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Obituary

One of our leading and most respected chemists died on June 20, 2009. Ralph F. Hirschmann had a distinguished 37 year career as a research scientist and research director at the Merck Research Laboratories followed by 19 highly productive years as a professor at the University of Pennsylvania. His research emphasized the application of chemistry to the solution of biological problems and spanned steroids, peptides, and peptidomimetics. He also made many important contributions to discovery and development of human therapeutic agents. He was widely respected as a mentor, teacher, colleague, and friend.

Dr Hirschmann was born on May 6, 1922 in Fürth, Bavaria, Germany. He attended the Gymnasium in Fürth until December 1936, when he and his parents fled Germany for the United States. After completing high school, he earned a bachelor degree in chemistry at Oberlin College in 1943. He became a naturalized US citizen the next year and served 3 years with the Army in the Pacific theater. Following World War II, he resumed his education and was awarded a Ph.D. in organic chemistry with Prof. William S. Johnson at the University of Wisconsin in 1950.

After the receipt of his doctorate, Dr Hirschmann accepted a position at the Rahway, New Jersey laboratories of Merck & Co., Inc. Shortly thereafter, he met Merck chemist Lucy Aliminosa and they were married in 1951. Ralph is survived by Lucy and their children, Ralph Frederick Hirschmann and Carla Hummel and their spouses Karen Montle Hirschmann and Paul Hummel. He was very proud of his family including his six grandchildren Brian, Lisa, Brendan, and Lauren Hirschmann, and Patrick and Christina Hummel.

Readers of this journal are most aware of Ralph Hirschmann's accomplishments and contributions to peptide science. Starting in the mid-1960s his group reinstituted the use of *N*-carboxyanhydrides as practical reagents for peptide synthesis using a water-based strategy with minimal side-chain protection [1]. The strategy and tactics proved sufficiently versatile for application to the first total synthesis of the enzyme, ribonuclease-S, simultaneous with Merrifield's solid-phase synthesis of ribonuclease-A. These syntheses provided the final proof that correct protein folding is intrinsic to the amino acid sequence and independent of the living system [2]. The method is also sufficiently practical to be used for a commercial synthesis of the peptide drugs, Enalapril and Lisinopril [3].

Ralph's multifaceted research career started in process research at Merck where he developed an improved synthesis of vitamin K. In the course of studies of rearrangements in the steroid backbone, especially the unexpected C-nor-D-homo rearrangement on solvolysis of 12β-hydroxylated sapogenins, Ralph recognized that the solvolysis outcome was under 'stereoelectronic control'. This important conclusion was subsequently defined in detail by Corey and associates. Ralph later demonstrated a practical path to the medicinally important 9α-fluoro, 11β-hydroxy steroids from 9β, 11β-steroidal epoxides in liquid HF.

As his research moved toward more medicinally directed outcomes, he developed the phenylpyrazole anti-inflammatory steroids, the most potent marketed class known then. The key issue of the time for steroid research being selectivity rather than potency, Ralph strove to direct the release of active steroid at the site of inflammation. He knew that levels of glycosidase, *N*-acetylglucosamidase were elevated in inflamed joints. He, therefore, prepared an inactive 21-acetylglucosamide of prednisolone which proved to be converted to the active drug at the inflamed site, a process Ralph called 'drug latentiation' and which later became more widely applied by others as the prodrug approach [4].

As the steroid field matured in the early 1960s, Ralph moved to his efforts in peptide research described above. A noteworthy follow-up of the ribonuclease synthesis was the use of *N*-carboxyanhydrides to generate combinatorial libraries of small peptides for biological screening at a time considerably preceding the heydays of combinatorial chemistry [5]. It was also at this time that Ralph's interest in the potential for cyclic peptides as medicinal agents emerged, first as applied to renin inhibitors and later to the study of somatostatin analogs.

