

MICHAEL ELLIOTT CBE
30 September 1924 — 17 October 2007



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Elected FRS 1979

BY JOHN PICKETT* FRS

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Michael Elliott was the leader of work at Rothamsted that invented and subsequently commercially developed the pyrethroids, a new class of insecticides. Michael made probably the greatest individual contribution to the control of insect pests that not only constrain global food production but also affect the health of ourselves and our livestock. In one of the first pioneering structure–activity relationship studies, Michael led the multidisciplinary team that invented the major pyrethroid insecticides bioresmethrin, permethrin, cypermethrin and deltamethrin. In the 1980s these represented two-thirds of the global pyrethroid market; at that time pyrethroids captured more than 25% of the total insecticide market and were used on 33 million hectares of crops (Wirtz *et al.* 2009). In 2002 deltamethrin was the world's largest-selling pyrethroid, with annual sales worth \$208 million (information from Cropnosis Ltd). In terms of human health, in 2009 it was estimated that pyrethroid-treated bednets significantly decreased the number of deaths due to malaria among children under five years of age by about one-fifth as well as reducing all incidents of malaria, and in 2011 the World Health Organization recommended its vastly expanded use.

BACKGROUND

Michael Elliott was born on 30 September 1924 at Thorngrove Road, East Ham, London, to devout Anglo-Catholic parents, Thomas William and Isabel Constance Elliott (*née* Burnell). Their life centred on St Albans Church in East Ham. As an only child Michael was rather solitary, although in his childhood he played happily with two friends on Tunbridge Wells Common. He formed an early interest in scientific and technical aspects of life and was particularly impressed by its systematic order and the structure of matter. His imagination expanded not only through his formal education but also through his use of the excellent public

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library facilities in Tunbridge Wells. Passing through the Convent School at Hawkenbury, Tunbridge Wells, and then St Peter's Elementary School, he received his final schooling at Skinners Company's School, Southbridge, Kent, where he was appointed School Librarian, became a lance corporal in the army cadet corps and obtained sufficiently good grades to be awarded an Open University exhibition in 1942. Dr Harold Cordingley, the chemistry master at Skinners, having himself been a pupil of Sir Christopher Ingold FRS, encouraged Michael in this subject, introducing him to the work of both Sir Christopher and Sir Robert Robinson FRS (PRS 1945–50) on the emerging views regarding electronic theory, and this led to his university education at Southampton culminating in a BSc (external, University of London) in chemistry in 1945. His postgraduate research for his PhD was on 'Experiments on the synthesis of the pyrethrins' under Professor Stanley Harper, initially at University College Southampton from 1945 to 1946, at which time the college moved to King's College, London, until 1947. He was awarded his PhD (external, University of London) in 1952. In 1948 he joined the Department of Insecticides and Fungicides at Rothamsted Experimental Station, now renamed the Department of Biological Chemistry and Crop Protection at Rothamsted Research. His recruitment to Rothamsted by the then head of department, Charles Potter, set him on the track that took him from the lead compound pyrethrin I, via resmethrin and its active isomer bioresmethrin, through to the photostable pyrethroids, all of which were subsequently exploited commercially. As recognition of these achievements he and his team twice earned Queen's Awards for or Technological Achievement, in 1976 and 1980.

In 1984 Michael retired from Rothamsted but continued to serve as a departmental consultant on chemistry and insecticides, his advice being eagerly sought. He also worked with his long-standing good friend and colleague, Professor John Casida (ForMemRS 1998; Member of the US National Academy of Sciences 1991), at the University of California, Berkeley, where they pioneered work on other pest toxicants that are still currently regarded industrially as potential leads for new pesticidal compounds. In 1989 Michael returned to Rothamsted as a Lawes Trust Fellow, continuing his consultancy.

INVENTION OF FIELD-STABLE PYRETHROIDS

Under Frederick Tattersfield, the first Head of the Department of Insecticides and Fungicides at Rothamsted, natural insecticides, including pyrethrum extract from the pyrethrum daisy *Tanacetum cinerariaefolium*, had been studied from the 1920s onwards. The extract from plants grown in Harpenden near Rothamsted had extremely high insecticidal activity and was supplied to Kenya to establish the pyrethrum-growing industry still extant today. In 1935 Charles Potter, who was recruited to the department in the mid 1930s, made the significant discovery that pyrethrum extract in mineral oil sprayed in darkened warehouses formed residual films that controlled pests of stored products for considerable periods and thus indicated the potential scope of pyrethrum extract and their pyrethrin components for insect control.

