

Obituary

Alfred Richard Green

Neuropharmacologist
1944-2020

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Alfred Richard Green, universally known by his middle name, was one of the UK's leading neuropharmacologists. He is best known for his work on the pharmacology of the neurotransmitter 5-hydroxytryptamine (5HT or serotonin), but he was experimentally at home with the whole gamut of neurotransmitters, including dopamine, noradrenaline, gamma-aminobutyric acid (GABA), and glutamate, on all of which he published from time to time.

Born in Windsor on 8 February 1944 and educated at King's School in Worcester, Richard never considered any other career than a scientific one, no doubt influenced by his entomologist father. He qualified with joint honours in chemistry and physiology from London University in 1966 and three years later took his PhD in biochemistry with a thesis titled *Effects of Hydrocortisone and Stress on Tryptophan Metabolism*, based on his work in the Department of Chemical Pathology in the Institute of Neurology in Queen Square, London, under the supervision of Gerald Curzon, who remained a lifelong friend. His work there was recognized by the Queen Square Prize for research in 1970. In 1987 London University awarded him the degree of DSc, based on his published work.

In 1970, at a time when BTA ("Been To America") was almost a compulsory qualification for UK scientists, Richard was appointed to an International Visiting Fellowship in the Laboratory of Preclinical Pharmacology in the National Institute of Mental Health in Bethesda, Maryland, where he worked with the Italian-American neuroscientist Erminio ("Mimo") Costa, among others, and identified a novel indolealkylamine, 5-methoxytryptamine, in rat hypothalamus, using a GC-MS technique that he and Steve Koslow had developed.

In 1973 Richard returned to the UK, this time as a Medical Research Council (MRC) Scientist in the recently established MRC Unit and University Department of Clinical Pharmacology in Oxford, under the leadership of David Grahame-Smith, with laboratories in the old Radcliffe Infirmary in Woodstock Road. This began a 13-year partnership that firmly established his credentials as an expert neuroscientist. The assay that he and Curzon had described in 1970 for measuring concentrations of 5HT and its metabolite 5-hydroxyindoleacetic acid (5HIAA) in the brain, and which was the method of choice until the advent of hplc in the late 1970s, came into good use, as Richard and David used the serotonin syndrome in experimental animals to study the effects of various pharmacological interventions to probe brain function. The principle was simple: inject a rat with tryptophan, a precursor of serotonin, plus a monoamine oxidase inhibitor, ensuring that brain 5HT concentrations rose sufficiently to stimulate post-synaptic 5HT receptors, causing a hyperactivity syndrome, in which forepaw treading was a major feature; David, a jazz pianist

in his spare time, used to mimic this when lecturing on the subject, likening it to piano playing. A comparable paradigm could be used to study the effects of dopamine, and other techniques were brought into play, such as lesioning selective parts of the brain.

Pharmacological studies in an isolated rat brain perfusion, developed by Frank Woods and Chris Graham, also played a part.

These types of experiments were simple and elegant, hallmarks of accomplished scientific investigation. They could be done very rapidly, and Richard was able to screen the effects of large numbers of compounds in a short space of time. This gave rise to a standing joke in the department that Richard must be working his way systematically through all the chemical compounds listed in the Merck Index, from A to Z, and could say on any day which page of the catalogue he had reached. It is even possible that Richard started the joke himself.

The main focus of the work was investigation of brain function in depression and the effects of potential treatments. Nor were the interventions limited to drugs. During one very prolific phase Richard turned his attention to the effects on neurotransmitter function of seizures induced by either electric shock, mimicking the clinical use of ECT in treating depression, or the chemical convulsants pentylenetetrazole, flurothyl, bicuculline, and isopropylcyclophosphate.

Richard's natural ability for collaborative research resulted in fruitful collaborations not only with other scientists in the department, such as Moussa Youdim, David Heal, and Martin Elliott, but also with the many clinicians who passed through, seeking training in basic techniques, scientific rigour, and the application of research techniques and findings to important clinical problems, all of which featured strongly in the departmental ethos. Psychiatrists David Nutt, Phil Cowen, and Guy Goodwin, among others, profited from working with Richard. Indeed, all those who were mentored by Richard expressed long-standing gratitude to him for his remarkable scientific ingenuity as well as his generosity and patience, which extended even to the eccentricities of psychiatrists in training.

In 1986 an opportunity came for Richard to take up the directorship of a newly established neuroscience research unit, funded by the pharmaceutical company Astra (later AstraZeneca), which occupied space in the Institute of Neurology in Queen Square. Richard carefully debated with himself the pros and cons of the move and discussed it with his colleagues. On the minus side, he was reluctant to leave the MRC Unit, of which he had been made Assistant Director three years before, and felt a deep loyalty to David Grahame-Smith. However, a job in Queen Square, where he had started his academic career, was attractive, and the opportunity to put his basic skills to use in the pursuit of new treatments with a pharmaceutical company was too good to pass up. He accepted.

