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Obituary

Jonathan B. Spencer (1960–2008)

Jonathan (Joe) Spencer, who at the age of 47 was tragically killed in a road accident in Cambridge, England, on April 6, 2008, was an outstanding enzymologist and chemical biologist who made indelible contributions to our understanding of biological catalysis. He was born in England, at Guildford in Surrey, on July 19, 1960, and apart from a short and highly productive spell at Texas A&M University, spent his working life at the Universities of Southampton and Cambridge. Joe built up a thriving international network of scientific collaborators as his reputation grew, and the shock and sorrow of this brutal loss will be widely felt by his many friends and colleagues in science, as well as by his close-knit family.

Joe obtained his B.Sc., a double Honors Degree in Biochemistry and Chemistry, from the University of Southampton in 1984. Because of illness during finals, he was awarded an aegrotat degree but, luckily for Joe's career prospects in research, his talents were recognized by Professor Peter Jordan (now Peter Shoolingin-Jordan), who appointed him as a research assistant. In all, Joe spent a total of ten happy years at Southampton University, obtaining his Ph.D. degree in 1990 and continuing as a Postdoctoral Fellow. The highlight of this part of his research career was a technical and intellectual tour de force in which he and Professor Jordan investigated the mechanism and steric course of the reaction catalyzed by the polyketide synthase multienzyme 6-methylsalicylic acid synthase from *Penicillium patulum* (Spencer and Jordan, 1992). The synthesis of the doubly labeled chiral malonate substrates required great skill and these were fully characterized using purified fatty acid synthase, whose steric course was known (Jordan and Spencer, 1991). These superbly designed and elegantly executed studies neatly overcame the notorious chemical lability of chiral malonyl thioesters and gave penetrating insight into the polyketide assembly mechanism.

In 1992, Joe moved to Texas A&M University, as a NATO Postdoctoral Fellow in the laboratory of the late A. Iain Scott. This was a natural step, given the shared interest in the Scott and Jordan laboratories at

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that time in the remarkable enzymology of the biosynthesis of vitamin B_{12} and other tetrapyrroles. Over the next two years, Joe played a full part in the Scott group's methodical, stepwise deconvolution of the successive enzyme-catalyzed steps that connect early tetrapyrrole intermediates such as uroporphyrinogen III to the complete corrinoids that are immediate precursors of vitamin B_{12}. These experiments foreshadowed several important themes in Joe's later, independent work: the gene deduced to encode each successive enzyme in the pathway was cloned and expressed in *Escherichia coli*. The enzyme was then purified, added to the characterized (^{13}C-enriched) product of the previous enzyme, and the progress of catalysis was monitored directly in an NMR tube. These efforts culminated in a landmark study in the cell-free biosynthesis of complex natural products. The resulting paper, published in one of the first issues of *Chemistry & Biology*, described how 12 purified recombinant enzymes were mixed together with δ-aminolaevulinic acid, S-adenosylmethionine, NADPH, and oxygen. After overnight incubation, this was found to give an astonishing 20%–25% overall yield of the metal-free corrinoid hydrogenocobyrinic acid, representing greater than 90% conversion in each of the seventeen individual catalytic steps involved (Roessner et al., 1994).

Joe came to Cambridge as a Royal Society University Research Fellow in 1994, was then appointed as a Lecturer in the Department of Chemistry in 2001, and was promoted to Reader in Biological Chemistry in 2004. During this period, he kept up a strong interest in mechanistic aspects of preparatively useful synthetic transformations, including several examples of Pd(II)-mediated catalysis, work that he published in a number of thoughtful papers. He also, in a rewarding partnership with Professor David O'Hagan at the University of Durham (now at the University of St. Andrews), helped elucidate the fascinating bacterial pathway which leads to secondary metabolites containing an unusual carbon-fluorine bond (Dong et al., 2004; Huang et al., 2006).

The main focus of Joe Spencer's work shifted decisively over the last few years toward the study of the biosynthesis of polyketides, of the vancomycin family of antibiotics, and of the aminoglycoside antibiotics. There is an urgent need for new and improved versions of such drugs to help combat the continuous threat of emerging drug-resistance in pathogens. It is here that he made perhaps his most influential contributions. Together with Professor Dudley Williams, for example, he carried out pioneering work on the biosynthetic genes and enzymes of the vancomycin-like glycopeptide chloreremomycin, (for example Choroba et al., 2000; O'Hare et al., 2006). There were also key contributions to understanding the pathway to teicoplanin, a glycopeptide with a distinctive fatty acyl side-chain that is key to its antibiotic action (Li et al., 2004).

