors obtained in terms of absorbed dose to water are also in reasonable agreement with those obtained at NPL and with those obtained from measurements in Cobalt-60 beams and the application of protocols. The results enable us to discuss the validity of the protocols at high photon energies, the validity of the methods used to convert from absorbed dose in graphite to absorbed dose in water and the validity of the indices used to specify the beams.

Brief mention will also be made of the establishment of a calibration facility for neutron monitors at ARL and of progress in the development of EPR dosimetry.

AU9716721

Automated Production of No Carrier Added Holmium-166

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An automated system has been developed to produce no carrier added ^{166}Ho from the decay of ^{166}Dy produced by neutron activation of $^{164}Dy_2O_3$. Targets consisting of 5-10 mg of $^{164}Dy_2O_3$ are irradiated in HIFAR at 5 x 10^{13} $n.s^{-1}.cm^{-2}$ for 12h then allowed to cool for 2 days. The irradiation can is then transferred to the automated system located in a 'hot' cell in the radiopharmaceutical research building.

A two dimension robotic arm encompassing a grab and motorized screwdriver is used to open the irradiation can. A second arm carrying a teflon tube introduces 9M HCl into the can to dissolve the target. A second tube carries the dissolved target via a peristaltic pump to a heated vial where it is evaporated to dryness under a flow of N_2. A Peltier cooled trap is used to prevent release of HCl fumes into the cell.

A motorized syringe pump dispenses 1 mL of 0.1 M HNO_3 to redissolve the digest which is then transferred by peristaltic pump via a hollow fibre filter and auto injector into an Aminex-A5 HPLC column. ^{166}Dy is eluted from the column in 0.132 M α-HIBA into a heated cyclone flask and evaporated to dryness under a stream of N_2 heated to about 50 C.

After two days the evaporated Dy/^{166}Ho digest is dissolved in another 1 mL of 0.1 M HNO_3 and injected onto the HPLC column. ^{166}Ho is collected in 20-25 mL of α-HIBA and evaporated to dryness as before at about 400 C to ensure complete decomposition of the α-HIBA. The product is finally dissolved in about 1 mL of 0.1 M HCl and pumped through a 0.22 μM filter to a product vial.

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STUDY OF RADIATION INDUCED STRUCTURAL CHANGES IN NITRILE RUBBER.

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Copolymers of butadiene (BD) and acrylonitrile (AN) (NBR rubber), have become important commercial material[1] . NBR rubbers are part of a larger classification of products often referred to as special-purpose rubbers. Oil resistance is the most important property of nitrile rubbers, and refer to the ability of the vulcanised product to retain its original physical properties such as modulus, tensile strength, abrasion resistance and dimensions, while in contact with oils and fuels.

Despite these reported advantages very few studies have been conducted[2] on the radiation yields and structural changes in nitrile rubbers during exposure to high energy radiation. In this study we are investigating the stability against gamma and UV radiation, to different doses in vacuum, of butadiene, acrylonitrile and NBR copolymers with different composition ratio BD/AN.

The mechanism of radiation induced structural changes is being investigated using experimental techniques such as ESR, NMR (Solid-state), FT-IR, RAMAN and UV spectroscopy. Also is being investigated the effect of irradiation on the mechanical properties of stressed and unstressed samples by TGA, DSC, DMA, Instron and Creep Test measurements.

So far the main effect have been a marked radiation-induced loss of unsaturation in the butadiene units, cis to trans isomerization and formation of crosslink structures (intermolecular and intramolecular).

One of the main challenges in the studies of NBR polymers is to observe directly the crosslinks produces by the radiation induced chemical reactions. IR spectroscopy is unsuitable because of the low molar absorvity of the peaks related to intermolecular crosslinking and the overlapping of the peaks (1630-1670 cm-1) related to intramolecular crosslinking (cyclization), with conjugated and nonconjugated (-C=C-; -C=N-) double bonds. A. K. Whittaker[3] has shown that crosslink structures in PBD can be detected and measured directly using solid-state ^{13}C NMR. This technique, and others, will allow us to detect and quantify the radiation induced chemical effects in nitrile rubber.

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The Effect of Radiation on the Properties of Poly(Tetrafluoroethylene-Co-perfluoropropylene)

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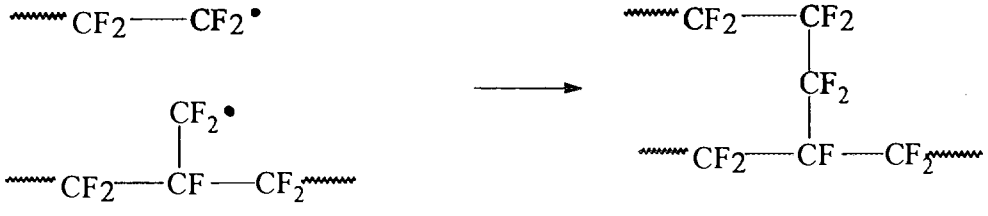
Abstract-
Fluoropolymers possess unique properties very different from their hydrocarbon counterparts. Poly(tetrafluoroethylene-co-hexafluoropropylene), also known as Teflon-FEP is commercially produced by copolymerisation of tetrafluoroethylene and perfluoropropylene. FEP is a semicrystalline thermoplastic which exhibits a number of characteristics such as chemical inertness, excellent weatherability, heat resistance and outstanding electrical properties[1].

Introducing the hexafluoropropylene (HFP) to the back bone of poly tetrafluoroethylene (PTFE) in the copolymerisation process results in the reduction of crystallinity of the fluoropolymer. This is due to the CF_3 side group disturbing the perfect symmetry of the PTFE structure. In addition, the melting point of FEP is decreased while the coefficient of friction is increased.

An interesting feature of this thermoplastic polymer is the predominancy of chain scission after irradiation, which can be attributed to an increase in polymer chain mobility. However it has been shown that irradiation at elevated temperature (above the Tg) under Nitrogen results in crosslinking[2]. The work by Bowers and Lovejoy related the crosslinking with an increase in the melt viscosity[2]. As yet there is no detailed mechanism describing the crosslinking/branching of FEP, although Bowers et al. suggested the following radical reaction from a knowledge of radical reactivities and chain mobility[3]. The combination of these two radicals was found to be the most important one leading to branching and crosslinking in FEP[3].



The purpose of this paper is to review the literature on FEP in conjunction with the current studies regarding the effect of irradiation at elevated temperatures leading to crosslinking of FEP. The mole ratio of ethylene to propylene is approximately 6:1 in the FEP sample used in this studies.

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AU9716724

SURFACE CORROSION ANALYSIS OF MACHINE ELEMENTS USING THIN LAYER ACTIVATION TECHNIQUE WITH THE PROTON BEAM FROM NATIONAL MEDICAL CYCLOTRON

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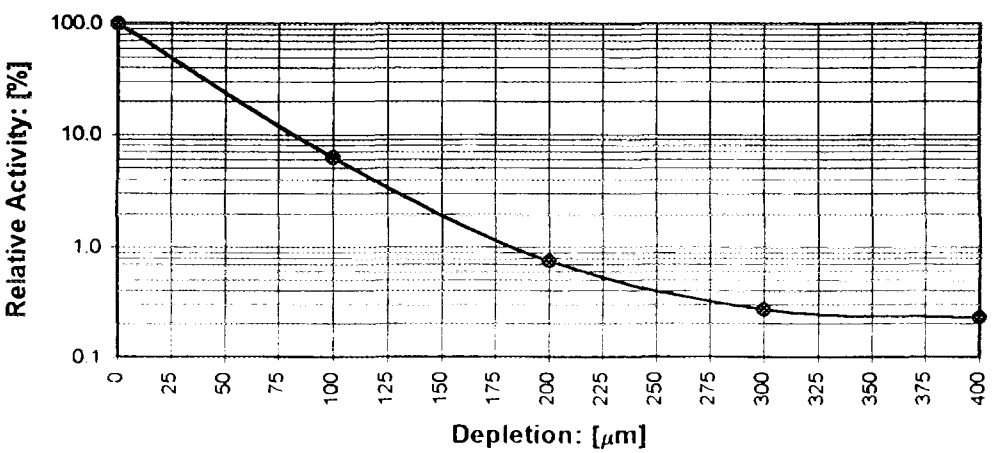
Introduction: The surface of metallic objects becomes activated when irradiated with a narrow energetic charged particle (eg. proton) beam. The depth of the activated region and the yield of the induced radioactivity depend on the charged particle energy and beam intensity respectively. The surface radioactivity of the irradiated object is depleted when the activated surface undergo wear or corrosion processes. Therefore, the quantitative assay of the remaining surface radioactivity could be used as a very effective method for monitoring wear or corrosion processes. This poster highlights some interesting results of the Thin Layer Activation (TLA) study currently undertaken at the Health Physics laboratory of the National Medical Cyclotron.

Material and Methods: A thick copper plate was irradiated with a narrow 30 MeV proton beam from the Cyclotron. The depth distribution of the major activation product (^{65}Zn) was calculated using the excitation function of ^{65}Cu(p,n)^{65}Zn reaction and experimentally verified by the surface etching with concentrated nitric acid. The surface activation pattern of the copper plate was visualised using the contact-autoradiography technique.

Results and Discussion: After the bombardment with the proton beam upto an integrated current of 200 μAh a contact-autoradiogram of the plate was made in order to visualise the size of the activated region. The active side of the plate then gradually etched out by immersing in a concentrated nitric acid bath for 120 s , 60 s, 90 s and 60 s (total etching time: 330 s). After each etching trial the surface activity of ^{65}Zn was counted with a NaI-Scintillator interfaced to a single channel analyser. The thickness (μm) of the depleted layer was evaluated from the weight of the copper plate precisely estimated with a chemical balance to an accuracy of 0.1 mg before and after each etching procedure. In Figure 1 the remaining surface activity of the copper plate is shown as function of the depletion thickness. This pilot experiment validates the feasibility of the application of 30 MeV proton beam from the NMC in thin layer activation (TLA) studies to quantify the wear and tear of various common machine elements eg. pistons, brake disks, gear and pinions of IC-Engines, turbine blades, ship propellers, ball bearings, machine tools, robotic arms, artificial heap joints etc.

Figure 1: Relative remaining surface activity of a thick copper plate irradiated with 30 MeV protons from the National Medical Cyclotron is shown as a function of depletion thickness.



