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CARL NIEMANN

1908—1964

A Biographical Memoir by
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Carl Heinemann

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BY JOHN D. ROBERTS

IN AN ERA when professors of scientific subjects are under heavy pressures to contribute simultaneously to research, to education, to the advancement of the scientific society, and to the advancement of society in general, the life of Carl Niemann provides a fine example of how individualism, tempered and disciplined by responsibility, can lead to an enviable balance of achievements—so much so as to merit description of the man as an “ideal” academic scientist.

Carl Niemann was born on July 6, 1908, in St. Louis, Missouri, the only child of Julius Henry and Ella Danner Niemann. Julius Niemann was a salesman for a local brewery, a large man, fond of hunting, and a strict disciplinarian. Carl took after his mother, to some degree in appearance, but more in having an outwardly quiet temperament, an instinctive feeling for others, and a high degree of manual dexterity. The available accounts indicate that his early childhood was not unusual, although it seems that visits to the households of his mother's relatives often provided a welcome relief from the strictness with which his father regulated his homelife. On entering Cleveland High School in St. Louis, Carl was so competent at carpentry that he started in the manual training rather than the college preparatory curriculum. His orientation changed when he took

high school chemistry, as a result of which his interest was kindled to the point that he set up a rather sizable laboratory in his home basement. In this he was encouraged by his uncle, George Danner, who procured chemicals and supplies for him from the Meyer Brothers Drug Company. A crisis seems to have occurred after his graduation from high school because his father wanted him to enroll in business school to learn accounting and this was far from his own inclinations. The intervention of his uncle seems to have been decisive in helping him move toward chemistry by way of arranging with Edgar Queeny, president and founder of Monsanto Chemical Company as well as a onetime employee of Meyer Brothers Drug Company, for a trial position as chemist in the Monsanto laboratories. During this period Niemann worked in his basement laboratory on weekends and attended Washington University night school. In 1926 he entered the University of Wisconsin, but when his father died in 1928 he came back to St. Louis to work another year for Monsanto while helping his mother adjust to their new circumstances.

The research career of Carl Niemann began after his return to Wisconsin in 1929 when he started his association with Karl Paul Link. The next five years, in his progression from undergraduate, to graduate student, to postdoctoral fellow, led to thirteen papers, all concerned with carbohydrates—being principally fundamental studies of the chemistry of uronic acids, substances which occur naturally along with cellulose and starch. Although he and Link were rather different types, they worked very well together and formed a lasting friendship. The last year of Niemann's Wisconsin career began with his marriage to Mary Parkhurst on August 15, 1934. Then, in 1935, the young couple moved to New York for a two-year stay at the Rockefeller Institute. Here, in collaboration with Max Bergmann, Niemann started the work on proteins and enzymes which was to become his major scientific interest.

It was an exciting time in protein research. Accurate analyses of the amino acid compositions of reasonably pure proteins were just being obtained, and Niemann and Bergmann were imbued with the notion that there could be a high degree of regularity in protein composition based on simple numerical rules. Thus, in several papers published between 1936 and 1939, they advocated that the numbers of amino acids in proteins might in general follow a stoichiometric law of $2^m \times 3^n$ where m and n are positive whole numbers. The published discussion of a paper given by Niemann on this subject at a 1938 Cold Spring Harbor symposium indicates substantial differences of opinion on the validity of the hypothesis, with Wrinch, White, and Mirsky in opposition. Niemann's replies were at all times beautifully phrased but had to be largely defensive because of the scarcity of accurate composition data.

