Jake MacMillan: A pioneering chemist in plant biology

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Jake MacMillan, who died on May 12, 2014 at the age of 89, was an organic chemist who made an enormous contribution to plant science, particularly in relation to the structure, biosynthesis, and analysis of the gibberellin plant hormones. Jake was born in Wishaw, Scotland, into a lower working class environment in which there was very little spare cash. Despite offers of a safe, steady job in a bank or an opportunity to become a professional soccer player, which—as sources of financial security—must have been very tempting, Jake was determined to pursue a career in chemistry and was the first in his family to attend university, obtaining his Bachelors of Science and Doctorate from the University of Glasgow. During his university years, Jake played soccer semiprofessionally, obtaining much-needed income to support his studies. Jake reminisced entertainingly about his education and career in an autobiographical article published in the *Annual Review of Plant Physiology and Plant Molecular Biology* (1).

After receiving his doctorate in 1948, Jake took a job in industry, joining a group of chemists at the Imperial Chemical Industries (ICI) Akers Research Laboratories near Welwyn, England to work on the isolation and structural determination of fungal metabolites as potential pharmaceuticals. Jake was involved in the discovery of a number of novel bioactive natural products; the most well-known was griseofulvin, an antifungal compound, still in medical use today (2). Jake maintained his interest in fungal metabolites throughout his career and they provided topics for many a doctorate student. It was at the Akers Laboratories that Jake first became involved with the gibberellins. These metabolites of the fungus *Gibberella fujikuroi* were discovered in Japan and came to the attention of the West in the late 1940s through entries in *Chemical Abstracts*. The profound effect of these metabolites on plant growth and development was of immediate interest to agriculturalists and motivated the ICI to investigate them further. The team's experience with submerged fungal cultures enabled them to isolate large quantities of the major metabolite, gibberellic acid (GA_3), and to determine its structure (3). The ability of GA_3 to restore growth to dwarf mutants suggested that these compounds may function as endogenous growth regulators in plants, and indeed extracts from several plant sources were found to have similar biological activity. Jake and colleagues were inspired to provide chemical support for this hypothesis and extracted milligram quantities of a gibberellin from 100 kg of immature seeds of runner bean, showing it to be identical to a minor *G. fujikuroi* metabolite, GA_1 (4). Thus, a new field was born and Jake was destined to play a major role in it.

After the closure of the Akers Laboratories in the 1960s, Jake decided to leave the ICI and join academia, taking up a position as lecturer in the School of Chemistry at Bristol University. A colleague of his at Bristol, Bob Binks, was setting up the fledgling technique of gas chromatography and Jake saw its potential for the gibberellins, particularly when combined with the analytical power of mass spectrometry. The development of combined gas chromatography-mass spectrometry (GC-MS) for the analysis of gibberellins and another plant hormone, abscisic acid, in plant extracts by Jake's group provided the first examples of the use of this technique in plant science (5, 6). By this time, the number of different gibberellins that had been characterized from *G. fujikuroi* and plant sources, many in Jake's laboratory, had grown substantially, with their nomenclature becoming haphazard and confusing. This haphazard nomenclature prompted Jake and the Japanese chemist Nobutaka Takahashi, who became a close friend of Jake's, to propose extending the numbering system that had been used for the fungal gibberellins, and this has proved to be a highly successful system (7).

Jake MacMillan and his wife Anne. Photograph taken by Dr. Eric Albone.

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Jake's expertise in structure determination and chemical synthesis was put to very productive use in the gibberellin field. The traditional approaches for structure determination, based on chemical degradation and conversion to compounds of known structure, or even the emerging NMR technology, were incompatible with the very low concentrations of gibberellins and other hormones present in most plant tissues. With the advent of GC-MS it was possible to use an alternative strategy in which candidate structures were synthesized and their mass spectra and GC retention times compared with those of the natural compounds. By this means many novel gibberellins were identified, including, importantly, metabolites and biosynthetic precursors of the bioactive compounds. Isotopic labeling of potential intermediates, combined with the rapid and unequivocal identification of products, enabled swift progress in determining the gibberellin biosynthetic pathways, for example in *G. fujikuroi*, in collaboration with Bernard Phinney of the University of California at Los Angeles, and in pumpkin seeds with Jan Graebe at the University of Göttingen, Germany (8, 9). The power of Jake's chemical approach attracted numerous collaborations with plant biologists, many of whom spent productive sabbaticals in Jake's laboratory. Jake recognized the importance of multidisciplinary research and, already in the 1970s was recruiting biologists and biochemists to his laboratory, which was extremely unusual for a chemistry laboratory at the time.

Toward the end of his time in the School of Chemistry, Jake became Head of Department and then Head of School. Although his calm, considered approach was well suited to the task, Jake did not take readily to this largely administrative role, and when he formally retired in 1990 he moved with some members of his group to the nearby Long Ashton Research Station to, in his own words, work as a postdoc. Indeed, Jake went back into the laboratory, as well as taking the opportunity to undertake considerable writing and reviewing. We at the Long Ashton Research Station benefitted immeasurably from having Jake as a laboratory member, and it was a sad loss when the association was broken in 2003 because of the closure of the Station. Jake maintained an enthusiasm for science to the end. With his passing gibberellin research has lost one of its founding fathers and greatest champions.

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