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AU9716725

THE RADIATION DAMAGE IN SILICON DIODES INDUCED BY STRAY FAST NEUTRONS FROM THE ANSTO CYCLOTRON

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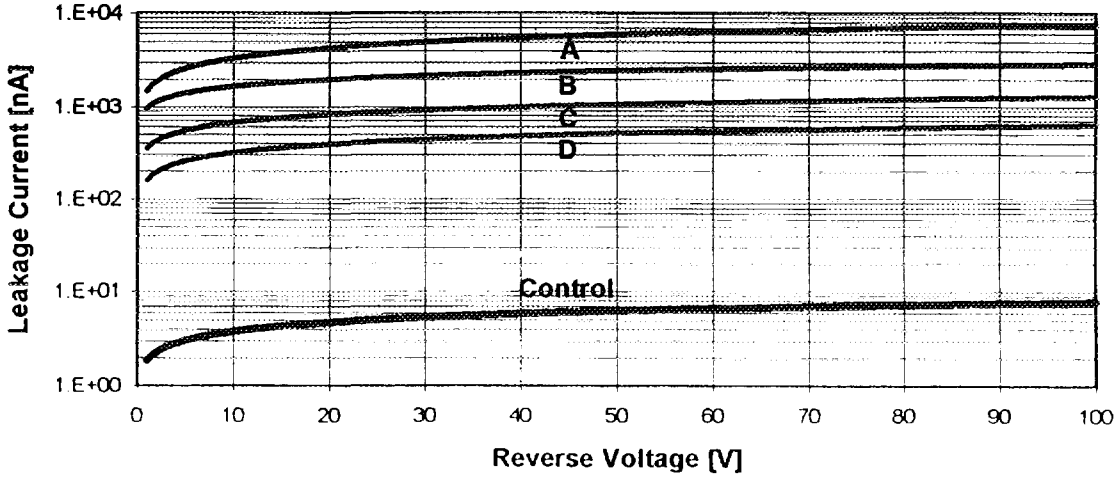
Introduction: Intense flux of fast neutrons are produced during routine isotope production runs at the National Medical Cyclotron. These stray neutrons induce irreversible displacement damage in the semiconductor devices, the vital building blocks of the various electronic instruments used in the facility. This poster highlights the results of the radiation hardness investigation study of commercial silicon diodes undertaken at the Health Physics laboratory of the National Medical Cyclotron.

Material and Methods: Four batches of small signal silicon diodes (IN 4007) with 5 diodes per batch were exposed to fast neutrons to a neutron flux of 2.03×10^{14} n.cm^{-2}, 3.18×10^{14} n.cm^{-2}, 5.50×10^{14} n.cm^{-2} and 2.89×10^{15} n.cm^{-2} in the radiation hardness testing device developed by the author (**B Mukherjee et al.** Development of a radiation hardness testing facility for semiconductor devices at a medical cyclotron. Nucl. Instr. Meth. (in print), October 1996. and **B Mukherjee et al.** Development of a simple neutron irradiation facility utilising the stray neutron field of a medical cyclotron. Appl. Radiat. Isot. 46(1995)1333).

Results and Discussion: The leakage currents (nA) of the diodes were measured at room temperature (22 °C) with reverse biased condition at 5 V, 10 V, 20 V, 50 V and 100 V using a Kiethley Model 617 Pico-Amperemeter and a Hewlett Packard Model HP 34401A Digital-Voltmeter. The hardness parameter (HP), spectral index (SI) and the displacement KERMA of the neutron flux were calculated from the neutron energy distribution. The average leakage current of the diode batches irradiated at various neutron flux levels as well as the un-irradiated control batch are shown as function of the reverse bias voltage in Figure 1. The results of this experiment were used to predict the "remaining life" of the detector electronics of the radiation monitoring instruments and the semiconductor temperature monitors for the cryogenic pumps located in the cyclotron vault and the beam room of the NMC. They also validate the feasibility of the commercial usage of this neutron irradiation facility for the hardness testing of semiconductor materials used in High Energy Physics (HEP) experiments (**M Edwards et al**. Neutron radiation damage studies of silicon detectors. Nucl Instr. Meth. A310(1991)283).

Figure 1: Leakage currents of silicon diodes irradiated with stray fast neutrons and the control batch are shown as functions of the reverse voltage. The average neutron flux for batch A, B, C and D was adjusted to 2.89×10^{15} n.cm^{-2}, 5.50×10^{14} n.cm^{-2}, 3.18×10^{14} n.cm^{-2} and 2.03×10^{14} n.cm^{-2} respectively.



Acknowledgments: Author wishes to thank Mr K Butterfield and Mr G Carter of the Physics Division of ANSTO for technical assistance and Mr C Jamieson, Manager RO for his support.

57.

Radiation effects on the liquid crystalline properties of poly(Allylsulfone)s

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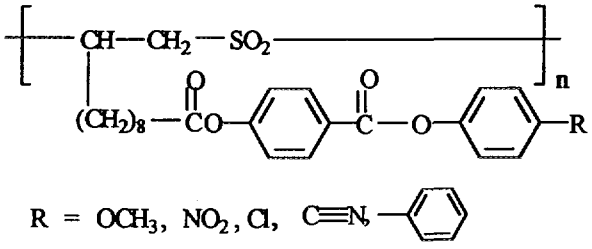
Properties of thermotropic liquid crystalline polysulfones with olefinic and mesogenic groups in the side chains have been studied.[1, 2] When poly(sulfone)s with alkyl side chains are γ-irradiated, main-chain scission takes place rather than cross-linking, because of the weakness and specificity of fracture of C-S bonds in the main chain.[3, 4] In this study, thermotropic liquid crystalline poly (allylsulfone)s which have different end groups on the side chain such as cyano, nitro, methoxy, phenyl, and chloro have been synthesised. The structures of polymers are as follow:



R = OCH_3, NO_2, Cl, C≡N,

The effect of γ-radiation on the thermotropic liquid crystalline properties of poly (allylsulfone)s have been investigated using CP-MAS-NMR, DSC, X-ray diffractometry , and CP-microscopy.

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THE RADIATION CHEMISTRY OF SYMMETRIC ALIPHATIC POLYESTERS

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Naturally occurring, symmetric polyesters, including polyglycolic acid, polylactic acid and polyhydroxybutyrate, have found biomedical applications in areas as diverse as the controlled release of pharmaceuticals and the manufacture of surgical sutures. As biomedical products, the materials require sterilization by high energy radiation. This has provided the motivation for the present work.

D'Alelio et al. have reported that linear, asymmetric polyesters undergo scission on irradiation, but that branched polyesters containing a methyl group in the diol segments undergo crosslinking. However, for the symmetric polyhydroxybutyrate, Carswell-Pomerantz et al. have reported that only scission occurs on radiolysis, with the evolution of CO and CO_2 as a result of the loss of ester linkages. These workers also found that $G(CO + CO_2)$ was approximately equal to G(S) for this polyester. By contrast, Collett et al. have reported that $G(S) = 1.26$ and $G(X) = 0.53$ for polylactic acid, which indicates that the polymer undergoes nett crosslinking on radiolysis to form a gel. They have also reported that poly(lactic-co-glycolic acid) should form a gel on radiolysis, since $G(S) = 1.66$ and $G(X) = 0.65$ for a 1:1 copolymer composition.

In the present work the radiolysis of polylactic acid and poly(lactic-co-glycolic acid) have been reinvestigated in order to resolve the differences between the work of Collett et al. and that of Carswell-Pomerantz et al. In these studies, ESR has been used to study the radicals formed, GPC has been used to investigate scission and crosslinking, GC has been used to study the small molecule volatile products and NMR spectroscopy has been used to identify and measure the new chemical structures formed in the polymers.

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KINETICS OF RADIATION-INDUCED APOPTOSIS IN NEONATAL UROGENITAL TISSUES WITH AND WITHOUT PROTEIN SYNTHESIS INHIBITION

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The difference in incidence of radiation-induced apoptosis between two neonatal urogenital tissues, kidney and testis, was analysed over a 24h period. In the rat, the two organs differ in their stage of development post-natally, with the testis approximating the adult form at birth, and the kidney remaining in a nephrogenic state until two weeks after birth. They have been shown previously to be radio-sensitive and -responsive, in specific cell populations in each organ - the nephrogenic zone in the kidney and the Sertoli cells in the testis. In the present study using 4-5 day old rats (N=4 for control or treatment sets), we have compared the kinetics of radiation-induced (5Gy of X-irradiation) apoptosis in the two tissues over a 24h period. Concurrent administration of cycloheximide (10mg/kg body weight, i.p.), a protein synthesis inhibitor, with radiation treatment was used to determine whether new protein synthesis had a role in induction of apoptosis in this *in vivo* model. Many chemotherapeutic drugs act via protein synthesis inhibition, and we believe that the results of this latter analysis may provide information for the planning of concurrent radio- and chemotherapy.

Apoptosis was quantified using morphological parameters, and verified by DNA gel electrophoresis for the typical banding pattern, and by electron microscopy. We studied the proliferative index in tissues, using [6-^{3}H]-thymidine uptake (1h prior to euthanasia and collection of tissues) and autoradiography as indicators of cell proliferation (S-phase). As well, by pulse-labelling 1h prior to radiation treatment, we able to analyse for S-phase cells undergoing apoptosis in another set of animals. Tissue was collected 2, 4, 6, 8, and 24h after radiation treatment. Expression of one of the apoptosis-associated genes, Bcl-2 (an apoptosis inhibitor/cell survival gene), was studied using immunohistochemistry. Apoptosis peaked at 4h in the testis and 6h in the kidney, emphasising the necessity of knowing tissue differences in radiation response if comparing changes at a particular time. A higher proportion (almost five fold) of the apoptotic cells died in S-phase in the kidney than the testis, over the 24h. Protein synthesis inhibition completely negated induction of apoptosis in both tissues. Necrosis was not identified at any time. In the control kidney, Bcl-2 expression was highest in the differentiated, non-nephrogenic zone, with expression increased in some cell populations of the nephrogenic zone after irradiation. In the testis, the Sertoli cells had high expression of Bcl-2 in control sections, with diminished, but not negated, levels after irradiation. Cycloheximide treatment greatly diminished Bcl-2 expression. The differences in response of the two tissues to irradiation relates to their innate cell (genetic) controls, which may be determined by their state of differentiation at time of treatment, or the tissue type. This *in vivo* study also suggests the model may be useful for analysis of other cancer therapies, for example polychemotherapies, or combinations of chemo-and radiotherapy.

AU9716729

TANDEM ACCELERATOR PRODUCTION OF Tb-149 FOR TARGETED CANCER THERAPY

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Alpha emitters are ideally suited to targeted cancer therapy of subclinical lesions as alpha particles have a high linear energy transfer (>100 keV/μm) which is about 100 times that of a beta particle. As the range in tissue is several cell diameters, it is possible to limit the radiation dose to the normal tissue, resulting in higher therapeutic ratio than is possible for beta particles. This offers a considerable advantage as the dose limiting tissue in radionuclide therapy are the stem cells in bone marrow. Currently, the only two actively researched alpha emitting radionuclides are ^{211}At and ^{212}Bi.

We have produced a new class of alpha emitter, ^{149}Tb, with a number of useful properties. The main features of ^{149}Tb are a 17% alpha, 79% electron capture and 4% positron branching ratios, with non-toxic daughters. The nuclide also has a number of gamma rays which can be used for imaging and detection during handling. We have produced ^{149}Tb at ANU using the ^{141}Pr(^{12}C,4n)^{149}Tb reaction and ^{142}Nd(^{12}C,5n)^{149}Dy⇨^{149}Tb with the Tandem accelerator. In addition, a number of other isotopes are generated as a by-product of the reaction which can be useful, but which also contribute to the contamination of the desired product. Peak yields for ^{149}Tb were found at 67 MeV and 100 MeV, respectively. For a current of 1 μA and operating at 5 MeV above the peak yield with a 10 MeV thick target, saturated activities of 2.5 μCi for Pr and 5.5 μCi for Nd targets are predicted. This Nd target value compares with a saturated activity of 3.6 μCi extrapolated from an half hour bombardment of a 14 MeV thick target with a 102 MeV, 0.33 μA beam. With an expected efficacy of 100 times that of ^{131}I for killing isolated cancer cells, the activity achievable on this accelerator should be adequate for in vitro tests of ^{149}Tb-labelled monoclonal antibodies against leukemia cells.

