

In Memoriam: Emeritus Professor Robin L. Willson

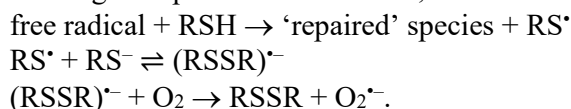
It is with great sadness that we announce the passing of one of the ‘founding fathers’ of the free radical and redox fields, Professor Robin Linhope Willson. He died peacefully at his home in Puerto Madryn, Patagonia, Argentina, where he had lived since retiring from Brunel University. He was 81 and leaves behind a wife Vicky, and two children, Emma and Suzy, from his first marriage to Hester Bowen who died in 1996.

In thinking about what highlights to include of the many discoveries associated with Robin Willson, and particularly those of the widest and most-enduring interest to the field of free radical chemistry and biology, the direct observation of the ‘repair’ of radicals formed from the antioxidants, vitamin E and thiols, by ascorbate (vitamin C) immediately springs to mind (Willson 1983a, 1983b). These observations were reported in a paper with John Packer and Trevor Slater in *Nature* in 1979 (Packer et al. 1979) and is Robin’s most cited work (~2000 citations). However, glancing through the list of Robin’s publications presents a great problem: where to start? This is because Robin led the way in so many different areas, and not just as a scientist, but also as a communicator, educator and inspiration behind the ‘Magic Pennies’ project, which opened the eyes of many children and young adults to the field of magnetism.

Robin was born in 1941 in Lytham St Annes, Lancashire, and his scientific career began as a radiation chemist in the mid-1960s in the laboratory of ‘Joe’ Weiss (of Haber-Weiss fame) at the University of Newcastle, UK, after having completed his undergraduate training at King’s College, Durham University. Joe Weiss had, more or less, invented the field of radiation chemistry of biomolecules with his paper in *Nature* in 1944. With George Scholes, Elie Hayon, Gabriel Stein and Alastair Johnson, the Newcastle group ‘spawned’ a large number of the radiation chemists who went on to have a major international impact in free-radical and radiation biology, including John Ward, Les Redpath and, of course, Robin. The Newcastle group focused on reactions of radicals produced on radiolysis of aqueous solutions of nucleic acids, and Robin’s first papers were in this area; he was awarded his PhD in 1966.

After the Cortina International Congress of Radiation Research in 1966, Robin took up a postdoc with Larry Myers at the Laboratory of Nuclear Medicine and Radiation Biology, University of California Los Angeles. While there, he played a major role in developing a nanosecond pulse radiolysis facility at General Atomics, San Diego (Theard et al. 1967). He also initiated the use of an early programmable Olivetti calculator for handling the data.

After his post-doctoral position in California, Robin was recruited by Ged Adams to strengthen the radiation chemistry group in the Gray Laboratory at Mount Vernon Hospital, Northwood, near London. In 1960, radiation chemistry was revolutionized by the development of kinetic spectrophotometry methods that allowed direct observation and monitoring of radiation-chemical intermediates following short (microsecond) pulses of radiation; the laboratory founded by L.H. Gray was a pioneer in this technique, and in his early years there Robin characterized key reactions relevant to radiation biology. The hydrated electron had been observed directly at Mount Vernon by Ed Hart and Jack Boag in 1962, and Robin’s observations of single electron transfer reactions between molecules of differing electron affinity led the way to a detailed and quantitative understanding of redox reactions involving free radicals (Willson 1970a, 1970b, 1971; Patel and Willson 1973; Forni and Willson 1984). Not least of these was the realization that superoxide radicals ($O_2^{\cdot-}$) could be formed as a consequence of radical ‘repair’ by thiols (RSH) (Adams et al. 1969), the thiyl radicals (RS^{\cdot}) forming disulphide radical-anions, that in turn reduced molecular oxygen to $O_2^{\cdot-}$:



This reaction has been subsequently shown to be ubiquitous and a critical process in biological systems.

Other examples of Robin's work at Mount Vernon included work on the reactions of nucleic acids with hydroxyl (HO^\bullet) and other radicals (Willson 1970c), and later work on radical damage to proteins and enzymes (Adams et al. 1972). The involvement of ascorbate in free-radical biology was a theme running through much of Robin's career, and at Mount Vernon he published, with Les Redpath, important work revealing how ascorbate reacted with oxidizing radicals and its effects on radiosensitivity (Redpath and Willson 1973).

