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Editorial

R.B. Merrifield: European footnotes to his life and work

Abstract: Some reflections on the life and work of RB Merrifield in the European context are given. Copyright © 2007 European Peptide Society and John Wiley & Sons, Ltd.

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Nobel Laureate Bruce Merrifield, enabling genius of peptide science, died on 14 May 2006 aged 84. His 1959 idea of peptide synthesis on an insoluble polymeric carrier was brilliantly original. It would probably have been dismissed as deluded by many if it had been aired generally at the time, and it failed at first. With patience and skill, he brought it to fruition, and published alone because there were no co-workers to credit. He persevered in the face of initial scepticism, with dignity. When glory came, he was self-effacing and bore no grudges. If he took personal pride in anything, it was the large family he left behind. Long before his passing, his concept of peptide synthesis was in use by thousands in diverse forms, advancing biological science, organic chemistry and medicine on multiple fronts. His was a life to celebrate in awe.

Merrifield was a member of the Editorial Advisory Board of *J. Peptide Science* from its birth, and so an appreciation here is appropriate, but while I was reflecting about this, several tributes appeared in other journals, and we have his autobiography [1]. In early 2007, a SciFinder subject search on 'Bruce Merrifield' gave 40 hits, a mixture of 2006 obituaries and appreciations published in his lifetime. Even this was incomplete, because SciFinder does not embrace newspapers or vehicles like semi-private newsletters. The many obituaries and articles published in the scientific journals are easily located through SciFinder or other means, and so are not listed here. Valuable contributions in more ephemeral publications include a 1984 interview of Merrifield conducted by J Murphy (Chemalog Hi-lites, May 1985, 7–9) and obituaries by R Perham (Independent, 31 July 2006), D Andreu (El Pais, 26 May 2006), and TH Maugh III (Los Angeles Times, 3 June 2006). So I came to the conclusion that a rounded memoir would be superfluous and repetitive, and decided to limit myself to a few general remarks and draw attention to some details in the European context.

Robert Bruce Merrifield was born at Fort Worth in Texas on 15 July 1921. He was an American through and through, but the known surnames in his incomplete family tree [2,3] are all West European, and indeed mostly English-sounding: Merrifield, Furlong, Lucas, Evans, Hickman, Welch, Boone, Wingate, and Lipscomb. Merrifield is certainly an English name, associated, particularly, with the West Country. Ordinance Survey maps show two villages called Merrifield in Devon. In America, the Laureate's paternal male line is traced to one Samuel Merrifield, who died in Virginia in 1780, but who was born in England, probably in 1720. Here a genealogical mist descends. This Samuel might have been the young burglar who was transported from Kent in 1737 to the penal colony in Virginia – his crime must have been slight or he would have been have been hanged in England at that time. Or he might have been another Samuel who emigrated of his own volition in 1747.

The seminal solid phase peptide synthesis (SPPS) paper [4], despite being by a solitary unknown, was noticed promptly in Europe. R.C. Sheppard drew attention to it in the Chemical Society's *Annual Reports on the Progress of Chemistry* for 1963 [5]. And Sir Robert Robinson, possibly the greatest organic chemist of the century, not only spotted the significance of the work, but descended on Merrifield at short notice to discuss the work soon after publication [6]. Robinson was also a Rockefeller-supported Laureate, then long retired from Oxford but still vigorous, with a little-known interest in peptides [7]. He even aired thoughts of a Merrifield Nobel Prize privately to Garland Marshall [8]. But generally the European response focussed more on the imperfections of the approach and the perceived conceptual flaws than its prospects. The 'paradigm shift' was too much to take for some of those trained up in the classical tradition of organic synthesis, which dictated that intermediates should be cleaned up and have proven identity at every possible stage. Some of the criticism was immoderate, patronising, and prejudiced. But, by my recollection of the discussions I was privy to, it was civil – I would not go so far as 'vehement and vitriolic' [9].