Richard thrived in his new environment, and ten years later was appointed Director of Global Discovery CNS & Pain Control at AstraZeneca R&D. Although he had an office in Loughborough, his line manager and research team were all based in Sweden, where he was primarily involved in preclinical development of novel neuroprotective agents for acute ischaemic stroke. He held that position until his retirement in 2007. But for Richard, the word "retirement" was code for the next phase of research. While still working with AstraZeneca he had been appointed Honorary Professor of Neuropharmacology in the School of Life Sciences in the University of Nottingham Medical School, and he continued in that capacity thereafter, renewing old acquaintances and enjoying new collaborations, investigating recreational drugs such as MDMA (ecstasy) and mephedrone, maintaining a fair rate of publishing, although eventually a diminishing one (Figure 1).

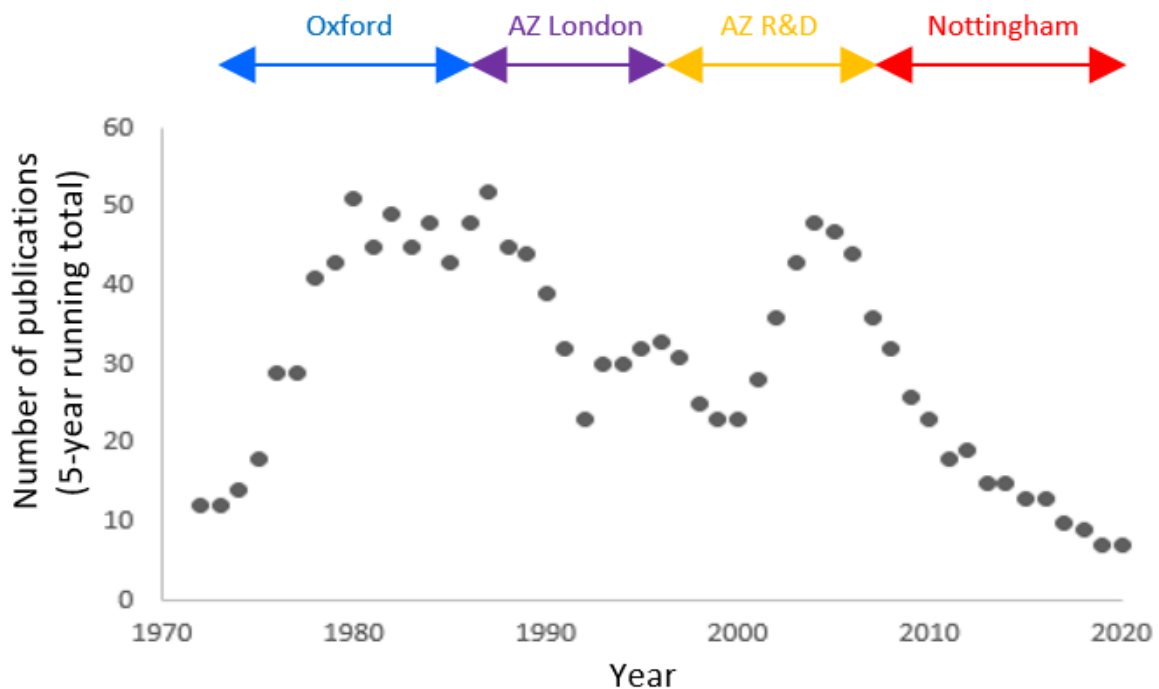


Figure 1. Numbers of publications in peer-reviewed journals (five-year running totals; n = 302)

It is a paradoxical truism that if you want something done, you should ask the busiest person. Richard was the man to ask. As well as pursuing a highly productive research career, he gave freely of his time to activities in three societies: the British Pharmacological Society (BPS), the British Association for Psychopharmacology, and the International Society for Serotonin Research (the “Serotonin Club”). His organizational skills were superb. Almost single-handedly he organized a meeting of the BPS in Oxford in 1984, celebrating the Society’s 50th anniversary, and in 1993 he organized a retirement symposium for Gerald Curzon at Queen Square. Table 1 shows the numerous services he performed for these societies at different times.