When Joe went on to explore the genes and enzymes involved in the biosynthesis of the aminoglycoside antibiotics butirosin and neomycin, he very quickly made some fascinating and unexpected discoveries. One particular highlight concerned butirosin biosynthesis, which is governed by the *btr* gene cluster in *Bacillus circulans*. Careful analysis of the steps leading to the unique (*S*)-4-amino-2-hydroxybutyrate (AHBA) side chain, which protects the antibiotic from several common resistance mechanisms, revealed an

unprecedented example of a biological equivalent of protective-group chemistry (Li et al., 2005). More recently, Joe and his colleagues used these insights to achieve in vitro enzymatic production of novel AHBA-bearing aminoglycosides (Llewellyn et al., 2007), which has very encouraging implications for the preparation of unnatural antibiotics via directed biosynthesis. Meanwhile, they correctly identified the previously misassigned function of the *btrD* gene, recognizing it as a specific deacetylase (Truman et al., 2007). Together with Professor Tom Blundell and his colleagues in the Department of Biochemistry in Cambridge, he undertook structural studies to underpin the mechanistic enzymology. As a result of this, they obtained the first X-ray crystal structure of any of the butirosin biosynthetic enzymes, that of the aminotransferase BtrR, which catalyzes two distinct steps in the pathway (Popovic et al., 2006).

Joe combined his scientific activities with a busy teaching and pastoral role in St. John's College, Cambridge, as Director of Studies in Chemistry. The undergraduates in his care, whether chemists or historians, soon learned to appreciate his friendly and positive approach. Joe was a convivial man and many of his friends and colleagues will cherish memories of relaxed evenings in his College or over a beer or glass of wine at Gregynog, the mid-Wales meetings of the European Society for Bio-Organic Chemistry (ESBOC), where he was a regular participant. My own scientific collaboration with Joe Spencer initially centered on polyether ionophore biosynthesis, in which the initial synthesis of the polyketide chain on a giant modular polyketide synthase is coupled to an origami-like process of oxidative cyclization to form the characteristic ether rings with complete regio- and stereospecificity (Gallimore et al., 2006; Harvey et al., 2006). However, the joint work soon expanded to include stereochemical aspects of catalysis in modular polyketide synthases more generally, as well as a host of new ideas at various stages of development. As with my previous long association with Professor Jim Staunton (who was a staunch supporter and mentor to Joe in the Department of Chemistry) it was a stimulating, productive, and enriching scientific experience for both research groups.

Joe's masterly capacity for taking a fresh look at long-standing problems and seeing important things previously missed by others was shown most clearly in the recent retrobiosynthetic analysis he carried out with Andrew Gallimore on the marine polyether ladder toxins, some of the largest (and most poisonous) nonprotein natural products ever discovered. The analysis (Gallimore and Spencer, 2006) revealed that the absolute stereochemistry of the ring junctions in these awesomely stereocomplex toxins could consistently be predicted on the basis of elegant and simple rules. Tantalizingly, the analysis also implies that the currently accepted structural assignment for maitotoxin is in error at a single ring junction (a junction already acknowledged to present difficulty for NMR-based assignment of stereochemistry). Although the matter has not yet been settled experimentally, I would not be surprised in the least to see Joe's predictions ultimately vindicated. As it happens, even this issue of *Chemistry & Biology* contains a new contribution from Joe's laboratory (Truman et al., 2008), reporting work done jointly with colleagues in Cambridge and Tübingen and describing the first example of reactivation of an ancestral enzymatic role for a bacterial protein by point mutagenesis.

Joe Spencer was an impressive and humane research scientist: sharply intelligent, completely fearless in tackling tough problems, calm and self-confident, honest and scholarly. He was also a gentle and approachable supervisor who could get the best from people and a warm, utterly reliable colleague, blessed with a well-developed sense of humor and a no-nonsense manner. His many collaborators invariably became his friends. At a recent scientific meeting, it fell to Joe to introduce my talk. Speaking about our scientific collaboration, his cheerful verdict was: "It's been great fun." I couldn't agree more. Despite the terrible loss, I remain profoundly grateful that I had the good fortune to work closely with him for the time I did, and I am utterly confident that his distinctive and stylish scientific legacy will prove of lasting value.

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