What is clear from the above list of accomplishments is Ralph's extraordinary ability to recognize important scientific concepts before they evolved into common practice. This was apparent to the powers at Merck and Ralph's administrative role grew extensively during the 1970s and 1980s to a point where he was responsible for much of the company's basic research. The emergence of important drugs for control of cholesterol, hypertension, river blindness, bacterial infection, and benign prostatic hyperplasia was in no small part a result of his leadership. The Merck years have been reviewed [6–7].

In the course of both his science and his administration, Ralph was always a teacher and a mentor, an aspect of industrial leadership that is not always appreciated outside the industry. Because this was such a strong part of Ralph's persona, it was not unexpected that he was so easily able to move into the academic environment after his retirement from Merck in 1987. He was invited to join the faculty of the University of Pennsylvania, where he served until 2006 as the Rao Makineni Professor of Bioorganic Chemistry. Concurrently, he held an appointment at the Medical University of South Carolina between 1987 and 1999. At the University of Pennsylvania, he established research collaborations with Profs Amos Smith and K. C. Nicolaou on design and synthesis of mimics of peptide beta turns and beta sheets. He also collaborated with Prof. Stephen Benkovic at Pennsylvania State University on catalytic antibodies for peptide synthesis. He mentored a total of 56 graduate students and postdoctoral fellows during this period.

The Merck research on somatostatin analogs had led to a proposed bioactive conformation involving a key beta turn. This

model also suggested that the backbone amide bonds primarily functioned as a scaffold rather than receptor-binding elements. Ralph had a keen interest in learning whether the next step to a nonpeptide scaffold based on this model could be accomplished. He and his academic colleagues proposed a glucose-based scaffold to replace the amide backbone and developed syntheses of these nonpeptide peptidomimetics, which incorporate key amino acid side chains of somatostatin. Remarkably, compounds active at somatostatin receptors were discovered, thus providing one of the earliest examples of the *de novo* design of such nonpeptide receptor ligands [8].

Ralph and his colleagues were aware that proteases bind their substrates and inhibitors by generating beta sheets, and at the time, limited work had been performed on models for such systems. They designed and synthesized a novel nonpeptide scaffolding for beta sheets based on repeating 3,5,5-trisubstituted pyrrolinones incorporating appropriate amino acid side chains. It was shown by X-ray crystallography that polypyrrolinones present these side chains and carbonyl hydrogen bond acceptors in a solid state conformation that mimics beta sheets [9]. In a demonstration of its potential utility, this system was used to prepare potent and orally bioavailable HIV-1 protease inhibitors [10].

Another long-term interest of Ralph's was the synthesis with minimal protection of large peptides and proteins for which practical methodology was extremely limited. He and his colleagues designed and synthesized a phosphonate diester hapten to mimic the transition state for amide bond formation. A monoclonal antibody induced from this hapten was shown to selectively catalyze coupling of activated alpha-amino acids and dipeptides with another alpha-amino acid or dipeptide to form di-, tri-, or tetrapeptides. These studies demonstrated the potential of this novel approach for catalyzing the coupling of large, unprotected peptide fragments [11].

Dr Hirschmann received numerous awards recognizing his achievements. He was presented with the National Medal of Science by President Clinton in 2000. Among several American Chemical Society awards he received were the Arthur C. Cope Medal (1999) and the Alfred Burger Award (1994). The American Chemical Society-administered Ralph F. Hirschmann Award in Peptide Chemistry was established in 1989. He also received the Alan E. Pierce Award (renamed the Bruce Merrifield Award) from the American Peptide Society (1983), the Dr. Josef Rudinger Award of the European Peptide Society (1996), and the Max-Bergmann-Medal of the Max-Bergmann-Kreis (1993). He was elected to the U. S. National Academy of Sciences in 1999.

Ralph Hirschmann will be remembered for his contributions to basic science and human therapy. Most of all, he will be fondly remembered because of the special relationships that he developed with his colleagues, students, and friends in both industry and academia.

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