Table 1. Society activities

Society	Activity	Dates
British Pharmacological Society	Editorial board, <i>British Journal of Pharmacology</i>	1976–84 & 1986-91
	Meetings Secretary	1986–88
	General Secretary	1989–91
	EPHAR Representative	2004–08
	Senior Editor, <i>British Journal of Pharmacology</i>	2006–12
	Member of Council and Trustee	2014–16
British Association for Psychopharmacology	Member, Council	1983–87
	Editorial board, <i>Journal of Psychopharmacology</i>	1987–91
	Member, Governance Panel	2014–16
	Chair, Governance Panel	2016–18
International Society for Serotonin Research	President	1994–96
	Treasurer/Secretary	1997–2004

In addition to these activities he also served at various times on the Editorial Board of the *European Journal of Pharmacology* and as an Executive Editor of *Neuropharmacology* and Managing Editor of *Psychopharmacology*.

All this time, prizes and honours kept coming Richard's way. The Queen Square Prize (1970) was a local award, but international recognition soon followed, with an Anna Monika Stiftung Prize for Studies in Depression (with David Grahame-Smith, 1977). He was William Evans Visiting Fellow in New Zealand's University of Otago in 2001 and the Inaugural Rapport Lecturer for the International Society for Serotonin Research in Sapporo, Japan, in 2006; the lecture was named after Maurice M Rapport who, with Irvine H Page and Arda A Green, isolated and characterized serotonin in 1948. The crowning accolade of this sort was the Lifetime Achievement Award that the British Association for Psychopharmacology gave him in 2010.

At other times he was Visiting Professor in the Department of Pharmacology in Imperial College School of Medicine, London (1991–96) and Honorary Professor of Pharmacology, De Montfort University, Leicester (1998–2005). The BPS made him a Fellow of the Society in 2005 and an Honorary Fellow in 2013, and the International Society for Serotonin Research made him an Honorary Member in 2006. But perhaps the honour that gave him the most pleasure was that of President Emeritus of the BPS, awarded in 2010. Richard had been Secretary of the Society in the days before the post of President was created, and when the Society decided to confer emeritus titles on all its past Presidents in 2010, it also decided that those who had been Secretaries, Presidents in all but name, should be honoured in that way (Figure 2).



Figure 2. Honours from the BPS: left—receiving the title of President Emeritus from Ray Hill in 2010; right—receiving an Honorary Fellowship from Phil Routledge in 2013

Richard's curriculum vitae boasts around 300 papers in peer-reviewed journals, a handful of books, 40 book chapters, and many presentations to learned societies. A breakdown of his most frequent collaborators is given in Box 1. His final research project began when he sent me an email in early 2018. Did I think that an investigation of post-war pharmaceutical advertisements would be of interest in studying the growth of modern therapeutics? I did, and together with Peter Haddad we started to look for material. Richard found a treasure trove of digitized adverts in the database of the *BMJ*, and we visited the archives of the Bodleian Library to unearth adverts that had been published in *World Medicine*. Richard, who had previously been a recipient of a W D M Paton award from the BPS for historical research in pharmacology, applied again and was given another award to fund the research. The work formed the basis of his final public lecture.

Box 1. Richard's co-authors on at least five papers in peer-reviewed journals

20 or more	10–19	5–9	
Colado MI	Aronson JK	Baldwin HA	Nelson RM
Cross AJ	Camerero J	Bloomfield MR	Nimgaonkar VL
Grahame-Smith DG	Cowen PJ	Boullin DJ	Orio L
Heal DJ	Curzon G	Bowdler JM	Ridley RM
O'Shea E	De Souza RJ	Costain DW	Robinson TN
	Elliott JM	Escobedo I	Saadat KS
	Esteban B	Gabrielsson J	Shortall SE
	Fone KC	Granados R	Snape MF
	Goodwin GM	Jones JA	Sydserrff SG
	Hainsworth AH	King MV	Vincent ND
	Marsden CA	Lambert DG	Williams JL
	Misra A	Marshall JWB	Woods HF
	Murray TK	Mechan AO	Youdim MBH
	Nutt DJ	Minchin MCW	
	Sanchez V		

Richard was a superb raconteur, with a fund of stories about academic life, fed by an unplumbable memory. This ability found its best expression in an easy lecturing style, with which he would marshal often complex ideas into a straightforward narrative, told with clarity and great humour. Recipients of a Paton award are required to give a lecture on the results of their research at a meeting of the BPS. Richard was therefore asked to give a lecture at a meeting of the Society in Dublin in March 2019 and did so with such success that he was asked to give a repeat performance at the Society's 2019 Winter meeting in Edinburgh. The hall for the plenary lecture was filled to capacity and the lecture was enthralling.

While we were doing the research Richard discovered, during a routine ophthalmic check, that he had a small ocular melanoma. It was successfully treated with local radiation, but as it turned out it had already metastasized. Richard faced his illness with characteristic equanimity and courage. He leaves his first wife, Susan, and their two daughters, Judith and Kirsty, and his second wife, Geraldine.