These attitudes lingered well into the next decade in some quarters, and even Bob Sheppard was hesitant to begin with. He did not engage seriously with SPPS until he was invited to speak to the 11th European Peptide Symposium at Vienna, where he set the intellectual scene for the development of his approach in a very important lecture [10]. Garland Marshall, Merrifield's first graduate student, was at

Figure 1 Merrifield in Uppsala, 1968. Courtesy of Kurt Esko and Ulf Ragnarsson.

that Symposium reporting on his own work [11], and felt somewhat thrown to the lions, whimsically noting [12]:

> It was exciting to receive an invitation ... to present our ACP work in Vienna in 1971, but I was not prepared for the warmth of the reception that I received. The established heads of many peptide laboratories, whose work I venerated, were more than generous with their criticisms ....

It is salutary for me to look back at my own reviewing of the time to see what light I saw SPPS in myself. I am glad to say that I never wrote anything at all barbed, but my comments were often mixed, and in retrospect seem more negative than they could have been. On the

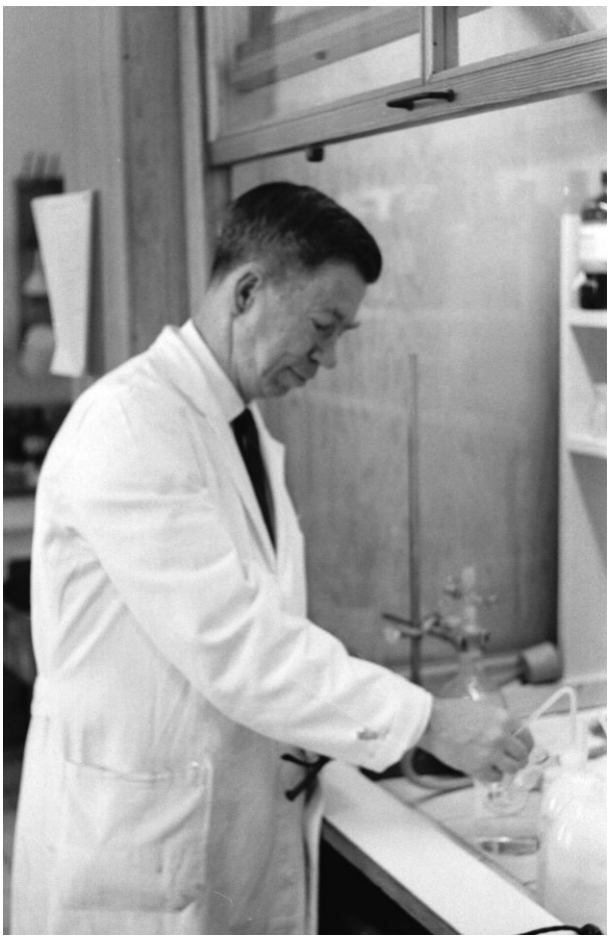

Figure 2 Merrifield in the laboratory, Uppsala 1968. Courtesy of Gunnar Lindeberg and Ulf Ragnarsson.

apoferredoxin and ribonuclease syntheses, for example I wrote in the first annual volume of the Chemical Society's *Specialist Periodical Reports on Amino Acids Peptides and Proteins*, reviewing 1968 literature [13]:

> **Repetitive Methods of Peptide Synthesis. –** *Synthesis on a Polymeric Support.* At the time of writing, the publication of a laboratory manual on this method is imminent, and the subject has recently been reviewed in the Japanese, Russian, Polish and German languages. The year under review has seen the announcement of the synthesis of two very large peptides by the 'solid phase' method (ribonuclease and apoferredoxin). These syntheses, particularly, the former of course, are staggering achievements, but the purity of the final products leaves much to be desired. The outstanding problem is that unless every coupling reaction proceeds to completion, the final peptide is inevitably contaminated with peptides differing from the required sequence by one or more amino-acid deletions. The difficulties of attaining quantitative reaction and of separating mixtures of very similar peptides increase with the length of the peptide chain, and the prospects for the application of 'solid phase' methods for the unambiguous synthesis of proteins seem slim at the present time. In the case of small peptides, the separation of the required peptide from any 'error' peptides does not

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Figure 3 Merrifield becomes an Honorary Doctor of the University of Uppsala 1970. Courtesy of Gunnar Lindeberg and Ulf Ragnarsson.

> pose serious problems: e.g. four recent reports describe syntheses of oxytocin in which the required protected nonapeptide precursor was obtained in a very pure condition by ammonolysis of the link between the protected peptide and the resin followed by simple reprecipitation or washing procedures.

