

Jeremy Randall Knowles (1935–2008)



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Jeremy Randall Knowles, who died on 3 April 2008, was one of the most brilliant biological chemists of his time. Born in Rugby in 1935, he was the son of an academic economist at Oxford. He was educated as a chemist, and started his research career in mechanistic organic chemistry, studying the mechanism of aromatic substitution reactions with R.O.C. ('Dick') Norman at Oxford. During his post-doctoral period at CalTech with George Hammond he decided to devote himself to enzyme mechanisms, but he always saw these with the eye of an organic chemist, albeit an organic chemist with an appreciation of what is important in biology.

He returned to Oxford in 1962 and became Fellow of Wadham College and University Lecturer in Chemistry. He quickly established himself as one of the most effective teachers and imaginative researchers among the University's chemists. Initially, he concentrated his research on the proteolytic enzymes, such as α -chymotrypsin, trypsin and pepsin, that had played so large a role in the development of our knowledge of enzymes and enzyme mechanisms. Once it became possible to apply the techniques of mechanistic organic chemistry to a broader group of enzymes he quickly did so, making major contributions to our understanding of triose phosphate isomerase, phosphoglycerate kinase and β -lactamase in the 1970s, as well as several others later on.

His collaboration with John Albery was tremendously productive. Around 20 papers, several of them classics, appeared between 1976 and 1989, but their discussions started long before that. Their paper on perfection in enzyme catalysis, illustrated with triose phosphate isomerase, influenced a generation of enzymologists, and their series of six consecutive papers in *Biochemistry* on proline racemase

(described by a cynic as devoting more than 30 pages of algebra to show how to move a proton from one side of a proline molecule to the other) said everything one might want to know about proline racemase, and at the same time advancing understanding of isotope effects. This series illustrated an important aspect of his attitude to research: he was never one to rush into print with half-formed ideas, preferring to wait until the research was complete before publishing it. He ran little risk of being scooped, however, as his ideas were usually so far ahead of anyone else's that he would be ready to publish his six papers before anyone else had finished planning the first experiment.

The title of an article he wrote for *Nature* summed up what he thought about enzymes: 'Enzyme catalysis: not different, just better'. On the one hand, yes, enzyme catalysis is just chemistry, with no magic added; on the other hand, it goes far beyond anything that a conventional catalyst can do, orders of magnitude faster, and orders of magnitude more specific. One of the first to take advantage of the new opportunities to generate mutant enzymes that came with the flowering of molecular biology, he was also, perhaps more important, one of the first to ask what was the point of it: should you generate new enzymes just because you can, or should you ask what you are going to learn from them? In this spirit he criticized the term 'enzyme engineering', pointing out that an engineer who designs a new bridge knows in advance what properties it will have.

Without Jeremy there would have been no Oxford Enzyme Group. In 1968 Sir Ewart ('Tim') Jones, Professor of Organic Chemistry and Chairman of the University Science and Technology Committee of the Science Research Council, informed his colleagues on the committee that they should support enzyme chemistry. On his return to Oxford he abruptly asked Jeremy, still a rather junior member of the Dyson Perrins laboratory, to write a position paper, adding that he had to have it by

8 a.m. the following morning. Jeremy not only produced it on time, but he wrote it so well that it opened the way for the Oxford Enzyme Group, founded in 1969, and flourishing for 20 years as a major focus for research on enzymes.

In 1974, Jeremy moved from Oxford to Harvard, where he remained for the rest of his life. For the first two decades there, he continued his research, and continued to produce memorable papers. No sooner did it become possible to study the stereochemistry of substitution at phosphorus atoms, a topic of great importance for understanding the many reactions that use ATP as a substrate, than he became one of the world leaders in the field.

His research output was not huge, around 250 publications in total, primarily because he was never willing to sacrifice quality for quantity. He told me once that at the time that he was offered a full professorship at Harvard he had commented to a senior professor there that he felt flattered because he had not published many papers, around 60, in fact, only to receive the caustic reply "At some universities we *read* the papers; we don't just count them."

As a teacher, whether in tutorials or lectures, Jeremy was quite exceptional. Those who heard him lecture in his early years at Oxford will remember his celebrated imitation of a globular enzyme, and anyone lucky enough to have had him as tutor will remember his capacity to convey the idea that there was nothing in the world more fascinating to discuss than aromatic nitration. During the period

of his work on catalytic perfection he was sometimes introduced as the perfect lecturer: with most speakers this would have been embarrassing, but with Jeremy it was accepted as a statement of fact. He had a sense of theatre and an ability to tell the story that made listening easy, and the meticulous preparation meant that every slide, every phrase, was honed. In science as much as in conversation he was witty and a pleasure to be with.

In 1991, he became Dean of Arts and Sciences at Harvard, after resisting earlier pressure to take on this enormous job in 1983. This meant, unfortunately, that his work in chemical research came to an end, but he compensated for this by becoming one of the most effective Deans the University has known. Starting at a time when the annual deficit of the Faculty exceeded 12 million dollars, he succeeded during the decade that followed not only in restoring financial equilibrium, but also in embarking on renewed expansion and renovation. After retiring from this task he returned to the Department of Chemistry and Chemical Biology, but it turned out that his days as Dean were not over, as he was persuaded to return as Interim Dean in 2006.

I should like to insert a personal note at this point. In 1964, Jeremy accepted five of us into his group as Part II (4th year of chemistry) research students, thereby increasing the size of his group overnight from one to six students. We all had clearly distinct projects, all of them leading to publications, all of them reasonably inter-

esting, even after the lapse of 40 years. We were all able to go to his office to talk with him when we felt like it, and we did. He allowed his students to argue with him about the principles of what we were doing, and we did. I had many arguments with him, but I don't remember a single occasion when he turned out to be wrong. Although he had largely abandoned doing any experiments with his own hands by that time, he proved to be very skilful when he wanted. The most refractory brownish oils that we had managed to synthesize could be persuaded to crystallize with the help of Jeremy's glass rod. In later years, he realized that it would be impossible to run a large group without some discipline, and, already by 1965, the Part II students of that year had a little less freedom to wander into his office whenever they felt like it than we had had, but, right until the end of his research career, he remained a very approachable supervisor.

I saw him for the last time in September 2006, when we were both in Oxford to celebrate the 80th birthday of R.J.P. ('Bob') Williams, with whom he had shared the teaching of chemistry to Wadham students in the 1960s. I doubt whether any of us thought that he was already ill and that he only had 18 months more to live. His death at the age of only 72 has deprived enzymology of one of its major figures.

In 1960, Jeremy married Jane Sheldon Davis, and is survived by her and their three sons, Sebastian (named in honour of Johann Sebastian Bach), Julius and Timothy. ■