In 1948 Charles, having been appointed Head of Department the year before, initiated a detailed programme of research on the natural pyrethrins and allied compounds, and it was this programme that Michael joined. On the basis of his postgraduate experience studying the chemistry of the pyrethrins under Stanley Harper and in collaboration with Leslie Crombie (FRS 1973), a long-term colleague from King's College, London, but by then working at Nottingham University, he was asked to investigate relationships between the molecular structure and

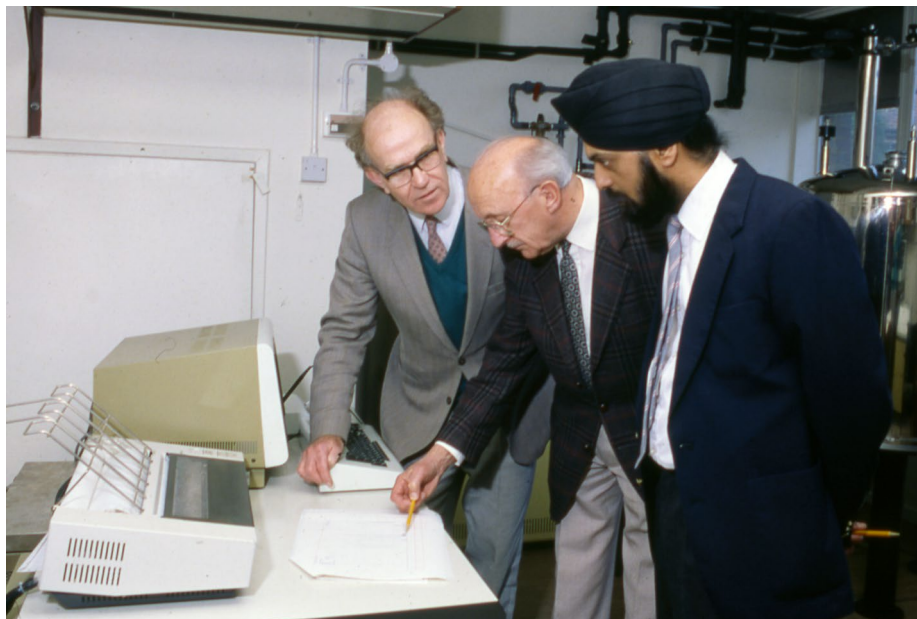


Figure 1. Michael at work in Rothamsted with his colleagues Norman Janes and Bhupinder Khambay in the late 1980s. (Online version in colour.)

biological activity of pyrethrins and related analogues. Others involved or associated at various times with the programme at Rothamsted included the chemists Norman Janes, David Pulman, Bhupinder Khambay and Ian Graham-Bryce FRSE, and the insect toxicologists Paul Needham, Roman Sawicki (FRS 1987), Andrew Farnham and John Stevenson (figure 1). Michael was always keen to recognize these essential and invaluable collaborations, and also eventually many others from industry. The contribution of Norman Janes was of major significance. He joined the team in 1962 at a crucial period and brought additional expertise, specializing in nuclear magnetic resonance spectroscopy. Their recognition of the salient structural features underlying the biological activity of the pyrethroids was a major outcome of this cooperation, which enabled outstanding scientific progress.

One of the first of his studies (1)* and reviewed later (8) showed that the relative potency of isomers of allethrin, originally synthesized by Milton Schechter and colleagues in the USA (LaForge *et al.* 1956), and the natural pyrethrins varied widely between insect species. Indeed, the natural esters were much more effective against pests of agricultural importance than the corresponding allethrin isomers were. A method for isolating pure (+)-pyrethrolone† as its monohydrate made adequate quantities of pyrethrins I and II (2, 3) readily available. Direct comparison of pyrethrin I and *S*-bioallethrin indicated that the natural ester was up to 100 times more active against some insect species (figure 2).