Robin also contributed significantly to the development of the use of 'electron-affinic' radiosensitizers to kill hypoxic cells (the radiation resistance of such populations of tumour cells is a common cause of the failure of radiotherapy to eradicate tumours). In particular, a prototypic nitroaromatic compound was shown by Adams, Robin, and colleagues to have efficacy in this regard (Adams et al. 1971). Robin, working with Lance Foster, gave the field a huge boost by demonstrating radiosensitization by another nitro compound, metronidazole, which was already in widespread clinical use against anaerobic infections (Foster and Willson 1973). Robin's interest in the redox chemistry of metronidazole, iron and thiols (Willson and Searle 1975; Bahnemann et al. 1978; Searle and Willson 1983) can, with hindsight, be seen to be a precursor (at least in part) to the concept of hypoxia-selective cytotoxins (Foster et al. 1976).

Robin moved in 1973 to Brunel University, a few miles from Mount Vernon, to join Trevor Slater (in the Department of Biochemistry) who already had major interests and a widespread network of collaborators working on free-radical induced lipid peroxidation (see photo below from 1978 taken at Brunel University, with Robin at top right, and Trevor Slater in the middle of the front row). Robin obtained a linear accelerator from Mount Vernon, and set up a pulse radiolysis facility at Brunel. The subsequent years coincided with an explosion of interest in free radicals in biology generally, and Robin's contributions expanded rapidly to include major contributions to diverse areas of free radical chemistry and biology. He enjoyed a fruitful collaboration with Klaus-Dieter Asmus of the Hahn-Meitner Institut, Berlin, demonstrating radical 'repair' of guanine radicals by thiols and phenothiazines (Willson et al. 1974) and later focusing on thiol and related radicals (Bahnemann et al. 1983a; Mönig et al. 1987). Robin rapidly became recognised internationally as an expert in sulphur radical chemistry (Dunster and Willson 1990).



At Mount Vernon, Robin had studied oxidation of proteins and enzymes by free radicals (Adams et al. 1972) and his interest widened at Brunel, extending studies to oxidation reactions driven by NO_2^{\cdot} (Forni et al. 1986), which later become of considerable interest in the context of the effects of peroxyxynitrite decomposition. Robin introduced useful reagents, including the now widely used oxidant probe ABTS, to monitor oxidizing radicals and also contributed to our understanding of the biochemistry of phenothiazines (Bahnemann et al. 1980, 1983b, 1983a; Forni et al. 1988). His interest in antioxidants extended beyond thiols and ascorbate: thus Robin demonstrated a dramatic difference in the protective effects on radiation-induced inactivation of alcohol dehydrogenase by ascorbate and urate, possibly associated with the formation of a urate peroxy radical (Kittridge and Willson 1984).

Focusing solely on scientific papers as Robin's only legacy, no matter how seminal or highly-cited, would be a mistake. In the wider context, his importance as the key driver in the formation of the Society for Free Radical Research – the major scientific organisation devoted to free radical and oxidant research – cannot be overemphasized. Robin's contribution to the development of the Society is well-documented (<https://www.sfr-europe.org/index.php/sfre/history>) and it is unlikely that the Society would have developed and been as successful as it has been, without his enormous efforts in its early years. In 1982, he organised a survey to determine whether there was national and international interest in 'an interdisciplinary group to promote discussion amongst chemists, biologists and the medical profession of free radical processes of industrial and medical importance'. The resulting strong and positive response resulted in the formation of an informal society (initially called the 'Antioxidant Society') on 1st April 1982. Following further discussions, including an open meeting at the CIBA Foundation, a decision was made to develop an international society that was independent of traditional chemistry or biochemical societies, with the inaugural meeting held at the Royal Institution on 9th July 1982 (see photo below, Robin is on the right hand side of the front row, next to Trevor Slater). A subsequent meeting held at Brunel University, organised by Robin and Trevor Slater, led to the adoption of the name 'Society for Free Radical Research', the development of its logo, and the society Constitution. From these beginnings, the various partner societies that make up the umbrella organisation – the 'Society for Free Radical Research – International' have developed: the Societies for Free Radical Research of Europe, Asia, Australasia and Africa, and the Society for Redox Biology and Medicine in the Americas.