AU9716730

Radiochemical Separation of Tb-149 after Tandem Accelerator Production

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B. J. Allen, G. Gooze, S. Imam, St. George Cancer Care Centre, Gray St. Kogarah, NSW 2217

Terbium-149 is produced by the heavy ion induced reaction of the type $^{142}Nd(^{12}C,5n)^{149}Dy \rightarrow ^{149}Tb$. This work concerns the separation of terbium from neodymium target, and other lanthanides produced by secondary reactions on neodymium target. Firstly, anion-exchange separation is carried out at room temperature using acid-alcohol media (90% methanol-10% 5M nitric acid) as eluent. But the separation is not satisfactory. To achieve satisfactory separation, cation exchange separation is performed under pressure at room temperature using 0.16M α-hydroxyisobutyric acid of pH 5 as eluent. The pressure is exerted from a nitrogen gas cylinder. The simplicity and efficacy of this method for the separation of terbium are discussed in comparison with the commercially available high performance liquid chromatography system.

AU9716731

IN VIVO RADIOCHEMICAL PROPERTIES OF TB-149: A NEW RADIOLANTHANIDE FOR TARGETED CANCER THERAPY

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G J Beyer, Ch Morel, R Offord, Yu Aleksandrova, S Jahn, Nuclear Medicine, Cantonal Hospital of the University of Geneva, Switzerland

^{149}Tb (4.15 h) decays by the emission of both 3.9 MeV alpha particles (17% branching) and positrons (4% branch), and uniquely combines both therapeutic and PET diagnostic properties. In this paper we report the production route, systemic studies of radio-lanthanides with EDTMP ligand, and the first ^{149}Tb phantom studies using PET.

The radio-lanthanides used in this study were produced at the ISOLDE (isotope separator on-line) facility at CERN. They are produced carrier free, isotopically and chemically separated (isobaric separation using cation exchange chromatography) in a form suitable for protein labelling. Batches up to 20 mCi of ^{149}Tb are available. We have established relationships between biokinetics, EDTMP concentration, and the ionic radius of the radiolanthanide used. The tumour to liver ratio in mice reaches a maximum value at 1 mM<[EDTMP]>10 mM and decreases from 10 by almost two decades according to the ionic radius of the lanthanide. For Tb, a tumour to liver ratio of 5 can be obtained, similar to Gd. No significant differences in the uptake in bone for all lanthanides in the EDTMP system were observed.

A fast blood clearance allows clear bone images to be obtained via PET at 60-90 min post-injection, as shown with rabbits using ^{142}Sm-EDTMP. The first phantom PET studies with ^{149}Tb are also reported.

We conclude that the fast biokinetics and the alpha decay mode open up new possibilities for a more efficient endo-radionuclide therapy using EDTMP. The high purity of the ^{149}Tb (isotopically separated and carrier free) produced in this way makes it very suitable for the labelling of octretides.

Radiolabelling of chelators for monoclonal antibodies

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St. George Hospital Cancer Care Centre, Gray St., Kogarah NSW 2217
Department of Chemistry, University of Technology, Sydney*
Department of Pharmacy, University of Sydney.**

Abstract

Two radiolanthanides, namely Terbium-152 and Samarium-153, which are primarily beta-emitters, have been used to radiolabel bicyclic anhydride of DTPA. In this study, contrary to the conventional procedure, the chelator is radiolabelled first and then conjugated to melanoma antibody 7.2.29, with an attempt to achieve a better radioimmunoconjugate with less damage to immunoreactivity of the protein.

These two radioimmunoconjugates were subjected to QC analyses. Their stability and biological effectiveness toward cancer cells were evaluated.

ATM Status of the Clinically Radio-Hypersensitive.

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[1]The Division of Cancer Services, The St George Hospital, Kogarah 2217, Sydney, NSW, Queensland Institute of Medical Research, Herston, QLD, Australia.

AIMS: To characterise the response to ionising radiation of normal tissues from patients that display early and acute hypersensitivity to radiotherapy.

INTRODUCTION: It is now well appreciated that standard clinical doses (1.8-2 Gy per fraction per day) produce predictable acute and late toxicity in most patients. Occassionally, however, the standard clinical dose produces acute and late toxicity which can exceed the norm both in their extent and timing. Such individuals can be said to be radio-hypersensitive. For example, the first sign available to the clinician of this radiosensitivity may be early or excessively severe mucositis when the oral cavity or the gut is treated, or early and severe skin changes (erythema, moist desquamation).

METHODS: Methods included Cell proliferation assays using MTT, Induced chromosomal aberration testing, Cell cycle response to radiation via FACs, mutation analysis of the Ataxia Telangiectasia (AT) gene, p53 and AT Western analysis.
RESULTS: Lymphocyte cell lines from all five clinically hypersensitive patients retained a significantly higher degree of induced chromosomal aberrations when compared to normal. This was in contrast to non-definitive cell proliferation results after radiation. A number of the patients also showed differences in the induction of G_2 cell cycle delay and p53 induction after radiation. Differences were observed in the proportion of the 350kd and 200kd AT protein hybridising fragment in Western analysis using an AT specific polyclonal - the importance of this result is under further investigation. There were no AT gene truncation mutations evident in any of the hypersensitive patients.

DISCUSSION: Our analyses confirmed the innate cellular radiosensitivity of the clinically radio-hypersensitive patients used in this study. This could in turn help to explain the good outcomes that most of these patients appear to have experienced from radiotherapy on the basis of complementary tumour radiosensitivity.

While a number of response indicators in the radio-hypersensitive patients point to some degree of overlap with the reported response observed in AT heterozygotes we found no indication of AT gene truncation mutations.

In vivo variation of micronuclei in BALB/c mice after low and high doses of gamma radiation

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[1]Department of Biomedical Sciences, and [2] Department of Pharmacy, The University of Sydney; [3]Biomedicine and Health, ANSTO; [4] St George Cancer Care Centre

An adaptive response to ionising radiation exists if a low level or priming dose reduces the effect of a subsequent high or challenge dose. This has been demonstrated *in vitro* using the frequency of micronuclei formation as a measure of radiation-induced DNA damage [1, 2]. The objective of this project was to use the same approach with an animal model to investigate the existence of an *in vivo* adaptive response.

The experimental design involved priming doses of 0.005 or 0.01 Gy and a challenge dose of 4 Gy administered 1, 2, 4, 8 or 16 hours after the priming dose. Ten mice at a time were housed in a perspex animal cage and irradiated using Co-60 gamma radiation. For every time point (1, 2, 4, 8 or 16 hours), there were four treatment groups of 5 mice for statistical analysis. The first group acted as a non-irradiated control (0 Gy). The second group of mice received only the priming dose (0.005 Gy), while the third group of mice received only the challenge dose (4 Gy). The fourth group of mice received both the priming and challenge doses 0.005 Gy + 4 Gy). The process was repeated for the second priming dose of 0.01 Gy. A total of 200 mice were used.

The animals were sacrificed by cervical dislocation 24 hours after receiving the challenge dose. Both femora were removed and cleared of adhering muscle tissue. The bone marrow cells of five mice were collected and the nucleated cells removed using filtration through a mixed cellulose column incorporating a self-locking filter. The cell suspension was placed onto microscope slides using a cytocentrifuge, air-dried and then stained for the micronuclei. Then the slides were coded, and reticulocytes were scored for the presence or absence of micronuclei.

Approximately 2500 cells were scored for each treatment point, and the number of micronuclei counted ranged from 3 to 125 in this sample size. While it appears that the adaptive response may be present in 2 of 9 groups of mice pre-exposed to 0.005 or 0.01 Gy, this experiment has demonstrated a high variability in micronuclei formation indicating that the technique lacks the necessary discriminatory quality for *in vivo* use.

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Pulse Radiolysis Studies on the Formation and Transformation of the One-Electron Reduced Intermediate of Kalafungin and an Analogue in Aqueous Solution.

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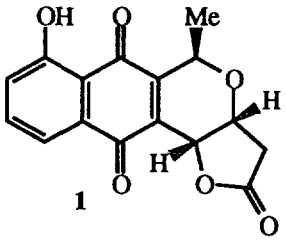
Kalafungin **1** is a member of the pyranonaphthoquinone family of antibiotics which are produced by various species of *Streptomyces* and have in common the benzoisochromanquinone skeleton. Apart from their already documented activity[1] against Gram-positive bacteria, fungi, and mycoplasmas, it has been suggested that *in vivo* reduction causes a transformation to an active hydroquinone form which functions as a bis-alkylating agent.[2] Moore[2,3] has suggested that these pyranonaphthoquinones may exhibit antitumour activity since the proposed mechanism of action resembles that of the anticancer agent mitomycin C **3**.[2]



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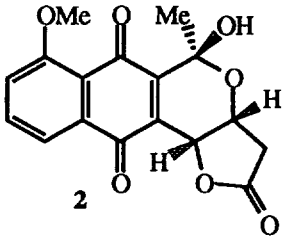

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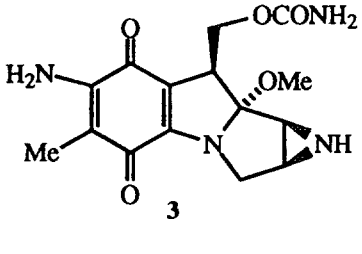

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Rapid one-electron reduction of kalafungin **1** and a closely related analogue **2** has been carried out using The University of Auckland's pulse radiolysis facility. Pulsed electrons (4 Gy in 200 ns from a 4 MeV linear accelerator) were delivered to de-aerated aqueous solutions (10 mmol.L^{-1} phosphate, pH 7.0) containing 0.1 mol.L^{-1} sodium formate and 50 - 200 μmol.L^{-1} kalafungin **1** or lactol **2** {equations (1)-(4)}. Under these conditions the one-electron reduced forms of **1** and **2**, A$^{\cdot}$, are produced by direct scavenging of the e^-_{aq} (k = ca. 10^{10} L.mol^{-1}.s^{-1}) and through fast electron transfer from the $CO_2^{\cdot}$ species (k = 10^9 L.mol^{-1} .s^{-1}). Radical formation and tranformations were followed by time-resolved uv/visible spectrophotometry.

$$H_2O \wedge\wedge\wedge\wedge\wedge \rightarrow e^-_{aq.} + .OH + H. + H_2O_2 + H_2 + H_3O^+ \quad (1)$$

$$e^-_{aq} + A \rightarrow A^- \quad (2)$$

$$.OH(H.) + HCOO^- \rightarrow CO_2^- + H_2O(H_2) \quad (3)$$

$$CO_2^- + A \rightarrow A^- \quad (4)$$

The A$^{\cdot}$ species exhibits a sharp absorption peak at 385nm, similar to that reported for the one-electron reduction of 5-hydroxy-1,4-naphthoquinone (juglone)[4], and is assigned as the protonated semiquinone species. The semiquinone species does not undergo disproportionation to form the parent compound and the hydroquinone, but, in contrast to the case of juglone which decays in a second-order radical process, the semiquinone is observed to undergo two consecutive first-order kinetic transformations. These transformations {with k(1) = 2.0 ± 0.5 x 10^3 s^{-1} and k(2) = 500 ± 50 s^{-1}} are independent of both the concentration of the parent compound and radiation doses (i.e. semiquinone concentration). The accompanying changes in absorption are consistent with the radical centre of the semiquinone species undergoing intramolecular rearrangement onto the fused non-aromatic ring structure of the compound. Possible ring opening mechanisms and the position of radical relocalisation will be discussed, as well as the involvement of radical transformation and redox chemistry in the biological activity of kalafungin **1**.