This discovery focused attention on the importance of multiple unsaturation in the side chain of the alcoholic component and this, combined with W. F. Barthel's observation (Barthel 1961) of the potency of simple chrysanthemates such as that of 2,4-dimethylbenzyl

* Numbers in this form refer to the bibliography at the end of the text.

† The original nomenclature used by Michael is adopted throughout.

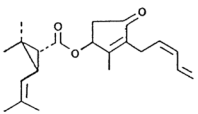
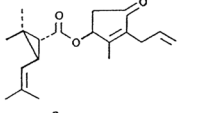
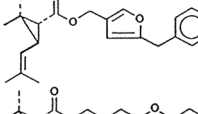
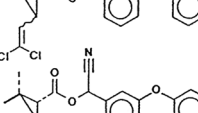
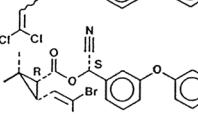
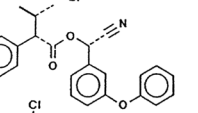
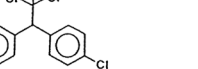
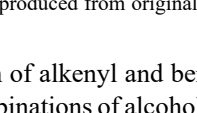
Date			Persistence in environment	Relative insecticidal potencies
—	PYRETHRIN I		Hours	50
1949	BIOALLETHRIN		Hours	25
1967	BIORESMETHRIN (NRDC 107)		Hours	100
1973	PERMETHRIN (NRDC 143)		Weeks	110
1974	CYPERMETHRIN (NRDC 149)		Weeks	290
1974	DELTAMETHRIN (NRDC 161)		Weeks	2300
1973	FENVALERATE (Sumitomo)		Weeks	94
pre 1950	DDT		Years	8

Figure 2. Development of field-stable pyrethroids. Potencies are mean values relative to 7–10 species. (Directly reproduced from original Rothamsted text.)

alcohol, stimulated an examination of alkenyl and benzyl chrysanthemates (4–7, 9–13). After synthesizing and testing many combinations of alcoholic nuclei and side chains, the particularly effective alcoholic component 5-benzyl-3-furylmethyl alcohol (12) was discovered and esterified with (+/–)-*cis-trans*-chrysanthemic acid to give resmethrin (NRDC 104), and with a new synthesis this was manufactured commercially. This in turn led to the synthesis of a resmethrin isomer, 5-benzyl-3-furylmethyl (+)-*trans*-chrysanthemate, known as bioresmethrin (NRDC 107) (figure 2), a compound that biochemical studies subsequently showed had the essential structural and stereochemical features necessary for great insecticidal activity, being relatively resistant to detoxification by insects. In addition, bioresmethrin has very low toxicity in mammals (the oral LD₅₀ (the median lethal dose) for rats is more 8000 mg kg^{–1}) even compared with that of the natural pyrethrins and other pyrethroids such as allethrin (LD₅₀ 500–800 mg kg^{–1}). Resmethrin and bioresmethrin were thus the first synthetic pyrethroids with greater insecticidal activity but lower mammalian toxicity than the natural compounds. Indeed, bioresmethrin has one of the greatest margins of safety (mammals:insects) of any known insecticide. The demonstration that potent insecticides could be designed by applying such principles within this group of compounds was highly significant.

Despite their valuable properties, resmethrin and bioresmethrin, like the earlier pyrethroid allethrin, are unstable in air and light and are therefore unsuitable for many applications, especially in agriculture. Nevertheless, their considerable insecticidal activity indicated the further possible potential for activity latent in their structures. John Casida's examination of the photodecomposition of bioresmethrin (Ueda *et al.* 1974) identified the isobutenyl side chain in the acid and the furan ring in the alcohol as vulnerable sites.