Niemann's last general paper on protein structure was published with Linus Pauling in 1939 and was a scathing (and effective) critique of the "cyclol" theory of protein structure proposed by F. C. Frank in 1933 and developed subsequently in detail by D. M. Wrinch. The general question was whether peptide chains are bonded to one another by hydrogen bonds or by addition of N-H of one chain to C=O of another; and the particular question was whether X-ray diffraction data obtained by Dorothy Crowfoot (Hodgkins) on zinc insulin could be interpreted as was done by Wrinch and Irving Langmuir, in favor of a cyclol-type structure. In the paper with Pauling, not much is said about the stoichiometry of amino acids in proteins and one has the feeling that Niemann was no longer prepared to defend the thesis that his earlier hypothesis was a general one. Pauling and Niemann did point out that, if the number of the residues along the main chain in simple proteins turns out to be 288 ($2^5 \times 3^2$), the reason must be biochemical in origin rather than deriving from a physical factor providing special stability for 288 residues.

After two years at the Rockefeller Institute, Niemann accepted a position as assistant professor of organic chemistry at the California Institute of Technology but took a leave of absence to spend a year at University College Hospital Medical School in London as a Rockefeller Foundation Fellow. Then, in 1937, he and his wife moved to Pasadena, where he was to spend the rest of his life.

By the time Niemann came to Caltech, the Gates and Crellin Laboratories, under the leadership first of A. A. Noyes and then of Linus Pauling, had become world famous in physical and inorganic chemistry. Among the professors, besides Pauling, were William N. Lacey, Richard C. Tolman, Roscoe G. Dickinson, and Don M. Yost, and at Niemann's rank as assistant professor were also Arnold O. Beckman, Richard M. Badger, and Ernest H. Swift. Up to 1937, almost all of the teaching and research in organic chemistry was carried on by Howard J. Lucas, who was an excellent researcher and a leader in America in developing the new field of physical organic chemistry. Niemann's appointment was made possible by a special grant from the Rockefeller Foundation to provide more balance in the organic area and fitted in with Pauling's growing interest in molecular biology.

During his first few years at Caltech, Niemann carried a moderate teaching load—five one-term courses each year—and began a program of research on compounds related to thyroxine, the thyroid principle; on the structure of sphingosine, a prevalent component of nerve tissue; and on histamine action. The work in thyroxine and histamine action was aimed at discovering the structural requirements for biological activity.

Shortly after the United States entered World War II, Niemann was made an official investigator for the National Defense Research Council and in partnership with Ernest H. Swift carried on an extensive research program on analytical methods for

chemical warfare agents. Particular emphasis was placed on procedures for rapid identification of new war gases which it was feared might be suddenly introduced on the battlefields or in cities by aerial attack. The work was carried on for Division 9 of the NDRC and was highly successful although, fortunately, its practical application in wartime work was primarily for identification of war gases manufactured by the Germans and uncovered by our invasion forces but not actually used in combat. The later stages of the NDRC work involved intensive field trials and Niemann spent much time at testing stations in Panama and Florida. Finally, in 1944 he served for several months as consultant to the General Headquarters Staff in the Southwest Pacific area. He was awarded a Presidential Certificate of Merit for his contributions to the war effort.

The postwar phase of Niemann's work was marked by the beginnings of his research on the action of the protolytic enzyme, α -chymotrypsin, one of the most fascinating, and as yet unsolved, problems of organic chemistry. The choice of this enzyme for study was not due to luck or a haphazard guess. Niemann recognized that α -chymotrypsin, although an extremely complex substance of unknown structure, was at least relatively stable and reproducible with a rather nonspecific mode of action. The relative nonspecificity of action meant that wholly artificial substances could be "digested" by the enzyme, and through measurements of the rates of these digestive-type processes, in relation to the structures of the substrates supplied, it was hoped to discover how the enzyme worked. The procedure was an essentially topological one and, in fact, something like trying to deduce the eating apparatus and habits of a creature living in a cave by throwing in variously shaped pieces of different kinds of foods and seeing which are consumed most readily, if at all.