No surprise there in finding that I failed to get the perspective quite right – not long before I had held out only limp hope that mass spectrometry would be of much use in the field [14]. But the exercise has at least given me the pleasure of noting that in the same Specialist Reports chapter, my crystal ball worked well for once [15]:

> It may even be that advances in nucleotide chemistry will overtake improvements in peptide synthesis: the best way of obtaining synthetic enzyme analogues might then be by instruction of biological protein-synthesising systems with artificial messenger molecules.

Who knows, perhaps the hypercriticism was a spur to Merrifield in his work, and retrospective wisdom is all too facile. But the disparaging remarks made, and the implications of naivety in some of them, are regrettable. I once heard the invaluable practical handbook of Stewart and Young [16] called 'A cookbook for the

Figure 4 Merrifield and his family in Sweden, 1984. Courtesy of Ulf Ragnarsson.

American housewife'. If optimism is an intellectual crime, Merrified committed it, but he identified and discussed key problems in his first major paper [4]. Unthinking he was not. He should have been more universally cheered on.

Merrifield was unabashed by the early reception, and there was some positive mid-sixties reaction in Europe. At that time, the European Peptide Symposia were very select, with attendance strictly by invitation. In Merrifield's words [17], with his emphasis 'This was *the* meeting for peptide chemists'. There was no European Peptide Society – another quarter century

Figure 5 Merrifield becomes an Honorary Doctor of the University of Barcelona 1986. Courtesy of David Andreu.

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would pass before that would crystallize – and the Symposium series was run by a European Peptide Committee. The series had something of the flavour of an exclusive club about it. Merrifield was invited to the 8th Symposium held at Noordwijk in the Netherlands in September 1966, and considered it a 'special privilege to attend' [17]. It was a compliment he repaid with interest by his frequent attendance thereafter [18].

The Noordwijk Symposium included a whole section devoted to SPPS, and it is evident from the Proceedings [19] that, despite the dominant scepticism, many European groups had picked upon the principle, and were working on detailed aspects or applying it. The familiar leading names Ovchinnikov, Patchornik, Rudinger, Wieland, and Zahn all stand out.

Merrifield himself reported on an insulin synthesis [20]:

> This synthesis of insulin illustrates the current state of development of (SPPS) and demonstrates the applicability of the method to the preparation of peptide chains of considerable size and complexity in a relatively short time and in good overall yield.

Also in the Noordwijk Proceedings is the first prominent use of the eponym 'Merrifield Synthesis', in the title of the contribution from Zahn's laboratory [21]. But the key advance made at that meeting was contact made between Merrifield and Shumpei Sakakibara, who described the use of HF for final deprotection [22] there, which led directly to the introduction of HF into the field. As Merrifield said [18], it was a 'good example of why such meetings are important'.

Figure 6 Merrifield speaking during the opening session of the 23rd EPS, Braga 1994, wearing the Silver Medal of the University of Minho which had just been presented to him. Courtesy of Hernâni Maia.

The diversification of the original principle had already begun, and the Noordwijk contributions illustrate that. The lateral thinking of Patchornik's group [23], turning the principle upside down and employing insoluble active esters for *N*-acylation of targets in solution (heralding the general use of insolubilized reagents) is of particular interest. Later on, the all-important Fmoc-polyamide version of SPPS was born and nurtured in Europe [5], and although the invention of the combinatorial principle is generally associated with Geysen [24] and in particular Houghten, [25] it had actually been worked out by Furka unknown to them some years previously in Budapest [26]. There was another paradigm shift there, and the initial reception of that idea bears some similarities with the SPPS principle itself. Revolutionary in its impact within a short period, there was nevertheless an induction period characterised by facetious comment about the so-called 'tea bag' principle, and Furka had been unable to stimulate any commercial interest.

To the University of Uppsala, where he was invited to spend a few months in 1968, goes the credit of making the first serious European academic award to Merrifield: he received an honorary degree there in 1970. He was later honoured by the Universities of Barcelona and Minho, and was the Josef Rudinger Awardee of the European Peptide Society in 1990. But, in his own words, the 'big one' was the Nobel Prize in 1984. When he heard the news he was surprised [27]. Nobody else was; many thought the Prize was overdue. His place alongside Emil Fischer, Max Bergmann, and Vincent du Vigneaud is well deserved.

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