Michael and Norman therefore synthesized alternative acids and alcohols (18, 19, 22–24) to identify the structural features governing relative toxicity to insects and mammals and sensitivity to light and air. New compounds were designed in which the light-sensitive centres were replaced with alternative units, retaining the chemical and stereochemical characteristics of the parent molecules while maintaining their behaviour in the biochemical systems of insects and mammals (figure 2). In the most effective acid components of many synthesized, the methyl groups in the isobutenyl side chain of chrysanthemic acid were replaced by halogens, especially chlorine and bromine (15). In addition, the influence of the stereochemical form of these acid components on the insecticidal potency of esters was established (20, 22). The novel alcohol component, 3-phenoxybenzyl alcohol, was discovered independently from a consideration of the structure of 5-benzyl-3-furylmethyl alcohol almost simultaneously by Michael and his team (14) and the Sumitomo Chemical Company (Sumitomo 1971) in Japan. In this, a *meta*-substituted phenyl ring is considered to simulate the stereochemical role of the natural cyclopentenone ring or a synthetic furan ring, and a phenyl group simulates the stereochemical role of the *Z*-conjugated diene in pyrethrolone. This work led to the synthesis of permethrin (16, 17) (figure 2), the first photostable pyrethroid.

The Sumitomo scientists also showed the enhancing effect of an α -cyano group in 3-phenoxybenzyl chrysanthemates (Matsuo *et al.* 1971; Ohno *et al.* 1974). Indeed, Michael later surprised his friend Takashi Matsuo (whose name was later changed to Noritada Matsuo) from Sumitomo by explaining that he visited London weekly to keep a close watch on such potential patent developments (figure 3). This was a key observation with far-reaching consequences made by Michael and his team, now including David Pulman, when esterification of α -cyano-3-phenoxybenzyl alcohol with the dihalovinyl acid components generated exceptionally powerful compounds (21, 22) with the combination of favourable properties not possessed by previous classes of insecticides. These showed exceptional toxicity to a wide range of insect species, persistence on foliar surfaces that was at least as great as that of established organophosphates and carbamates, and susceptibility to active metabolizing systems such as those of mammals and in the soil. Moreover, the new insecticides differed from the organochlorine compounds in three important respects: they were effectively involatile and thus not transported in the atmosphere (a major route by which DDT has been spread), they did not accumulate in fatty tissues, and they were rapidly degraded in soil, so that residues did not accumulate to contaminate the environment.

Because each α -cyano ester had three chiral centres, there were potentially eight isomers, which could all be expected to have differing biological activities. Work on the dihalovinyl esters with simpler alcohols had established that only the *1R cis* and *1R trans* forms (and not the *1S cis* and *1S trans*) were effective (20). The diastereoisomeric mixture of esters from the *1R cis* dibromoacid (synthesized stereospecifically for the purpose) and (*RS*)- α -cyano-3-phenoxybenzyl alcohol was already recognized as a powerful insecticide, but storage in hexane yielded crystals of the α -*S*-diastereomer, which bioassays showed to be by far the more active of the two isomers. In fact, this crystalline ester, named deltamethrin, proved to be the



Figure 3. Michael and his wife, Margaret, at the Gold Shrine in Kyoto. (Photograph taken by Noritada Matsuo in the late 1990s.) (Online version in colour.)

most powerful insecticide, irrespective of class, available at the time (21). It was originally manufactured by Roussel-Uclaf in France, using an innovative commercial system to give the single crystalline isomer from eight possible isomers (Lhoste 1982) and was one of the first pure optical isomers of commercial bioactives, including pharmaceuticals.

Resmethrin and bioresmethrin and the three main photostable pyrethroids invented at Rothamsted, namely permethrin, cypermethrin and deltamethrin, have been developed commercially. These extremely potent insecticides have opened the prospect of controlling pests at lower rates of application, thus introducing much less insecticide into the environment. They are all sufficiently active to be recommended for practical application at doses from 200 g ha⁻¹ down to less than 5 g ha⁻¹ for deltamethrin, far below the most potent of standard insecticides of other groups particularly against a range of lepidopterous larvae. Lepidoptera and Coleoptera are highly destructive pests on many crops such as cereals, potatoes, cotton, soya, apples, pears, plums, peaches, grapes, olives, coffee and vegetables. Globally, more insecticides are used to protect cotton than any other crop, and deltamethrin is one that has been extensively used. Not only are Rothamsted pyrethroids applied to agricultural crops but they are also used in the health, garden and household markets. Permethrin is still widely used to treat clothing and mosquito nets to reduce the impact of insect-transmitted diseases, including malaria (Lengeler 2004; World Health Organization 2012).

