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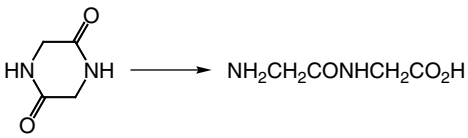
Editorial

A Peptide Centenary Celebration

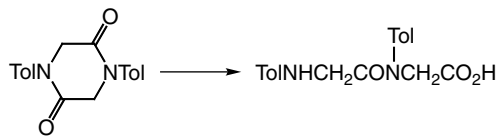
The 27th Symposium of the European Peptide Society, at Sorrento in the late summer of 2002, more or less coincided with the centenary of peptide science, which is popularly reckoned to have been fathered by the great Emil Fischer (1852–1919), and set on its path in 1901. In that year, Fischer and Fourneau described the first free peptide preparation by partial hydrolysis of diketopiperazine.

Actually, Theodor Curtius, with whom Fischer was barely on civil terms, had made a blocked peptide 20 years previously, and was about to report the azide coupling method, probably the first reaction to be delineated which can be recognized as part of the armoury of modern peptide synthesis. Further, Fischer's diketopiperazine starting material had been characterized by Curtius, and although Fischer did not cite it, even the partial hydrolysis of diketopiperazines had precedent.

Curtius deserves a lot of the credit, possibly even the lion's share, and we should not forget Ernest Fourneau (1872–1949) either, who returned to his native France after his time with Fischer and had a distinguished career there as a medicinal chemist. But Fischer had the star quality, and in any case won his fame in multiple ways — for the lock and key concept, in carbohydrate chemistry and in stereochemistry as well as in amino acid and peptide chemistry. His 1902 Nobel Prize was for carbohydrate and purine work; he had hardly begun his onslaught on peptides then. As Fruton remarked in a survey of the early days of our subject at the 19th European Peptide Symposium, 'The public accolade went to Fischer but the verdict of history went to Curtius'. Also, history is more convoluted than hagiography, and all scientists are, to a degree, children of their times. Even the great, like Newton, have stood on the shoulders of giants — in Fischer's case the giant from whom his scientific descent can be traced is Liebig, through Kekulé and von Baeyer. But all the world loves megastars and centenaries, and deep-seated tradition is not easily budged, even if slightly unsound, so a special *Celebration of 100th Anniversary of Emil H. Fischer's first synthesis of a peptide* was included in the Sorrento programme.



Scheme 1 Preparation of glycylglycine [1]. Conditions: rapid heating to b.p. in conc. HCl, followed by cooling, whereupon the dipeptide hydrochloride crystallized; the free peptide was liberated with Ag_2O and crystallized from aq. EtOH as analytically pure flakes with a mother-of-pearl lustre (*perlmutterglänzenden Blättchen*).



Scheme 2 A precedent for Scheme 1 [2]. Conditions: hot conc. HCl. Tol = *o*-tolyl.

The classic 1901 paper on which on which the Sorrento Celebration was hung contains a crisp statement setting out the problem of chemical protein synthesis. After an introduction surveying attempts to obtain protein-like materials by fusing amino acids with or without additives such as urea or formaldehyde, he continues

> ..... Aber alle von ihnen beschreibenen Produkte sind amorphe, schwere charakterisierenbare Substanzen, über deren Struktur man ebensowenig wie über den Grad irhrer Verwandtschaft mit den natürlichen Proteïnstoffen etwas sagen kann.
>
> Will man auf diesem schwierigen Gebiete zu sicheren Resultaten kommen, so wird man zuerst eine Methode finden müssen, welche es gestattet, successive und mit definierbaren Zwischenstufen die Moleküle verschiedener Aminosäuren anhydridartig aneinander zu reihen.
>
> *Freely translated:*
> ..... But all the products described are amorphous substances which are difficult to characterize, about whose structure one can say as little as one can about their relationship to natural proteins.

> If reliable results are to be obtained in this difficult field, a method must first be found which allows different amino acids to be arranged in sequence, by condensation one at a time with characterizable intermediates.

He then proceeds to describe the preparation, characterization, some reactions and the modern naming of glycylglycine. It is humbling to see in this and Fischer's later work just how much could be achieved with relatively primitive glassware to work in, and little more than combustion analysis, titrations and colour tests to monitor progress — no spectroscopy, no chromatography: a bit like trying to paint works of art in the dark with a bucket and mop.

Although there can be donnish carping at proclaiming this undoubtedly seminal paper as the origin of peptide synthesis, the Sorrento Celebration on 3 September 2002 nevertheless had validity, for two reasons.