In addition to directing the Brunel Biochemistry Linear Accelerator Radiation facility, Robin played a very active role in driving the development of Biochemistry at Brunel, serving as head of Department between 1984-1987, as a leader in the development of world-wide-web services at the University and as a co-founder (with Maurice Kogan and Patrick Riley) of the National Conference of University Professors.

As a committed and enthusiastic lecturer and educator, Robin gave many school and public lectures and media interviews related to medicine, nutrition, radiation and the environment. He also had many wider educational interests beyond the field of free radical research, with these being particularly reflected in the 'Magic Penny Society' (<http://www.magicpenny.org/engsociety2.htm>) which he established to help demonstrate magnetism in a fun way. This led to the development of the Magic Penny Magnet kit, which was launched at Brunel in November 1995. This kit (sponsored by Brunel, the Institute of Physics and the Royal Institution, and illustrated below) is now into its 4th edition, and is particularly popular in USA. A scientific paper describing how magnetic coins and specially designed magnets can be used in mathematical studies of circle packing was published in 2015 to widespread acclaim. This led the former Vice-Chancellor of Brunel University, Michael Stirling, to state that "it will be for his work with Magic Pennies that Robin might one day be most remembered". The charitable foundation (The Magic Penny Trust) sponsored grants to many deserving educational charities (totaling over £50,000 (US\$60,000) over a twenty-year period.



Robin's involvement with the National Conference of University Professors led to a visit to Argentina, where he helped teach courses on free radicals organized at the Universidad de Buenos Aires, Argentina, by Alberto Boveris in the 1980s and 1990s. He was to meet his second wife there, and when he retired from Brunel University in 1997 he moved to Patagonia, where he continued working in Ciencias y Artes on educational projects related to astronomy and exploration, until his activities were curtailed by a diagnosis of motor neuron disease. This illness did not diminish his enthusiasm for science, and he continued discussions with colleagues until the disease was highly advanced.

This short description of Robin's diverse contributions to radiation- and free-radical chemistry and biology has only skimmed the surface. Few scientists in free radical research have had such a broad impact across so many areas, yet at the same time making such seminal discoveries that one cannot write for long about any single topic in this wide area without encountering and exploiting the insights Robin contributed to. His enthusiasm, insight and knowledge will stay with us for many years to come.

Michael J. Davies
 Kelvin J.A. Davies
 Barry Halliwell
 Malcolm J. Jackson
 Giovanni E. Mann
 Giuseppe Poli
 Rafael Radi
 Patrick A. Riley
 Helmut Sies
 John F. Ward
 Peter Wardman
 John Willson

References

- Adams GE, Aldrich JE, Bisby RH, Cundall RB, Redpath JL, Willson RL. 1972. Selective free radical reactions with proteins and enzymes: Reactions of inorganic radical anions with amino acids. *Radiat Res.* 49:278-289.
- Adams GE, Armstrong RC, Charlesby A, Michael BD, Willson RL. 1969. Pulse radiolysis of sulphur compounds. Part 3. Repair by hydrogen transfer of a macromolecule irradiated in aqueous solution. *Trans Faraday Soc.* 65:732-742.