The generally favourable toxicological and environmental properties of the photostable pyrethroids have been detailed in several authoritative reviews (for example Vijverberg & Van den Bercken 1990; Aldridge 1990). The excessive use of pyrethroids invites selection for resistance (Rothamsted Research 2004), and experiments to understand the underlying

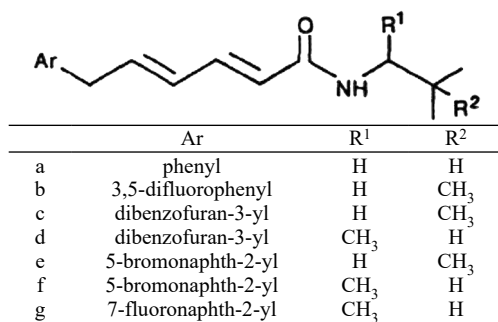


Figure 4. Structures of synthetic isobutylamides. (Reproduced with permission from (25). Copyright © 1986 Taylor and Francis.)

mechanisms and provide strategies for limiting resistance development were pioneered by Roman Sawicki and continue at Rothamsted. Because synthetic pyrethroids have very low solubility in water and are strongly adsorbed on soil particles, they are greatly resistant to leaching through soil (Kaufman *et al.* 1981). These observations, along with the fact that very small dosages are needed for insect control, reduce the likelihood that any pyrethroid will contaminate groundwater. Despite their strong adsorptive characteristics, pyrethroids are readily biodegradable in soil, with half-lives ranging between 2–4 days and 12–16 weeks (Roberts 1981). This is in sharp contrast with the chlorinated hydrocarbon insecticides, whose soil persistences are frequently measured in years. Hydrolysis of the ester linkage is a major degradation route for all of the pyrethroids, accompanied by hydroxylation, ring cleavage and attack at the cyano group when present, leading eventually to CO₂ and water.

The value of pyrethroids, natural or synthetic, rose from about US\$10 million in 1976, before the more stable compounds were available, to an estimated US\$1400 million in 1990. To this total British Technology Group licensed products (invented at Rothamsted) contributed about US\$800 million (59%). By 2002 the contribution remained significant at US\$525 million (40%), with deltamethrin being the biggest selling pyrethroid, worth US\$200 million.

Michael was keen to retain financial support, first from the Agriculture Research Council (ARC) and then the Agricultural and Food Research Council, later known as the Biotechnology and Biological Sciences Research Council, for the basic science underpinning his research. From the early 1960s the National Research Development Corporation (NRDC) funded and patented Michael's inventions, hence their NRDC numbers (figure 2), and supported the more applied aspects of the work. From 1981 this role was taken over by the British Technology Group (BTG).

FURTHER AREAS OF INTEREST

Throughout his career Michael had a vision for the discovery of novel pest control agents. In the 1980s he investigated variations in the naturally occurring isobutylamides (analogues of natural products in black pepper, *Piper nigrum*) (25, 27) (figure 4). Colleagues at Rothamsted (Andrew Farnham and Roman Sawicki) revealed the existence of negative cross-resistance to these compounds, which were up to four times more effective against houseflies resistant to pyrethroids than to susceptible strains (25).

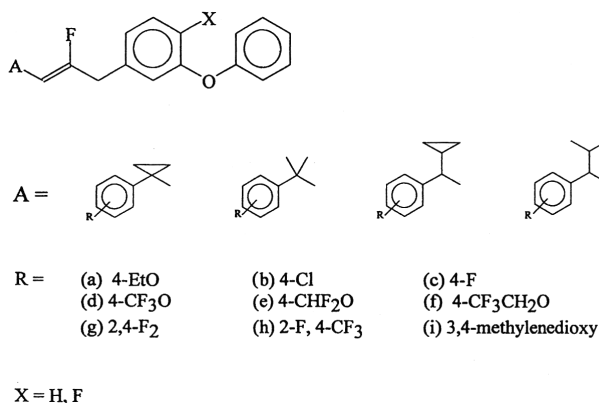


Figure 5. Active non-ester pyrethroid structures containing fluorine. (Reproduced with permission from Khambay *et al.* (1999). Copyright © 1999 John Wiley & Sons Inc.)