Acknowledgements: AINSE Grant 96/016

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THE RADIATION CHEMISTRY OF HOECHST 33258 AND ITS POTENTIAL RADIOSENSITIZING ANALOGUES

by

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A series of bis-benzimidazole compounds were synthesized by the Hoechst Pharmaceutical company in the late 'sixties. Potential chemotherapeutic properties did not come to fruition. However interest was maintained in Hoechst 33342 and Hoechst 33258 due to their enhanced fluorescence upon binding to DNA, which has resulted in their widespread use as dyes for the visualization of DNA.

Collaborative research between Peter MacCallum Cancer Institute and The University of Melbourne is developing the above parent compounds as potential radiomodifiers (to be used in conjunction with radiotherapy treatment). This project has investigated the photochemistry and radiation chemistry of the halogenated analogues m-I Hoechst and o-I Hoechst (which are being developed as potential radiosensitizers).

Results from UV experiments have been presented at previous meetings. In summary the major conclusion that was reached from this work was that under aqueous conditions, when all of the compound is in the minor groove of DNA, both compounds are approximatelyh equally efficient at inducing a DNA strand break for a given number of dehalogenation events. Therefore, the difference between the two compounds appears to be a difference in UV induced dehalogenation efficiency.

However, in order to design halogenated ligands that are radiosensitizers, it is clearly important to direct some fundamental investigations into the radiation chemistry of these compounds. Pulse radiolysis experiments were utilized to shed light on this question.

Studies were conducted on Hoechst 33258, phenyl Hoechst, m-I Hoechst and o-I Hoechst. The chemical interaction between the Hoechst analogues and the radiolysis products of water (the hydroxy radical and the aqueous electron) were investigated by saturating aqueous solutions with nitrogen or nitrous oxide (an electron scavenger) and using 2-propanol as a hydroxy radical scavenger.

Hoechst 33258 was investigated at pH 5 and pH 9. Transient absorption spectra of micromolar solutions saturated with nitrogen or nitrous oxide suggest the formation of hydroxyl radical adduct(s). The rate of formation of these transient spectra was observed to be dependent on the concentration of Hoechst 33258. Phenyl Hoechst, m-I Hoechst and o-I Hoechst were studied at pH 5. Spectra again suggest the formation of hydroxy radical adducts and that both m-I Hoechst and o-I Hoechst react with aqueous electrons.

The Effects of Cosmic Radiation on Implantable Medical Devices

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Metal oxide semiconductor(MOS) integrated circuits, with the benefits of low power consumption, represent the state of the art technology for implantable medical devices. Three significant sources of radiation are classified as having the ability to damage or alter the behavior of implantable electronics; Secondary neutron cosmic radiation, alpha particle radiation from the device packaging and therapeutic doses(up to 70 Gy) of high energy radiation used in radiation oncology.

The effects of alpha particle radiation from the packaging may be eliminated by the use of polyimide or silicone rubber die coatings. The relatively low incidence of therapeutic radiation incident on an implantable device and the use of die coating leaves cosmic radiation induced secondary neutron single event upset(SEU) as the main pervasive ionising radiation threat to the reliability of implantable devices. The most sensitive circuit structure within a typical microcomputer architecture is the RAM due to the small amount of charge used to store information. Those systems in which critical controlling software is in RAM, as opposed to ROM, are especially prone to SEUs in the form of memory bits changing state. In this case, single bit upsets should be corrected via a memory error detection and correction scheme.

A theoretical model which predicts the susceptibility of a RAM cell to secondary neutron cosmic radiation induced SEU is presented. The pacemaker and implantable cardioverter defibrillator (ICD) market demand high device longevity to avoid the patient discomfort and risk associated with device replacement. However, the model indicates that reducing supply voltage, to increase device longevity, leads to an exponential rise in SEU sensitivity. Furthermore, the resistive load NMOS memory cell modeled in this work has a higher sensitivity to upset then comparable CMOS cells due to the contribution of diffusion in the charge collection process. As part of the model development a previously unreported method for calculating the collection efficiency term in the upset model is presented along with an extension of the model to enable estimation of multiple bit upset rates. Shielding considerations unique to the implantable device were also considered.

An ICD is used as a case example to demonstrate model applicability and test against clinical experience. A total of 579 devices are included in this study, implanted in patients in 53 different cities and 10 different countries worldwide. The model correlates well within the statistical uncertainty associated with both the theoretical and field estimate. The predicted Soft Error Rate(SER) is 4.8×10^{-12} upsets/(bit hr) compared to an observed upset rate of 8.5×10^{-12} upsets/(bit hr) from 20 upsets collected over a total of 284672 device days. Note, that the predicted upset rate may increase by up to 20% when consideration is given to patients flying in aircraft. The upset rate is also consistent with the expected geographical variations of the secondary cosmic ray neutron flux, although insufficient upsets precluded a statistically significant test.

In summary, the consistency between model calculations and clinical and experimental observations is convincing evidence that the observed single and multiple bit upsets are attributable to secondary neutron cosmic radiation. This is the first clinical data set obtained indicating the effects of cosmic radiation on implantable devices. Importantly, it may be used to predict the susceptibility of future implantable device designs to the effects of cosmic radiation.

PULSE RADIOLYSIS STUDIES ON DNA-BINDING RADIOPROTECTORS

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Abstract

Hoechst 33342 and newly-synthesised analogues exhibit radioprotective activity in cultured cells and *in vivo*, as described in accompanying abstracts. These minor groove binding ligands bind at discreet sites in DNA, characterised by 3 to 4 consecutive AT base pairs, and DNA sequencing studies have shown focussed radioprotection at these binding sites (1). There is evidence that the bound ligands also confer more "global" protection including the intervening DNA between the binding sites (2). The observed focussed radioprotection could be explained by H-atom donation from the ligand to radiation-induced carbon-centred deoxyribosyl radicals (1), but this mechanism is unlikely to account for the global radioprotection. We now report pulse radiolysis studies on another possible mechanism, namely reduction of transient radiation-induced oxidising species on DNA by the ligand, which is consistent with the report of reduction of $G^{\bullet+}$ by TMPD (3). Oxidation of deoxyguanosine (dG) by $Br_2^{\bullet-}$, produced by radiolysis of Br- in N_2O-saturated solutions, in the presence of Hoechst 33342 results in the appearance of a transient ligand species which is kinetically resolvable from that obtained from direct oxidation of Hoechst 33342 by $Br_2^{\bullet-}$. A plot of reaction rate *versus* ligand concentration indicates that the rate constant for reduction of $G^{\bullet+}$ is approximately 3×10^8 dm^3 M^{-1} sec^{-1}. Similar experiments with DNA, rather than dG, also revealed a transient species corresponding to oxidation of the ligand, but the absolute rate of oxidation was considerably slower for the DNA-bound ligand compared to that for oxidation of the free ligand by $G^{\bullet+}$. These results are clearly consistent with the proposed mechanism of radioprotection by Hoechst 33342 and its analogues, moreover, pulse radiolysis may provide a very useful endpoint for screening new analogues, as a preliminary to radiobiological evaluation.

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RADIATION-INDUCED CROSSLINKING OF POLY(ETHYLENE) - LOCATION OF CROSSLINKS AND AFFECTS ON CRYSTALLINITY

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ABSTRACT

The issue of the distribution of radiation-induced crosslinking reactions in semi-crystalline polymers has been of much theoretical and practical interest in the past. While is has been long acknowledged that crosslinking can occur in the disordered amorphous regions, the role of the crystalline region, and the interface between the crystalline and amorphous regions is less well resolved. For example, Patel and Keller have shown that crosslinking does not appear to occur in single crystals of poly(ethylene) which have had the surface removed by treatment with nitric acid. This is consistent with the results of Dole and coworkers who studied the yields of radicals and crosslinks, as well as the decay of free radicals produced by gamma irradiation More recently, however, Tabata has demonstrated crosslinking both within the crystalline regions and at the ends of low molecular alkane molecules in the crystalline state. In particular Tabata suggests that radical reactions within the crystalline regions results in the formation of radical pairs. It is apparent therefore that the issue of the distribution of radical reactions is far from being satisfactorily resolved.

NMR spectroscopy has long been a method used in the study of radiation-induced crosslinking in polymers. The NMR techniques used to date include high resolution solution-state ^{13}C NMR, solid-state CPMAS ^{13}C NMR, and ^{1}H NMR of the crosslinked polymer above Tg (or Tm). In this paper we are concerned with the last two techniques, both of which are sensitive to changes in molecular motion in the crystalline and amorphous regions.

Samples of linear low density poly(ethylene) were crosslinked by gamma irradiation up to 5 MGy. Measurements were made of the decay of the transverse ^{1}H NMR magnetization, and of the ^{13}C CPMAS NMR spectra as a function of temperature. The T_2 decay of the molten polymers can be decomposed into three exponential processes, which are assigned to chains in bundles of incipient crystallites, chains in intermediate regions, and chains in disordered regions, in order of increasing T_2. On irradiation, the proportion of the chains with the shortest T_2 initially decreases. This is ascribed to the formation of defects in the crystallites, and is in agreement with the observed decrease in the heat of fusion on irradiation. Irradiation to higher doses leads to further crosslinking in all three domains of the polymer. The changes in the relative intensity of the 13C NMR signals as a function of temperature are interpreted in terms of restriction of the alpha transition of the crystallie regions by crosslink formation.

Synthesis and Characterisation of Functionalised Diamino-dithiol Ligands for Radionuclide Complexation.

