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Editorial

A Tribute to Ralph F. Hirschmann

This issue of *Journal of Medicinal Chemistry* is dedicated to Ralph F. Hirschmann in honor of his scientific achievements and his leadership in the field of medicinal chemistry over the past 40 years. Twenty-eight papers, written by former associates at Merck and by other scientists from the United States who were influenced by his work, are published here. These papers describe a remarkable range of achievements made possible by the creative use of modern medicinal chemical methods. These achievements illustrate the intellectual excitement found in medicinal chemistry today and reflect the impact Ralph Hirschmann has had on the field.

Ralph Hirschmann was born in Bavaria in 1922 and came to the United States with his parents in 1937. After receiving his baccalaureate degree at Oberlin College in 1943 and serving in the U.S. Army, he began graduate studies at the University of Wisconsin, where he received his Ph.D. degree in organic chemistry in 1950 under the guidance of Professor William S. Johnson. He began his career as a steroid chemist in the research laboratories of Merck, but soon showed his penchant for solving problems at the interface between chemistry and biology. A notable achievement during this phase of his career was his use of steroidal *N*-acetylglucosamides to direct anti-inflammatory agents to their site of action, thus demonstrating both the "prodrug" concept and the targeted drug release concept long before these terms entered our scientific vocabulary. In the 1960s with Robert G. Denkewalter, he led Merck's peptide group to the first total synthesis in solution of an enzyme, ribonuclease S. To achieve this goal, a new approach for the controlled synthesis of peptides was developed that used *N*-carboxy anhydrides (NCAs) both to protect and activate most of the amino acids, a method that now is utilized for the commercial preparation of enalapril and lisinopril. The NCA strategy was made possible only after very careful organic process research under his leadership identified the precise conditions needed for success. This careful mechanistic organic approach, which characterizes all of his research, was applied to the discovery of a number of amino acid protecting groups, most notably the *S*-acetamidomethyl (Acm) group. In each case the new protecting groups served to overcome significant limitations of the existing synthetic methods. Hirschmann's approach to peptide research influenced a generation of younger peptide chemists and the careful application of modern organic chemistry to peptide chemistry has become a modus operandi in this field.

In the early 1970s, Hirschmann began to assume increasing responsibility for management of research at Merck, which culminated in his appointment as Vice President and Senior Vice President of Basic Research from 1976 to 1984 and Senior Vice President of Chemistry from 1984 to 1987. One of his major contributions during this time was to identify new ways that medicinal chemists could facilitate biological discovery by applying chemistry at an early stage in the discovery process and to encourage this approach when it was proposed by others. Examples include the preparation of synthetic substrates for renin assays in the late 1960s so that the search for renin inhibitors could be initiated, the support of extramural angiotensin II receptor binding assays in the early 1970s in an early attempt to identify non-peptide AII receptor antagonists, and the use of an immobilized enzyme for the preparative synthesis of poly(I:C), an interferon inducer. I can also recall Ralph telling me around 1972 about his group's earlier attempts to prepare what have come to be called "peptide libraries", which he produced by allowing mixtures of NCAs to react in solution so as to generate vast numbers of peptide-derived pharmacophores. (In view of the numerous venture capital companies founded recently for that purpose, I wish I had paid more attention.) Another early contribution was to encourage the use of modern biophysical methods, especially NMR and X-ray crystallography. As Head of Medicinal Chemistry at West Point, he became a champion of computerized molecular modeling for drug discovery. He also championed the early use of molecular biological techniques and worked to integrate all of these emerging methods into the traditional medicinal chemical approaches. These examples help to illustrate the creative environment that was fostered at that time and that contributed to the concurrent discovery of VASOTEC, PRIMAXIN, IVOMEC, and MEVACOR while he led the chemical research enterprise.

The Hirschmann approach to medicinal chemistry integrates chemistry and biology to produce research and

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achievements not attainable by either discipline alone. What is most characteristic of his approach is the way the medicinal chemist is called upon to lead the discovery process by knowing how and when molecular modifications and synthesis of small or macromolecules can be used to facilitate the discovery process. To achieve this, the medicinal chemist must have a deep understanding of the mechanistic and structural biochemistry involved.

Ralph Hirschmann's scientific contributions to peptide chemistry and medicinal chemistry have been recognized by the American Peptide Society (Alan E. Pierce Award in 1983), the American Chemical Society (Division of Medicinal Chemistry Award in 1986), and the New York Section of the ACS (Nichols Medal in 1988). He is a member of the American Academy of Arts and Sciences and a past Chairman of the Board of Trustees for the Gordon Research Conference. He served on the Medicinal Chemistry Study Section for NIH and on the Pimentel Committee of the National Research Council, which published the report *Opportunities in Chemistry*. In 1989, Merck Sharp & Dohme established the ACS "Ralph S. Hirschmann Award in Peptide Chemistry" to pay lasting tribute to his achievements.

Upon his "retirement" from Merck Sharp & Dohme in 1987, he was appointed the first Research Professor of Chemistry at the University of Pennsylvania. He also is University Professor of Biomedical Research at Medical University of South Carolina and consults for several newer pharmaceutical endeavors. His return to academic research led to the discovery of novel peptidomimetics that act at somatostatin, Substance P, and other peptide receptors, suggesting that his keen insights into medicinal chemistry have not diminished. All of us who have contributed to this issue, as well as the many others who were unable to participate at this time, are delighted and wish him continued success.

Daniel H. Rich, *Guest Editor*
University of Wisconsin—Madison