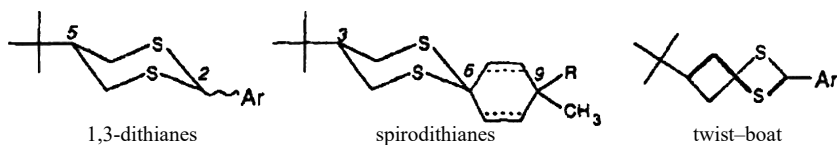


Figure 6. Dithiane structures. (Reproduced with permission from (28). Copyright © 1992 American Chemical Society.)

Just before his retirement from Rothamsted, Michael discovered a series of non-ester pyrethroids (26) in which the ester linkage, the primary site for metabolism and degradation, had been replaced by an alkyne. These compounds had low toxicity to fish and had the potential for controlling soil pests. Continuation of this work project, also funded by BTG, was progressed by Bhupinder Khambay and led to the discovery and patenting of a series of fluorinated non-ester pyrethroids (figure 5) (Khambay *et al.* 1999).

After retirement from Rothamsted, Michael visited John Casida's laboratory at Berkeley during 1986–88. There he discovered novel dithiane analogues (figure 6) (28) that interfered with the γ -aminobutyric acid-gated chloride channel with an activity comparable to that of established insecticides.

All these aspects are still very well represented in the currently active intellectual property of the global agrochemical industry.

Michael was also responsible for giving direction to my own early career studies, resulting in the first identification of aphid sex pheromones (Dawson *et al.* 1987), which arose from his long-argued recommendation for this research direction.

MICHAEL THE MAN

On 2 August 1950 Michael married Margaret Olwen James, to whom he remained devoted throughout his life; Margaret survived him by 6½ years. Karen Mair was born in 1954 and Fiona Anne in 1955; together with their four grandchildren, Matthew, Imogen, James and

Christopher, they formed a close family, offering great support to Michael throughout his career and into his retirement until his death on 17 October 2007.

Michael was a kind, popular and modest colleague, friend and family man who, after his retirement, was known to some only as a practitioner of his favourite hobby, photography. From his early youth he had had wide interests beyond science, and his retirement enabled him to devote more time both to his family and to them. In addition to keenly following new scientific advances, he and Margaret indulged their other interests, including modern literature, art and classical music, good food and wine, hill walking and tending their immaculate house and garden; but his greatest interest was in photography. In retirement he was able to combine his scientific activities with 'spending more time with his family'. On one occasion he declined a last-minute invitation to attend a scientific meeting, saying that he had a prior engagement. He did not see the need to add that the appointment was to go bowling with his grandson.

Michael was popular with his colleagues; he showed great concern both at a personal level and in developing their career development. He always acknowledged their contributions to the work. He shared the department's interests in squash, swimming and, in the early years at Rothamsted, old cars, although this enthusiasm diminished with the advent of more reliable models.

Early in their marriage, Margaret's patience was severely tested when she found the engine of their elderly car in parts spread on the dining-room table. On his retirement he and Margaret moved to Cranleigh in Surrey to be near their daughters' families. Having installed a darkroom in the roof of the house, Michael indulged his photographic talents and became an active member of Cranleigh Photographic Club. Indeed, his grandsons Matthew and James have inherited his passion and are now accomplished wildlife photographers, concentrating on animals in their natural environment. Michael was a modest man, and his Rothamsted colleagues were not surprised to learn at his funeral that his photographic colleagues had no idea of his scientific achievements and honours.

He once said that as a young man he had seriously considered photography as a career, rather than chemistry. How fortunate it is for the world's agriculture, disease control and pest control that Michael Elliott chose chemistry.