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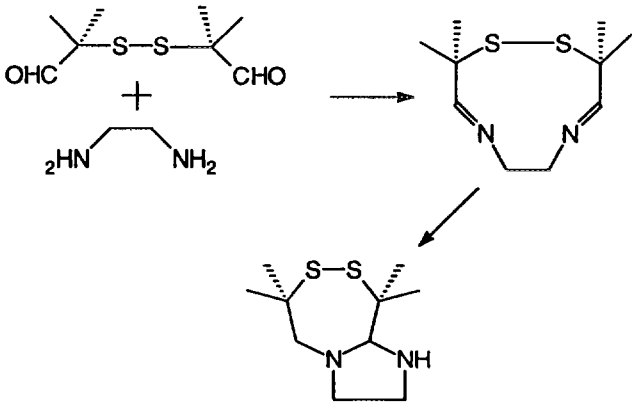
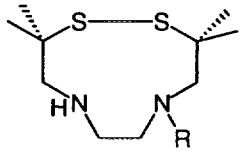
Tc-99m is the most widely used diagnostic agent in nuclear medicine. Re-188 ($t_{1/2}$ 17 h, 155 keV γ 15%, β^- Emax 2.1 MeV), with its similar chemistry, has been postulated as a suitable therapeutic analogue for the diagnostic radionuclide. The development of the $^{188}W/^{188}Re$ generator which produces carrier-free and salt-free ^{188}Re has created considerable impetus for the production of a "matched-pair" of radiopharmaceuticals for diagnosis and treatment of disease.

The organic ligands used to complex these agents frequently determine physiological half-life, stability and mode of excretion. Nitrogen and sulfur containing ligands, specifically diamino-dithiol ligands have been explored by us and others for this purpose. We have been interested in selective monofunctionalisation of the diamino-dithiol backbone, to allow for linkage onto other carrier molecules such as peptides or antibody fragments.

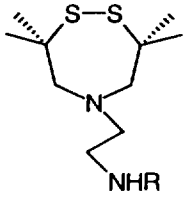
Ligands with the generic structures illustrated in **I** and **II** have been synthesised from the readily available bicyclic precursor (Scheme 1). The ligands have been characterised by the usual methods. Preliminary labelling methods with perrhenate have been attempted.

Scheme One





I



II

SEMICONDUCTOR DOSIMETERS FOR MIXED RADIATION FIELDS

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Accurate mixed radiation field dosimetry is important both health physics applications and for therapies that make use of mixed fields. One such therapy is Boron Neutron Capture Therapy (BNCT). Current clinical trials of BNCT make use of filtered neutron beams from reactors, however accelerator based beams are the most likely candidates for installation in hospitals. Both of these neutron sources have a significant concomitant gamma component. The epithermal energy range of the neutrons involved means that many dosimetry techniques developed for fast and thermal neutron fields are unsatisfactory.

We have characterised and used P-I-N diodes as neutron dosimeters and Metal Oxide Semiconductor Field Effect Transistors (MOSFETs) as gamma dosimeters in mixed gamma neutron fields.

The P-I-N diode neutron response energy dependence is similar but not the same as tissue KERMA. Its response to photon radiation is negligible. The diodes are used in passive mode (ie with no external connections during irradiation). Defects introduced into the silicon lattice lower the carrier lifetime and give a measurable change in the forward voltage characteristic of the diode. We have used P-I-N diodes to measure dose distributions though out phantoms exposed in various neutron beams including the epithermal BNCT beam on the High Flux Reactor (HFR) at Petten in the Netherlands, the BNCT epithermal neutron beam on the Medical Research Reactor (BMRR) at Brookhaven National Laboratory and the fast neutron therapy (FNT) beam at the Harper Hospital/Detroit Medical Centre. These measurements were compared with Monte Carlo simulations of the doses within these phantoms and with other measurement techniques.

MOSFET dosimeters were also exposed in the above mentioned mixed radiation fields. It was found that MOSFETs had some response to thermal and epithermal neutrons. This response was found to be dependant upon the packaging of the MOSFET. Detailed MCNP Monte Carlo neutron photon and electron transport models were done of the MOSFETs in order to determine their response functions. It was necessary to use ^{6}LiF covers to minimise the neutron contribution to the response of MOSFETs. These covers were also modelled using MCNP. When the Monte Carlo generated MOSFET neutron response was taken into account good agreement was obtained between MOSFET measurements of gamma dose in phantoms and doses predicted by Monte Carlo or by other measurement techniques. The behaviour of the MOSFETs with gate voltage, temperature, and photon energy was also studied.

P-I-N diode and MOSFET dosimeters are good candidates for on-line dose monitoring applications in clinical BNCT and in other mixed field therapies. There small size and instant readout gives them an advantage for such applications.

Curing of Phenylethynyl Terminated Resins.

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The curing of two phenylethynyl terminated composite resins was investigated under thermal and γ-irradiation conditions. The resins, PETI5A and DFB/BPF have been specially developed by NASA[1,2] for high temperature aerospace applications, and as such have been synthesised[1,2] with a high degree of aromaticity and hence lack of aliphatic protons.

The thermal curing occurs via the thermal decomposition of the resin to form radicals which initiate the addition polymerisation which proceeds through the ethynyl units. The decomposition processes at the cure temperature of 360°C lead to the formation of a very dark coloured resin. The radiation cured resin was significantly lighter in colour, indicating less degradation of the resin.

In order to reduce the degree of thermal decomposition during polymerisation, γ-radiation induced cure was attempted at 300°C.

The loss of ethynyl bonds was monitored for both the thermal and radiation induced curing with FT-Raman Spectroscopy and the formation of a polymer network was observed using Differential Scanning Calorimetry (DSC).

The maximum Glass Transition Temperatures (T_g) for the resins was found to be 245 ± 2°C for DFB/BPF in 60 minutes and 360 ± 2°C for PETI5A in 100 minutes for thermal cure at 360°C. Similar values were observed after γ-irradiation to doses of approximately 40 kGy for DFB/BPF and 80 kGy for PETI5A when irradiated at 300°C.

Thermogravimetric Analysis (TGA) shows us that the thermal decomposition process is 100 times less apparent at 300°C than at 360°C.

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OXYGEN DERIVED FREE RADICALS IN RENAL INJURY: EPR DETECTION AND MODULATION

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Oxygen-derived free radicals (OFRs) may be initiated by a short period of ischaemia followed by reperfusion. The effect in tissues is then similar to damage initiated by radiation-induced OFRs. OFRs have been implicated as one of the main mediators of damage to parenchymal and vessel cells of the kidney in ischaemia-reperfusion injury. One of the OFRs, ·NO, is a vasodilator, reacts with superoxide, and is thought to be an important effector molecule in renal pathophysiology. Modifying ·NO production after reperfusion is a potential method of limiting free radical production as well as modifying local blood flow.

In the present study, we report the detection of ·NO in isolated ischaemia-reperfused rat kidneys, and in their perfusate. Detection of ·NO relies on the formation of a stable iron(II) complex, namely $[Fe(MGD)_2NO]$ (MGD = N-methyl-D-glucaminedithiocarbamate) and its subsequent characterisation with multifrequency electron paramagnetic resonance (EPR) spectroscopy. Experiments have been performed in control ischaemia-reperfused kidneys, and in the presence of the ·NO synthase inhibitor, N-nitro-arginine methylester or a ·NO generator, nitroprusside. At this stage of our experiments, reperfusion was studied only in the acute phase (60 minutes or less). Renal function (Na excretion, GFR) was measured for all groups, and a comparison was made between the EPR and function results and renal pathology.

Although these novel studies are in their initial and trial stages, we have some evidence that modulating the level of ·NO after ischaemia-reperfusion does limit the amount of ischaemia-reperfusion induced injury, at least in the acute phase.

MICROBEAM DOSIMETRY USING X-RAY FILM

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Concern for astronauts in space began research into the effects of microbeam radiation on the tissue of the central nervous system[1]. Since then, it has been proposed that microbeam x-ray radiation could be used to administer radiotherapy and radiosurgery for lesions in the brain[2].

We are investigating the microbeam dose from a collimated superficial x-ray source using x-ray film dosimetry. A variable width collimator was used with widths of 5000 μm, 1000 μm, 500 μm, 100 μm, 50 μm and 10 μm to define the microbeam. This was placed at the end of an 8 cm diameter, 30 cm FSD (film source distance) cone. The film was placed on a 5 cm thick perspex phantom. The cone, in turn, rested on the phantom. The film used was Kodak X-Omat V Diagnostic Film and was read with a MacBeth TD-92 transmission reader with an improvised 100 μm aperture.

All data were fitted to a Gaussian curve using Sigmaplot. The peak values decreased with the decrease in slit width, and the values for the FWHM converged to a minimum value. The idealised peak height, for zero resolution, is obtained from the Area Under Curve/Slit Width. The results reveal an anomaly for the slit widths less than 100 μm, for which the dose appears to be up to 4 times that of the uncollimated beam dose. This may be due to an edge effect as the film is especially sensitive to low energy x-rays. Thus the smaller slit widths (<100 μm) could exhibit an increased fraction of low energy scattered photons from the edge of the aperture, and this would show as an increase in dose because of the increased sensitivity of the film to lower energy x-rays.
Aluminium filters are to be added to the system to eliminate the edge effect for the smaller slit widths, so that a more reliable dose measurement can be found.

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BORON DOSE ENHANCEMENT FOR CF-252 BRACHCYTHERAPY

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Monte Carlo modelling of a Cf-252 source in water (1) and in tissue (2) has shown that there is a significant therapeutic advantage obtained if B-10 is present in the tumour cells. This study analyses the advantage in terms of therapeutic margin, defined as the distance from the border of the treatment volume (3) where boron-loaded tumour cells will receive a therapeutic dose.

Calculations were made with MCNP version 4a on a Pentium 60 MHz computer. Large voxel sizes allowed 70 minute runs to achieve statistical uncertainties of 5% or less for 100,000 source neutrons. Later runs with smaller voxels confirmed the accuracy of the initial calculations. Calculations were made for treatment volume radii up to 11 cm and 30 ppm boron-10. The therapeutic margin for radii in the range 3-9 cm is approximately 10% of the tumour radius. This results in a 30% increase in the volume inside which peripheral tumour cells may receive a therapeutic dose. The median therapeutic ratio within the therapeutic margin varied from 1.05 at 3 cm up to 1.25 at 10 cm. Thus there is little benefit for less advanced tumours with thickness less than 3 cm. However, cervical cancer frequently presents in an advanced state in Southeast Asia and in Aboriginal communities in Australia, partially attributable to low Pap smear screening rates (4).

These conclusions support the development and testing of boron compounds in in vitro and in vivo models for cervical cancer.

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EXIT IN THE EMULSION POLYMERIZATION OF VINYL ACETATE

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In most emulsion polymerizations the exhaustion of the separate monomer phase is followed by a decrease in conversion rate due to the decrease in monomer concentration in the latex particles. The unusual feature of vinyl acetate is that the rate remains constant throughout most of the period of decreasing monomer concentration.

There are two postulated mechanisms consistent with the observed kinetics.[1] Both require that $k_{ex} = k_{tr}C_p$ and this can be tested with a gamma radiolysis experiment.[2] (k_{ex} = exit rate coefficient, k_{tr} = rate coefficient for transfer to monomer and C_p = monomer concentration in particles).

An automatic tracking device (developed by David Sangster) measures the meniscus height in a dilatometer every three seconds. When the dilatometer is removed from the gamma source initiation by radiolysis stops allowing k_{ex} to be determined directly from the relaxation data.