The work in α -chymotrypsin led to more than ninety research

publications in about fifteen years, one of the most important being a summary article published in *Science* in March 1964. Niemann's view of his achievements in the research on chymotrypsin was a characteristically modest one and was laid out in the conclusion of his article in *Science*:

"In 1906 Fischer described the approach to elucidation of the chemical synthesis of a protein in terms that might be applied today to elucidation of the mechanism of action of an enzyme. The approach, he said, is that of a pedestrian who 'seeks his way step by step with careful attentiveness and who must examine many roads until he has found the right one. On his long and troublesome travels, not only does he learn to recognize completely the geography and topography of the country, but also he becomes intimate with the tongue and culture of its inhabitants. When he finally has reached his goal, he is able to locate himself properly in every corner of the country and this will be possible for other people also if he writes a book about it.' As for elucidation of the mechanism of action of α -chymotrypsin, the pedestrian has barely begun his journey, and this review is his first letter home."

The spirit in which Niemann's work on chymotrypsin-induced reactions was carried out was almost as important as the specific achievements. There was no striving for a quick, clever solution to the mechanistic problem but instead the approach was meticulously designed to give a broad spectrum of results with which theoretical approaches could be tested. The emphasis was on the determination of accurate values of experimental reaction-rate parameters characteristic of a variety of substrates and, particularly in the early stages, there was little attempt to discuss the mechanistic implications of the results.

The typical thoroughness of Niemann's work is illustrated by a statement from his first major paper with Huang on chymotrypsin in 1951:

"In this study, consideration was given to (a) the possibility of interaction of the enzyme with the buffer components, (b) the dependence of the activity of the enzyme on the pH of the reaction system, (c) the possibility of inhibition of the hydrolytic reaction by one or both of the hydrolysis products, (d) the development of suitable rate expressions and the determination of rate constants and (e) the possibility of the inhibition of the hydrolysis of the above substrates by their D-antipodes."

Later papers developed other important aspects of chymotrypsin methodology, including ways of analyzing the rate curves and the effects on the rates of salts, nonaqueous solvents, inhibitors, dimerization of the enzyme, and even adsorption of the enzyme on the walls of the containers. These studies were especially significant in showing the limitations which have to be placed on comparisons drawn between results collected under different experimental conditions.

Niemann had very clear ideas about the practice of laboratory work. Although several generations of students used essentially the same instruments and methods, he refused to set up standard procedures. It was his conviction that absence of standard procedure was some protection against determinate errors which otherwise might avoid detection. In addition, he would not hire technicians to do any of the work although some of the rate measurements seemed repetitive to his co-workers.

A considerable breakthrough came in 1960 with the discovery that the normal relative stereospecificity of chymotrypsin which markedly favors hydrolysis of L- over D-amino acid derivatives could be overturned by suitable substituent groups. The consequences of this discovery were developed in considerable detail by Niemann and Hein. Of particular importance was the concept of "wrong-way" binding which emphasizes that enzyme-substrate complexes may be combined at the active site in such a way as to be unproductive for the normal hydrolysis reaction.

The value of this hypothesis lies in its ability to explain why there has been no clear correlation between how firmly substrates of different structures are bound by the enzyme and the rates at which they hydrolyze. The hypothesis was further developed by assuming that relative affinities could be assigned to the substituent groups which are found in different substrates for various interaction sites in the enzyme—the aim being to permit prediction of the favored orientation of a substrate at the active site which, of course, might or might not be favorable for hydrolysis.

These ideas were not developed without opposition, and many of the Niemann papers either involved long battles with unsympathetic referees or contained detailed defenses of ideas attacked by critics. In these, Niemann was unfailingly courteous, but his command of language was such that a courteous reply could be incisively, if not stingingly, to the point.

The professional stature of a scientist can usually be established rather well from his published work provided reasonable account is taken of the mood of the times in which it was accomplished. Personal stature is often more ephemeral, having to be based on testimony deriving from recollections of close, or not so close, associates in the absence of soul-searching autobiographical material. Carl Niemann was not one who left a mass of heterogeneous memorabilia for posterity to use in constructing a personal image. Although he died wholly unexpectedly, just before he was to depart on a European vacation, his correspondence files were almost completely bare, it being his custom after answering a letter to consign both the letter and the carbon of his reply to the wastebasket. In striking contrast, he had very complete files of his reprints and manuscripts, often including early as well as final versions of his papers. There can be no clearer message of what the man himself regarded as important.