- Adams GE, Asquith JC, Dewey DL, Foster JL, Michael BD, Willson RL. 1971. Electron affinic sensitization. Part ii: Para-nitroacetophenone: A radiosensitizer for anoxic bacterial and mammalian cells. *Int J Radiat Biol.* 19:575-585.
- Bahnemann D, Asmus K-D, Willson RL. 1980. Free radicals and the anti-inflammatory action of the phenothiazine: Metiazinic acid (soripal). In: Usdin E, Eckert H, Forrest IS, editors. Phenothiazines and structurally-related drugs: Basic and clinical studies. New York: Elsevier/North-Holland; p. 99-102.
- Bahnemann D, Asmus K-D, Willson RL. 1983a. Free radical induced one-electron oxidation of the phenothiazines chlorpromazine and promethazine. *J Chem Soc, Perkin Trans 2.* 1661-1668.
- Bahnemann D, Asmus K-D, Willson RL. 1983b. Phenothiazine radical-cations: Electron transfer equilibria with iodide ions and the determination of one-electron redox potentials by pulse radiolysis. *J Chem Soc, Perkin Trans 2.* 1669-1673.
- Bahnemann D, Basaga H, Dunlop JR, Searle AJF, Willson RL. 1978. Metronidazole (flagyl), misonidazole (ro 07-0582), iron, zinc and sulphur compounds in cancer therapy. *Br J Cancer.* 37:16-19.
- Dunster C, Willson RL. 1990. Thiyl free radicals: Electron transfer, addition or hydrogen abstraction reactions in chemistry and biology, and the catalytic role of sulphur compounds. In: Chatgililoglu C, Asmus K-D, editors. Sulfur-centered reactive intermediates in chemistry and biology. New York: Plenum Press; p. 377-387.
- Forni LG, Mora-Arellano VO, Packer JE, Willson RL. 1986. Nitrogen dioxide and related free radicals: Electron-transfer reactions with organic compounds in solutions containing nitrite or nitrate. *J Chem Soc, Perkin Trans 2.* 1-6.
- Forni LG, Mora-Arellano VO, Packer JE, Willson RL. 1988. Aminopyrine and antipyrine free radical-cations: Pulse radiolysis studies of one-electron transfer reactions. *J Chem Soc, Perkin Trans 2.* 1579-1584.
- Forni LG, Willson RL. 1984. Electron and hydrogen atom transfer reactions: Determination of free radical redox potentials by pulse radiolysis. *Methods Enzymol.* 105:179-188.
- Foster JL, Conroy PJ, Searle AJ, Willson RL. 1976. Metronidazole (flagyl): Characterization as a cytotoxic drug specific for hypoxic tumour cells. *Br J Cancer.* 33:485-490.
- Foster JL, Willson RL. 1973. Radiosensitization of anoxic cells by metronidazole. *Br J Radiol.* 46:234-235.
- Kittridge KJ, Willson RL. Uric acid substantially enhances the free radical-induced inactivation of alcohol dehydrogenase. *FEBS Lett* 1984; 170:162-64.
- Mönig J, Asmus K-D, Forni LG, Willson RL. 1987. On the reaction of molecular oxygen with thiyl radicals: A re-examination. *Int J Radiat Biol.* 52:589-582.
- Packer JE, Slater TF, Willson RL. 1979. Direct observations of a free radical interaction between vitamin e and vitamin c. *Nature.* 278:737-738.
- Patel KB, Willson RL. 1973. Semiquinone free radicals and oxygen. Pulse radiolysis study of one electron transfer equilibria. *J Chem Soc, Faraday Trans 1.* 69:814-825.
- Redpath JL, Willson RL. Reducing compounds in radioprotection and radiosensitization: model experiments using ascorbic acid. *Int J Radiat Biol* 1973; 23:51-65.
- Searle AJF, Willson RL. 1983. Stimulation of microsomal lipid peroxidation by iron and cysteine. *Biochem J.* 212:549-554.
- Theard LM, Peterson, FC, Willson, RL, Ward, JF, Myers, LS, Jr., and Ingalls, RB 1967. A high-resolution pulse-radiolysis apparatus - some initial studies with systems of biological interest. *Radiat. Res.* 31:582.
- Willson RL. 1970a. Pulse radiolysis studies of electron transfer in aqueous disulphide solutions. *Chem Commun.* 1425-1426.
- Willson RL. 1970b. Pulse radiolysis studies of electron transfer reactions in aerobic solution. *J Chem Soc, Chem Commun.* 1005.
- Willson RL. 1970c. The reaction of oxygen with radiation-induced free radicals in DNA and related compounds. *Int J Radiat Biol.* 17:349-358.
- Willson RL. 1971. Pulse radiolysis studies of electron transfer in aqueous quinone solutions. *Trans Faraday Soc.* 67:3020-3029.
- Willson RL, Asmus K-D, Wardman P. Interaction of a dGMP radical with cysteamine and promethazine: a possible model of DNA repair. *Nature* 1974; 252:323-24.
- Willson RL. 1983a. Free radical protection: Why vitamin e, not vitamin c, β -carotene or glutathione? In: Editor N, editor. *Biology of vitamin e.* London: Pitman; p. 19-44.
- Willson RL. 1983b. Free radical repair mechanisms and the interactions of glutathione and vitamins c and e. In: Nygaard OF, Simic MG, editors. *Radioprotectors and anticarcinogens.* New York: Academic Press; p. 1-22.
- Willson RL, Searle AJF. 1975. Metronidazole (flagyl): Iron catalysed reaction with sulphhydryl groups and tumour radiosensitisation. *Nature.* 255:498-500.