One aspect of relaxation experiments which is often overlooked is the effect of the heat of reaction on the temperature of the reaction mixture.[3] It was found that the temperature increased by as much as two degrees when the dilatometer was placed in the γ-source and the polymerization recommenced. This means that on removal from the source the reaction temperature decreases, the reaction mixture contracts and if this contraction is not taken properly into account, it appears as more conversion than there actually is. In other words the relaxation appears to take much longer than it should and entirely spurious interpretations may result.

In order to compensate for this effect the temperature and contraction of the reaction mixture were monitored (out of source) while the temperature of the water-jacket was lowered through the range appropriate to the particular experiment. These data were used to construct a calibration curve which, together with a sensitive temperature probe in the dilatometer, was used to correct the conversion/time data obtained during the relaxation experiment.

The system relaxes very quickly at 50°C, within the 3 second reading interval and therefore too fast to measure with our experimental setup. This is to be expected as $k_{tr}C_p \approx 5$ s^{-1} giving an expected half life for the relaxation of 0.14 s. However at 2°C the half life is about 10 times greater and measurement was possible giving $k_{ex} = 0.4 \pm 0.1$ s^{-1} which is consistent with the product $k_{tr}C_p \approx 0.5$ s^{-1} at 2°C.[4,5]

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RADIATION STABILISATION of HYPERSWOLLEN POLYMER

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If sodium dodecyl sulphate, SDS, is added to a latex of poly(vinyl acetate), PVAc in water, to give an overall SDS concentration greater than 4.5 mM, the polymer latex particles swell reversibly to a final volume of the particles up to fifty times their original volume. 96% of the increase is due to water carried in with the SDS. The swelling is attributed to the formation of polymer micelle complexes (PMCs) along the polymer chains. The charges on these PMCs repel, thus expanding the particles. Entanglement of higher molecular weight chains inhibit swelling beyond an equilibrium value.[1]

If, however, the swollen particles are irradiated in a gamma source and then dialysed, they shrink only slightly to approx. forty times the original volume indicating that the charges are attached irreversibly to the PVAc chains. The maximum effect is observed at 12 kGy (dose rate 0.12 Gy/s) and at a molecular ratio PVAc : SDS of 12; both of which indicate that grafting has occurred.

We believe that the radical products from the radiolysis of water abstract hydrogen from the methylenic groups of the surfactant tail and from the VAc units of the polymer. The resulting surfactant radicals react with those on the polymer chains giving a strong co-valent bond. On dilution or dialysis the excess surfactant is removed leaving the permanently grafted molecules still attached to the chains. The chains thus have a structure similar to an entangled polyelectrolyte and the repulsion between the charges on the grafted surfactant molecules keeps the particles expanded. If a salt solution is added, the repulsions are reduced by ionic electrostatic shielding and the particles shrink accordingly until a salt concentration is reached at which coagulation occurs.

These microgels are novel materials and we have been investigating their potential for new and useful purposes. The stabilised latices show a remarkable increase in colloidal stability towards coagulation in sodium chloride solution. The stabilised particles do not coagulate in salt solution 400 times as concentrated as that in which as-prepared unstabilised latices coagulate.

PVAc	initial	<–[SDS]–>	final	$[NaCl]_{coag}$
330 ppm	0 mM	after dialysis	0 mM	0.006 M
330 ppm	20 mM	dialysed	0 mM	0.022 M
1500 ppm	20 mM	diluted 4x	5 mM	0.8 M
330 ppm	20 mM	irrad'd+dialy	0 mM	1.8 M

In 2% VAc monomer / 20 mM SDS solution the nonstabilised expanded particles contract as the PMCs are displaced by monomer but stabilised particles remain the same size. This suggests that their use as an expanded seed for further polymerisation could have advantages.

These are examples of the unusual properties we have found in working on these systems and suggest additional novel uses. We are interested in cooperating on different practical applications of the reversible super-swelling and of the stabilised swollen particles.

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A RADICAL APPROACH TO THE IODINE-THIOSULFATE REACTION

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Although the reaction between iodine as triodide, I_3^-, and thiosulfate in aqueous solution has been used in analytical chemistry for over 100 years it was only in 1992 that the full details of its mechanism were elucidated by Scheper and Margerum using rapid flow techniques. They postulated the following mechanism from kinetic data alone and stated that the two intermediates, $I_2S_2O_3^{2-}$ and $IS_2O_3^-$ did not absorb light in the wavelength range in which I_3^- does.

$$I_3^- + S_2O_3^{2-} \rightleftharpoons I_2S_2O_3^{2-} + I^-$$

$$I_2S_2O_3^{2-} \rightleftharpoons IS_2O_3^- + I^-$$

$$IS_2O_3^- + S_2O_3^{2-} \rightarrow I^- + S_4O_6^{2-}$$

By forming I_3^- through fast reactions of radicals produced by pulse radiolysis of aqueous solutions containing iodide at high concentations and thiosulfate at low concentrations, and by studying the spectra and decay of transients on the millisecond time scale, we have obtained results which are consistent with their quantitative scheme and show evidence for a change in kinetic order in $S_2O_3^{2-}$ at low thiosulfate and high iodide concentrations predicted by their model, but not detectable by their technique. However in contrast to their findings we have found direct spectrophotometric evidence for the intermediates $I_2S_2O_3^{2-}$ and $IS_2O_3^-$.

Additive Effects in Radiation Grafting and Curing

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Detailed studies on the accelerative effect of novel additives in radiation grafting and curing using acrylated monomer/oligomer systems have been performed in the presence of ionising radiation and UV as sources. Methyl methacrylate (MMA) is used as typical monomer for these grafting studies in the presence of the additives with model backbone polymers, cellulose and polypropylene. Additives which have been found to accelerate these grafting processes are: mineral acid, occlusion compounds like urea, thermal initiators and photoinitiators as well as multifunctional monomers such as multifunctional acrylates.

The results from irradiation with gamma rays have also been compared with irradiation from a 90W UV lamp. The role of the above additives in accelerating the analogous process of radiation curing has been investigated. Acrylated urethanes, epoxies and polyesters are used as oligomers together with acrylated monomers in this work with UV lamps of 300 watts/inch as radiation source. In the UV curing process bonding between film and substrate is usually due to physical forces. In the present work the presence of additives are shown to influence the occurrence of concurrent grafting during cure thus affecting the nature of the bonding of the cured film. The conditions under which concurrent grafting with UV can occur will be examined. A mechanism for the accelerative effect of these additives in both grafting and curing processes has been proposed involving radiation effects and partitioning phenomena.

ABSORBED DOSE OPTIMIZATION IN THE MICROPLANAR BEAM RADIOTHERAPY

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Abstract

Recent advances in synchrotron generated X-ray beams with high fluence rate, small divergence and sharply defined microbeam margins permit investigation of the application of an array of closely spaced, parallel or converging microbeams for radiotherapy.

The proposed technique takes advantage of the repair mechanism hypothesis of capillary endothelial cells between alternate microbeam zones, which regenerates the lethally irradiated capillaries. Unlike a pencil beam, more accurate dose calculation, beam width and spacing are essential to minimise radiation damage to normal tissue cells outside the target. The absorbed dose between microbeam zones should be kept below the threshold for irreversible radiation damage. Thus the peak-to-valley ratio for the dose distribution should be optimized.

The absorbed dose profile depends on the energy of the incident beam and the composition and density of the medium. Using Monte Carlo computations, the radial absorbed dose of single 24 x 24 μm^2 cross-section X-ray beams of different energies in a tissue/lung/tissue phantom was investigated. The results indicated that at 100 keV, closely spaced square cross-sectional microbeams can be applied to the lung. A bundle of parallel 24 μm-wide planar microbeams spaced at 200 μm intervals provides much more irradiation coverage of tissue than is provided by a bundle of parallel, square cross-sectional microbeam, although the former is associated with much smaller Peak (maximum absorbed dose on the beam axis) -to-Valley (minimum interbeam absorbed dose) ratios than the latter. In this study the lateral and depth dose of single and multiple microplanar beams with beam dimensions of width 24 μm and 48 μm and height 2-20 cm with energy of 100 kev in a tissue/lung/tissue phantom are investigated. The EGS4 Monte Carlo code is used to calculate dose profiles at different depths and bundles of beams (2 x 2 cm^2 to 20 x 20 cm^2 square cross section) with a 150 μm, 200 μm and 300 μm beam spacing. The peak-to-valley ratios are compared at different depths, bundles, heights, widths and beam spacing to determine the optimum parameters for irradiation.

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Free Radicals in the Aqueous Environment

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The chemistry of the degradation of organic herbicides and fungicides in natural systems is important in determining operationally important parameters such as witholding times before planting or consumption. Disappearance rates in the field are frequently many time larger than expected from reactions such as hydrolysis and photochemical- and radical-initiated reactions are frequently cited as causes of the degradation reactions.

Reactions of OH and O_2^- radicals and secondary radicals derived from these are increasingly postulated as being important in many aqueous environmental reactions. Free radical reactions may contribute to the degradation of organic pesticides and are directly implicated in the use of radical generating systems such as Fenton's Reagent or hydrogen peroxide in the removal of chlorinated organic chemicals from drinking water.

Natural sources of these radicals in aqueous systems are predominantly photochemical reactions or reactions initiated by transition metal ions. Hydrogen peroxide is present in many aqueous environments in relatively high concentrations and we are attempting to establish the presence of superoxide radicals in natural systems. The measurement of stationary state concentrations of free radicals as low as 10^{-15} M is a challenge to analytical and free radical chemists. Long term scavenging studies are difficult and generally non-specific.

Current ideas will be reviewed and our approach to the measurement of superoxide in natural systems will be outlined.

KINETIC STUDIES OF ION - RECOMBINATION IN GASES

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Subsequent to primary ionisation/excitation and dissociation events in irradiated systems, the medium relaxes by various secondary processes which may also be precursors to lasting chemical and physical changes in the system. Pulse radiolysis techniques can be successfully utilised to directly observe such processes so that kinetic parameters may be determined to subsequently accurately model these processes in irradiated systems.

Time resolved microwave absorption techniques on a Febetron 706 pulsed electron beam system have been used to study ion recombination in simple gas systems. The microwave absorption method relies on the mobility of charged species within the system and effectively measures an ac-conductivity of the irradiated medium. The technique has a time resolution of about one nanosecond.

The decay of conductivity in irradiated gases over the pressure range 50 to 1500 torr has been measured on time scales from 10 nanoseconds to 10 microseconds. Bulk gas pressure and ion densities were such that measurements yielded recombination coefficients for dimeric rare gas cations with thermal electrons. The recombination rate constant, α_T, is shown to be both independent and dependent on the total pressure in the system.

$$\alpha_T = \alpha_2 + \alpha_3 [M]$$

α_T has values up to $\sim 10^{+14}$ L. M^{-1} s^{-1}

Total recombination coefficients α_T have been measured for the noble gases helium, neon, argon, krypton and xenon. Measurements have also been made for the simple diatomic molecules nitrogen & hydrogen.

All the systems studied, except for argon, show both two and three body processes occurring. The three body or "assisted" process requires the thermalisation of electrons in the neighborhood of the positive ion prior to capture. The two body effect is thought to be a radiative or dissociative process.

The mechanistic implications of the pulse radiolysis results will be discussed in detail.