Carl Niemann in middle life was a good-looking man of somewhat more than medium height with an unostentatious, ur-

bane appearance and an unusually pleasant and calm speaking voice. He was not a man who bustled or became outwardly excited and yet, in talking with him, one could sense a considerable inner tension and drive. He was a highly effective person. His less efficient colleagues never ceased to marvel at how he worked day after day (and many evenings) with his office door wide open. He always had a cheerful welcome for anyone wishing to consult with him, but as soon as the business at hand was over, one sensed he was, while remaining completely polite, beginning to think about the next phrase of the manuscript before him. He was a craftsman of scientific writing; each paper was written, rewritten, and rewritten again before he was satisfied. He usually worked on one thing at a time—in the midst of an important paper, letters went unanswered, forms remained uncompleted; only the business one could transact with him orally made much headway.

A picture of Niemann as a strongly independent, research-centered scientist would be quite incomplete. He was tenaciously independent, even if quietly so, but at the same time he believed that independence in an academic environment carried with it the obligation to be responsible, and in every commitment he took on he was always completely responsible. He disliked administrative work but he was a fine administrator, having for many years heavy responsibility as the Chairman of the Divisional Graduate Committee. It was administration on his own terms—he had independence of action in an important but limited area and, furthermore, the work was largely seasonal, leaving him with much free time for his research. In addition, he was in almost constant demand for service on Caltech committees and he was exceptionally effective in such work, not only because of his sensitivity to other people's ideas and difficulties, but also because of his rare sense of humor which was particularly useful for reducing arguments to their proper perspective.

Niemann was elected to the National Academy of Sciences

in 1952 and was very interested in its affairs. He attended almost every annual meeting and served during the last two years before his death as Chairman of the Chemistry Section. For ten years he was a member of the Editorial Board of *Organic Reactions*, an annual collection of review chapters on important synthetic methods. It was a tedious job but was suited to his habits by virtue of being seasonal and was rewarding through association with the other editors, particularly Roger Adams of the University of Illinois, who founded the series in 1942.

Niemann had many interests outside of his scientific work. He read widely and had a detailed knowledge of the history of the Civil War. He loved the outdoors and enjoyed traveling with his wife and two daughters. Under the guidance of his good friend, Carl S. Marvel, Niemann became an ardent and expert birdwatcher, and at one time or another he sighted most of the important species of the land and water birds of the United States.

Carl Niemann was a scholar and a scientist of the first rank. He was devoted to the principles of both academic freedom and academic responsibility. His legacy is a corps of superbly trained and loyal students, a deeper understanding of the chemistry of life, and the many results of his efforts on behalf of the California Institute of Technology. He died very suddenly at the height of his career. His many friends will not soon forget the way in which he enriched their lives and the scientific profession.

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KEY TO ABBREVIATIONS

Anal. Chem. = Analytical Chemistry

Arch. Biochem. = Archives of Biochemistry

Arch. Biochem. Biophys. = Archives of Biochemistry and Biophysics

Biochim. Biophys. Acta = Biochimica et Biophysica Acta

Cold Spring Harbor Symp. Quant. Biol. = Cold Spring Harbor Symposia
on Quantitative Biology

J. Am. Chem. Soc. = Journal of the American Chemical Society

J. Biol. Chem. = Journal of Biological Chemistry

J. Ind. Eng. Chem., Anal. Ed. = Journal of Industrial and Engineering
Chemistry, Analytical Edition

J. Nat. Cancer Inst. = Journal of the National Cancer Institute

J. Org. Chem. = Journal of Organic Chemistry

Proc. Nat. Acad. Sci. = Proceedings of the National Academy of Sciences

Proc. Soc. Exp. Biol. Med. = Proceedings of the Society for Experimental
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