First, historical; less heralded than the Fischer and Fourneau paper, but chronologically almost a bullseye centenary, is the fact that on 22 September 1902, at a scientific meeting in Karlsbad which was reported later that year [3], Fischer pointed out that glycylglycine and analogous compounds seemed to lie between the so-called peptones and the amino acids, and introduced the terminology dipeptide, tripeptide etc for them.

> Der Redner macht deshalb den Vorschlag, in Anlehnung an die bekannte unterscheidung der Kohlenhydrate als Disaccharide, Trisaccharide, usw. die Körper vom Typus des Glycyl-glycins Dipeptide zu nennen und anhydridartige Kombinationen einer grösseren Anzahl von aminosäuren als Tripeptide usw. zu bezeichnen.
>
> *Freely translated:*
> The speaker [i.e. Fischer himself] therefore proposed, following the established classification of carbohydrates as disaccharides, trisaccharides and so on, to name compounds of the glycylglycine type dipeptides, and condensed combinations of higher numbers of amino acids tripeptides and so on.

Exactly when and where peptide science began may be a bit obscure, but the first public use of the term peptide can be dated with precision. If we cannot be certain of our science's birthday, or even its father's name, we can at least know for sure who its Godfather was, and exactly when he named its materials.

Second, consistent with the many passages of great foresight which can be found in Fischer's writings — he seems to have anticipated genetic engineering, for example — the Sorrento Celebration was essentially forward-looking, with enthralling addresses by seven leading figures. We are delighted to be able to present six of these lectures in this Special Issue, and thank the Lecturers for taking the trouble to write them up. The missing one is 1988 Nobel Laureate Robert Huber's 'Molecular Machines for Protein Degradation'; its absence is a disappointment, but we could hardly expect the special privilege of being the vehicle for its publication, as Google trawling shows that he gave a lecture with that title during 2002 in quite a few locations.

The driving force behind the Sorrento Celebration was Murray Goodman, and the idea of pulling its contributions together in a Special Issue of our Journal was also his. He has been a supportive member of the Editorial Board from its very beginning, and we thank him for this idea, his parting gift on stepping down. And we congratulate him on the fact that, more than 50 years on from finishing his PhD, he is still a dynamic influence in peptide science.

We can also link in here that the publication of this Special Issue coincides with the tenth anniversary of the launch of our Journal, under Conrad Schneider as Founding Editor.

A Special Issue which thus celebrates not only Emil Fischer's legacy but also Murray Goodman's Golden Jubilee in the field and the tenth anniversary of our Journal clearly deserves a special cover illustration, and we are grateful to Stephen Kent for suggesting and providing one.

Closely associated with the Sorrento Celebration was the publication of the first volume of a new *Houben-Weyl* on peptides (and peptidomimetics), in English; this first volume has been reviewed [4]. The monumental complete work of five volumes is now available, and it will be the subject of an Editorial Review in this Journal shortly.

JOHN JONES
Editor-in-Chief

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3. Fischer E [Autoreferat]. Über die Hydrolyse der Proteïnstoffe. *Chemiker Zeitung* 1902; **26**: 939 (reprinted in the first volume of the 1944 reprinting of Fischer's collected works in the field which is cited below, pp 621–623).
4. Jones J. Houben-Weyl commemorates a Hundred Years of Peptide Chemistry. *European Peptide Society Newsletter* 2002; **27**: 1–4.

GENERAL BIBLIOGRAPHIC NOTE

The most recent, and now most accessible, summary of the early history of peptide chemistry is in the introductory chapter by F. Naider and M. Goodman in the *Houben-Weyl* volume (E22a) mentioned above. For previous more in-depth accounts, see: (a) P. Walden, *Geschichte der Organischen Chemie seit 1880*, Berlin, 1941; (b) J.S. Fruton, The Synthesis of Peptides, chapter 1 in *Advances in Protein Chemistry*, 5,1949; (c) J.S. Fruton, *Molecules and Life*, New York etc, 1972; (d) J.S. Fruton, 'From Peptones to Peptides — a Historical Retrospect' in *Peptides 1986* ed. D Theodoropoulos, Berlin etc, 1987; (e) T. Wieland and M. Bodanszky, *The World of Peptides. A Brief History of Peptide Chemistry*, Berlin etc, 1991. On Fischer himself, see the two volumes of his collected works in the field, *Untersuchungen über Aminosäuren, Polypeptide und Proteine* (Berlin, 1906 and, edited by M. Bergmann, 1922; both volumes reprinted Ann Arbor Michigan, 1944) and his autobiography *Aus Meinem Leben* (Berlin, 1922, reprinted in the original German, but with a detailed Prologue and Epilogue in English by B. Witkop, Berlin, etc, 1987).