The Sonochemical Dissolution of Colloidal CdS

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Abstract

The passage of ultrasonic radiation through water leads to the formation and subsequent violent collapse of gas/vapour filled microbubbles in solution. The collapse of these microbubbles is extremely rapid, resulting in a virtually adiabatic process in which high temperatures and pressures are produced. Infact, the conditions are vigorous enough to lead to the thermal homolysis of water molecules within the microbubble, resulting in the formation of the highly reactive hydrogen and hydroxyl radicals. These radicals can recombine or, in the presence of air, react with oxygen to produce a number of chemically active species which can readily diffuse into the bulk solution. The dissolution of colloidal CdS at pH=10.5 appears to be due to the reaction of H_2O_2 and O_2^- with the colloid. It was found that the reaction could be inhibited by the addition of Na_2S to the colloidal solution. Results also show that the reactions involved in the presence of Na_2S are complex and that sulfur oxyanions most likely partake in the overall scheme once they are formed.

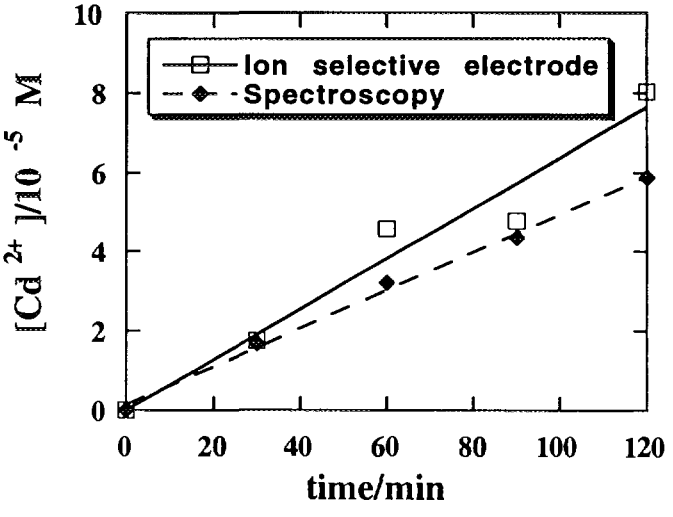

Figure 1. The concentration of aqueous Cd^{2+} plotted against the sonication time. The Cd^{2+} concentration was measured directly using an ion selective electrode (-□-) and compares well with an indirect measurement (-♦-) of the concentration obtained from the absorbance of the colloid at 300 nm.

Radiochemical Studies of Photopion Reactions at Intermediate Energies

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This work reports the radiochemical yield measurements of (γ,π^-xn) [where x is the number of emitted neutrons] and (γ,π^+) reaction products induced by bremsstrahlung of end-point energies (E_0) from 40-1200 MeV over a wide range of targets (^{7}Li to ^{209}Bi). With the aid of appropriate radiochemical separation the (γ,π^-xn) and (γ,π^+) products are identified applying Gamma spectrometry. The yield values are presented as a function of E_0, target mass (A_t) and x. The present results are compared with those obtained from Monte Carlo calculation based on PICA (Photon Induced Cascade Analysis) Code. The yields for (γ,π^-) and (γ,π^+) are found to be constant for target mass, A_t>30. PICA reproduces the A_t-independence, but underestimates the (γ,π^-) yield by 35% and overestimates the (γ,π^+) yield by 100%. The underestimation of observed yield ratio, $Y(\gamma,\pi^-)$ /$Y(\gamma,\pi^+)$ by PICA is 33%. The results are discussed in the light of photopion reaction mechanism and nuclear structure.

Evaluation of Di-Amino Phenol Substituted EDTA for use in Radiolabelling Proteins with ^{64}Cu.

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In recent years considerable effort has been directed towards synthesis of bifunctional chelating agents for coupling radiometals to proteins for tumour targeting. Of particular interest is the design of chelators for radiolabelling with copper. Two isotopes of copper have been identified as showing potential in the development of diagnostic and therapeutic agents. Copper-64 ($t_{½}$ = 12.4 h, β^+) for use in PET imaging and ^{67}Cu ($t_{½}$ = 12.4 h, γ = 185 keV, β^-_{max} = 390 keV) for use in therapy. This study involves a high yielding synthesis of a novel di-amino-phenol substituted EDTA (DAHA-EDTA) ligand and its radiolabelling chemistry with ^{64}Cu produced at the national medical cyclotron (NMC).

High activity levels (upto 59.2 GBq EOB) of ^{64}Cu is co-produced during the production of ^{67}Ga from enriched ^{68}Zn. Waste eluent from the NMC ^{67}Ga production was evaporated to dryness and found to contain by products such as ^{57}Ni, ^{57}Co, ^{64}Cu, ^{67}Cu and ^{55}Co. A new method involving low acid concentration aqueous/organic mixtures with an anion exchange (AG 1-X8, BioRad) have been used to isolate the carrier-free ^{64}Cu. The specific activity of the ^{64}Cu (5×10^{14} Bq/g) was found to be higher than that produce by Australian radioisotopes (ARI).

The synthesis of the ligand involves the refluxing of EDTA anhydride in the presence of 4-nitro-2-amino-phenol in acetonitrile to produce the di-nitro derivative (DNHA-EDTA) in > 95% yield. The DNHA-EDTA is then reduced in the presence of activated palladium charcoal with sodium borohydride under an inert atmosphere at room temperature. The reaction mixture was acidified and the catalyst removed to obtain the final product, DAHA-EDTA.

Copper complexes of DAHA-EDTA were prepared over a range of pH's (pH 3 - 7). Complexation of the copper was assessed by ITLC-SG analysis (Methanol : Water (9:1)). Complexation of the copper is greater than 99% within 1 min at room temp. Serum stability of the unsubtituted di hydroxy derivative (DHA-EDTA) is good with only 2.1% dissociation of the copper in 72 h.

Labelling of proteins (B72.3, DD-3B6/22 and streptavidin) has been achieved with the DAHA-EDTA ligand. The procedure involves the addition of the copper / ligand complex to the protein at > 3mg/ml in the presence of excess 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC). The reaction mixture is left to incubate for 1 h at 37°C and radiolabelled protein is then isolated using size exclusion chromatography.

OXIDATION OF AMINO ACIDS AND PROTEINS BY PEROXYNITRITE

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We have recently demonstrated that a range of amino acids and proteins exposed to free radicals or other reactive oxygen species can acquire new chemical reactivity characteristic of the hydroperoxide group [1]. The proteins were peroxidized by the hydroxyl or peroxyl free radicals, by products of the reaction between H_2O_2 and reduced transition metals, or by exposure to neutrophils stimulated to undergo the respiratory burst. Further studies demonstrated that decomposition of the protein hydroperoxides leads to the release of a range of new reactive substances, including alkoxyl, superoxide, carbon dioxyl and other unidentified carbon-centred free radicals [2]. These findings suggested that proteins exposed to free radicals and other strong oxidants generated by living organisms may be the source of damage to tissues even at sites distant from the original point of generation of the reactive species. In examining the ability of biologically significant oxidizing agents to generate protein peroxides, we have studied protein peroxidation by peroxynitrite ($ONOO^-$), known to be a potential source of tissue damage. Treatment of bovine serum albumin, lysozyme, apotransferrin, insulin or human serum albumin with peroxynitrous acid (POXNA) led to formation of hydroperoxide groups on the proteins, detected by their reaction with iodide. Under optimum conditions, up to one peroxide group formed on each molecule of protein. The peroxides could be reduced by treatment with GSH, ascorbate, mercaptoethanol or borohydride.

It is generally believed that the active oxidant derived from POXNA is the hydroxyl radical or an activated form of POXNA. Hydroxyl radical scavengers, antioxidants, or metal chelators, were unable to affect the quantities of peroxides generated by POXNA. These findings suggest that the oxidation was not mediated by the hydroxyl free radicals.

The iodide assay cannot be applied to the measurement of peroxides in presence of nitrite, which is a contaminant of most solutions of POXNA. Nitrite can be easily removed from proteins by molecular filtration, but this method cannot be applied to amino acids. We have therefore applied an amino acid peroxide test based on chemiluminescence, which shows promise for general peroxide detection.

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DETERMINATION OF AMINO ACID AND PROTEIN PEROXIDES BY THE XYLENOL ORANGE-Fe(III) COMPLEX

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Oxidative stress imposed on living organisms is believed to lead to the depletion of their antioxidant defences, followed by chemical changes in the cell constituents. These may ultimately develop into pathological conditions such as cancer or cardiovascular disease.

The nature of the agents of oxidative stress triggering these events suggests that they can induce the formation of peroxides *in vivo*. Therefore an obvious methodology potentially useful in the studies of oxidative stress is the assay of peroxides. In practice this has proved difficult because of the relative instability of peroxides in biological systems and the lack of peroxide assays with the required specificity and sensitivity. Most of the assays in current use can only be applied to lipid peroxides. Most require several procedural steps, including the extraction of the lipids with organic solvents, which can introduce major errors in the estimation of the peroxides. Perhaps most importantly, it is by no means certain that lipids are the first or the most significant targets of the agents of oxidative stress. It is now clear that many of these agents can peroxidize proteins quite efficiently [1]. An assay of peroxides which could be applied to tissues or simple tissue extracts would prove extremely useful in the studies of the phenomenon of oxidative stress.

With this purpose, we have tested the ability of two peroxide assay techniques to measure the formation of amino acid and protein peroxides in aqueous solutions irradiated with X rays, using a modification of the method based on the oxidation of Fe(II)) by peroxides and compexing of the Fe(III) produced by xylenol orange [2]. The molar extinction coefficients of the peroxides tested were determined by comparison with the well-tested iodometric assay [3]. We have extended this work to the detection of all organic peroxides in human blood plasma or serum subjected to oxidative stress, where the iodometric assay proved difficult to apply and unreliable because of the binding of iodine to the blood components. Preliminary results suggest that exposure of serum to γ radiation leads to immediate peroxidation of the proteins, with a delay before generation of lipid peroxides.

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DNA-PROTEIN CROSSLINKS INDUCED BY PROTEIN PEROXIDES

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Free radicals are known to interact with all cell components. Because proteins represent the largest component of most cells on a mass basis, apart from water, reaction with this type of molecule is a likely occurrence. Our research interest has been one particular product of such a reaction, the hydroperoxide adduct. We have demonstrated its formation on BSA, lysozyme and insulin, as well as several amino acids, as a result of exposure to free radicals generated by a variety of means (1,2,3). *In vitro*, these protein peroxides could be reduced by glutathione peroxidase/GSH or by ascorbate, but the reaction was slow and in some cases incomplete. Their relatively long half-life prompted us, therefore, to study the effect of the peroxide adducts on other biomolecules. In the study reported here, we investigated the action of protein peroxides on DNA, using BSA or insulin as model proteins.