HONOURS, DEGREES AND AWARDS

Civic honour

1982 CBE

Degrees (University of London)

1945 BSc (Lond.) (special chemistry), undergraduate at University College of Southampton

1952 PhD (external, University of London)

1971 DSc (University of London)

Fellowships

1979 Royal Society

1984 Kings' College, University of London

1984 Royal Society of Chemistry

1996 US National Academy of Sciences (Foreign Associate)

Honorary degrees

1985 DSc, University of Southampton

Other distinctions

1975 Burdick and Jackson International Award for Pesticide Research (American Chemical Society)
 1976 Queen's Award for Technological Achievement to Rothamsted Experimental Station, for work on first-generation pyrethroid insecticides (NRDC 104, 107)
 1977, 1980 Agricultural Research Council Awards to Inventors
 1978 Second Holroyd Memorial Lecturer and Medallist, Society of Chemical Industry, London
 1978 UNESCO Science Prize, a biennial award, to the research team at Rothamsted Experimental Station, for developing pyrethroid insecticides
 1978/89 John Jeyes Medallist and Lecturer of the Chemical Society, London
 1980 Queen's Award for Technological Achievement to Rothamsted Experimental Station, for work on second-generation pyrethroid insecticides (NRDC 143, 149, 161)
 1982 Royal Society Mullard Medallist
 1983 Awarded la Grande Medaille de la Société Française de Phytiatric et de Phytopharmacie
 1984 First Royal Society of Chemistry Fine Chemicals and Medicinals Group Award
 1986 British Crop Protection Council Medal for outstanding service to British crop protection
 1988, 1992 British Technology Group (BTG) Awards to Inventors
 1989 Wolf Foundation Prize in Agriculture
 1989 Prix de la Fondation de la Chimie, Paris
 1993 Environment Medal of the Society of Chemical Industry, London

Appointments

1948 Scientific Officer in the Department of Insecticides and Fungicides at Rothamsted Experimental Station
 1969, 1974 Visiting lecturer at University of California, Berkeley
 1979 Deputy Chief Scientific Officer, Head of Department and Deputy Director, Rothamsted Experimental Station
 1986–88 Visiting Research Scientist at University of California, Berkeley
 1989–2007 Consultant on chemistry of insecticides (UK), Lawes Trust Senior Fellow

ACKNOWLEDGEMENTS

I thank Andrew Farnham, Norman Janes, Bhupinder Khambay, David Pulman and John Stevenson for assistance in the preparation of this memoir.

The frontispiece photograph was taken in 1984 by Godfrey Argent and is reproduced with permission.

AUTHOR PROFILE

John Pickett FRS

Having received his honours BSc chemistry degree in 1967 and his PhD in organic chemistry synthesis in 1971 from the University of Surrey, John Pickett completed his training in organic chemistry with a postdoctoral fellowship at the University of Manchester (later the University of Manchester Institute of Science and Technology) from 1970 to 1972. He joined the Brewing Industry Research Institute in 1972, studying the chemistry of malt and hops for new brewing processes. In 1976 he joined the Insecticides and Fungicides Department (later the Department of Biological Chemistry) and was appointed Head of Department in 1984 on the retirement of Michael Elliott and, concurrently in 2007, Scientific Director of the Rothamsted Centre for Sustainable Pest and Disease Management. In 2010 he relinquished these positions on being awarded the first Michael Elliott Distinguished Research Fellowship at Rothamsted. As well as fulfilling this prestigious new role, he continues to contribute to the Chemical Ecology group and is still very much involved with research activities in the UK and around the world. He has more than 520 publications and patents. John's contributions to the field of chemical ecology have been acknowledged with the 1995 Rank Prize for Nutrition and Crop Husbandry, election to the Fellowship of the Royal Society in 1996, election as a Member of the Deutsche Akademie der Naturforscher Leopoldina in 2001, award of the International Society of Chemical Ecology Medal in 2002, appointment to CBE for services to biological chemistry in 2004, and (jointly) the Wolf Foundation Prize in Agriculture in 2008, among many other international measures of esteem. He also presented, in 2008, the Royal Society's premier lecture in the biological sciences, the Croonian Prize Lecture, and in 2009 the Cornell University Lecture. In August 2012 he was awarded the International Congress of Entomology Certificate of Distinction, presented at the XXIV International Congress of Entomology in Daegu, Korea. In April 2014 he was elected a Foreign Associate of the US National Academy of Sciences. In June 2014 he became President of the Royal Entomological Society.

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