Solutions of BSA or insulin were irradiated with gamma rays to produce protein peroxide adducts. After complete reduction of the radiation generated H_2O_2 with a small amount of catalase, the protein solutions were incubated at 37° with DNA (pBR322 ± EcoRI, pGEM-T, and λ/HindIII). This treatment led to retarded migration and band broadening during agarose gel electrophoresis. The extent of retardation was proportional to incubation time and protein peroxide concentration. Control samples of DNA incubated with unirradiated protein showed the same electrophoresis pattern as a sample of DNA on its own. The gel shift induced by incubation with irradiated BSA or insulin could be reversed by post incubation digestion of the sample with proteinase K, prior to electrophoresis. It could be prevented by increasing the ionic strength of the solution before protein/DNA incubation, but an increase in the salt concentration at the end of the incubation period had no effect. From these observations, we deduced that incubation of DNA with peroxidised proteins led to formation of covalent crosslinks between the molecules.

A DNA gel shift could also be prevented by complete reduction of the protein peroxide groups before incubation. When the peroxide groups were allowed to partially autodecompose over a period of days, the gel shift was progressively decreased.

To determine whether secondary radicals arising from the decomposition of the protein peroxide groups were responsible for the crosslinks, we included free radical scavengers during incubation. Of the scavengers DMSO, sodium formate, mannitol, tert-butanol, Trolox and ascorbate, only sodium formate was able to prevent a gel shift, and this was probably due to its salt effect rather than to any radical scavenging. Despite these negative scavenger results, we cannot conclude that secondary radicals do not lead to the observed crosslinks between protein molecules and DNA. From our data we know that the two types of molecules must be in very close proximity before crosslinks can be formed. It is, therefore, possible that the scavengers do not have access to any secondary radicals that may form in the space between protein molecule and DNA.

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MODIFICATION OF RADIATION DAMAGE IN MOUSE LUNG BY DNA-BINDING RADIOPROTECTORS

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Abstract

The limited diffusion of Hoechst 33342 through cell layers, which has been exploited in mapping the location of cells in multi-cellular spheroids (1), and *in vivo* (2), reflects a general characteristic of DNA-ligands. This property may confer special advantages on DNA-binding radioprotectors in the context of radiotherapy, where it is important to minimise delivery of the radioprotector to the tumour. For example, one might expect limited diffusion to capillaries and systemic uptake following topical application to epithelial cells, which can be dose-limiting tissues in radiotherapy. These potential applications will require delivery of sufficient concentrations of the DNA-binding radioprotectors to cells *in vivo*. In this context, the findings of Young and Hill (3), who could not detect any radioprotective effect in an *in vivo* setting, is of concern. We have re-examined this question by investigating radioprotection in the mouse lung model (4). A single intravenous injection of Hoechst 33342 (80mg/kg) given 30min prior to the lung irradiation, extends the radiation dose required for death in 50% of mice at 16 weeks post irradiation, from 19Gy to 23Gy (ie: a DMF of 1.2). This is similar to the extent of radioprotection reported by Travis *et al* (5) for WR2721 (300 mg/kg) in this model. These results auger well for the potential of the more potent radioprotectors, and indeed preliminary experiments with methlyproamine in the mouse lung model suggests a DMF of 1.35.

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RADIOPROTECTION OF MOUSE CNS ENDOTHELIAL CELLS *IN VIVO.*

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Abstract

Radioprotection using the minor groove binding DNA ligand Hoechst 33342 has been demonstrated *in vitro*, and more recently *in vivo*, in mouse lung (1). Intravenous administration was used for the lung studies, and both endothelial and alveolar epithelial cells showed good up-take. Radiation damage to the endothelial cell population has also been postulated as important in late developing radionecrosis of spinal cord and brain. Endothelial cell density in brain can be readily determined by a fluorescent-histochemical technique. Treatment with a monoamine oxidase inhibitor and subsequent injection with L-DOPA results in an accumulation of dopamine (DA) in CNS endothelial cells. DA is converted to a fluorophore by exposure to paraformaldehyde, and cell numbers assayed by fluorescence microscopy.

Earlier studies used this technique to monitor post-irradiation changes in endothelial cell density in rodent brain and showed the loss, within 24 hours, of a sensitive subpopulation comprising about 15% of the endothelial cells (2). Ten minutes after intravenous injection of Hoechst 33342 (80mg/kg) the ligand is confined by its limited penetration to the endothelial cells in mouse brain. When we irradiated at this time, there was protection against early endothelial cell loss. Ablation of the sensitive subpopulation in unprotected mice takes place over a dose range of 1 to 3 Gy γ-rays, but doses between 12 to 20 Gy are required in the presence of ligand. This protection equates to a very high dose modification factor of about 7 and possibly reflects a suppression of apoptosis in the sensitive endothelial subpopulation.

The extent to which there is enhanced survival in the endothelial population as a whole and how the observed protection affects late CNS necrosis development has yet to be determined. However present results clearly show potential for the use of DNA-binding radioprotectors with limited penetration for investigations into the relative significance of endothelial and parenchymal damage in normal tissues responses to ionising radiation.

References

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OXIDATION OF URATE BY A THERAPEUTIC NITRIC OXIDE/AIR MIXTURE

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Little is known about the potential toxicological consequences of therapeutic exposure of lung tissue to inhaled nitric oxide (NO). This route of administration is currently being successfully employed for the treatment of pulmonary hypertension and other lung pathologies including acute reperfusion injury in lung transplant patients. The toxicity of NO lies in its ability to act as an oxidant either in its own right or in concert with oxygen or with the superoxide free radical. One important interaction may be the reaction of these products with protective antioxidants in the lung epithelial lining fluid. One such antioxidant found in significant concentrations in both upper and lower airways is uric acid. In the present study, urate solutions (30μM) were exposed to a therapeutic concentration of NO gas, (35 ppm in air), for up to 90 minutes. Oxidative changes were followed spectrophotometrically and by HPLC. Significant loss of uric acid was observed with a concomitant formation of nitrite and allantoin, the stable oxidation product of NO and the major oxidation product of uric acid, respectively. No oxidation of urate was observed in the presence of air alone or when urate was incubated with nitrite. Uric acid oxidation could also be prevented by passing the NO / air stream through 10% KOH before the uric acid solution. This strategy removed trace amounts of higher oxides of nitrogen, (especially NO_2), from the NO / air stream. Thus, therapeutic inhalation of NO may deplete soluble antioxidants such as uric acid, especially during long-term chronic exposure unless care is taken to minimise formation of higher oxides of nitrogen.

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MODELLING ACCELERATED FRACTIONATION IN RADIOTHERAPY

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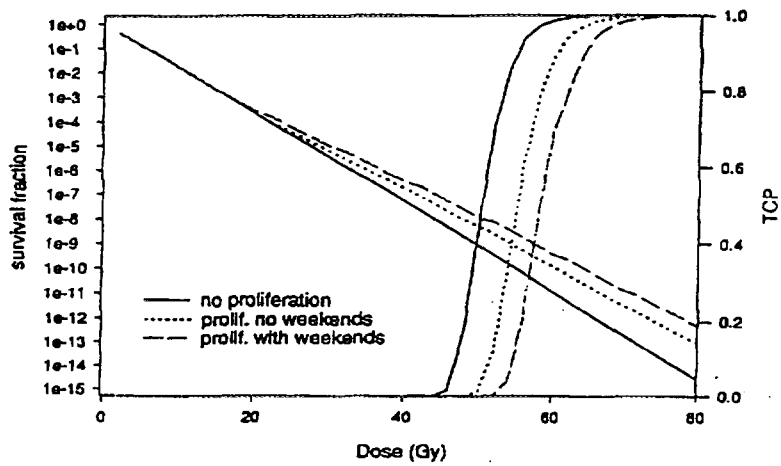
This study was undertaken to investigate optimum treatment schedules for highly proliferative tumours. The linear quadratic model is used to predict the most effective fractionation regimes. It should be pointed out that greater early effects are associated with improved tumour control, as such these data should be treated as a useful guideline and should never be used out of context with clinical experience.

The linear quadratic model with proliferation has been used to investigate the effect on cell survival and associated tumour control probability (TCP). Figure 1 shows the impact of giving the standard 2 Gy per day on cell survival and associated TCP.



α=0.35 Gy^{-1}, β=0.035 Gy^{-2}
T_p=6 days, T_k=10 days
ρ=10^{7}cm^{-3}, V=100 cm^3

Figure 1: Change in cell survival and TCP with dose given in standard fractionation

Note from the graph that with a time for kick off to accelerated proliferation of 10 days this gives a time margin of about 20 days before the survival lines start to diverge significantly. Hence accelerated fractionation with weekend breaks might be appropriate provided the treatment is delivered within 20 days.

The CHART regime of 36 fractions at 1.5 Gy in 12 days (Saunders *et al.* 1988, cited in Fowler J F, *Brit. J. Radiol.* 62: 679-694, 1989) and various other schedules are compared in terms of cell survival, biologically effective dose and TCP. Theoretical late normal tissue complication of these schedules will also be examined.

Using the linear quadratic equation with proliferation to match early effects versus a standard fractionation schedule of 31 fractions at 2 Gy/fraction. The BED calculation shows that the late effects are 43 Gy^3 lower for the CHART regime compared with the standard schedule while early effects are equivalent.

The linear quadratic model predicts that accelerated schedules can be used to increase the tumour control probability. However you rarely get something for nothing. The three things that need to be balanced against this prediction are patient scheduling, tolerance of early effects and sufficient repair between fractions.

Sonoluminescence from aqueous solutions containing surface active solutes

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Abstract

The sonoluminescence generated in water with pulsed 500 kHz ultrasound has been studied in the presence of different chain length aliphatic alcohols and the surfactant sodium dodecylsulfate(SDS). The ultrasound pulse widths used ranged from 1 ms to 10 ms, with duty cycles (on/off ratios) of 1:3 to 1:9. We found that the sonoluminescence from the initial pulses was very low but increased in intensity and reached a maximum after 10 to 50 pulses, for all systems studied, depending on the pulse width and duty cycle. In the presence of alcohol the maximum signal decreased with increasing alcohol concentration, and the signal decline was more pronounced with increasing chain length of the alcohol. In the presence of SDS the opposite trend was observed; the maximum signal was significantly enhanced over that obtained in pure water. However, on the addition of 0.1 M NaCl to the SDS solution the emission signal decreased markedly. This result is significant since the addition of 0.1 M salt to pure water gave the same intensity as that of pure water. These results have been interpreted in terms of the ability of the alcohols to enhance bubble coalescence during pulsing. The higher the alcohol concentration in solution, the greater the amount that will be adsorbed at the bubble/water interface. This will have the effect of lowering the interfacial tension of the bubbles and therefore decreasing the barrier to coalescence. The more bubbles that coalesce the fewer there will be to contribute to the sonoluminescence signal. SDS also adsorbs at the bubble/water interface and lowers the interfacial tension, but in addition its localisation at the bubble/water interface generates a repulsive barrier between bubbles due to the negative charge of the surfactant head group. This electrostatic barrier retards the process of bubble coalescence hence the enhancement of the sonoluminescence signal over the signal seen in pure water. This model is supported by the observation that 0.1 M salt decreases the emission signal. The electrolyte will decrease the repulsion between the "charged bubbles", thereby making bubble coalescence more probable. The role of surface active solute molecules, in general, on the sonoluminescence yield from a pulsed ultrasound signal will be presented.

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LIST OF PARTICIPANTS

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