



**Hans Neurath**

1909–2002

BIOGRAPHICAL

*Memiors*

*A Biographical Memoir by  
Edmond H. Fischer  
and Earl W. Davie*

©2013 National Academy of Sciences.  
Any opinions expressed in this memoir are  
those of the authors and do not  
necessarily reflect the views of the  
National Academy of Sciences.



NATIONAL ACADEMY OF SCIENCES

# HANS NEURATH

October 29, 1909–April 2, 2002

Elected to the NAS, 1961

Hans Neurath, one of the foremost scientists of the 20th century and a man considered one of the founding fathers of modern protein science, passed away on Friday, April 2, 2002.

He was the founding chairman of the Department of Biochemistry at the University of Washington School of Medicine in Seattle. After his administrative retirement as department chairman, he became the associate director of research at the Fred Hutchinson Cancer Research Center in Seattle and then, after reaching emeritus status at the University of Washington, he became director of the German Cancer Research Center in Heidelberg, Germany. He returned to the University of Washington two years later.

Hans was the founding editor of *Biochemistry*, one of the most prestigious journals in the field and the flagship of some twenty journals published by the American Chemical Society. In 1992, at age 81, he founded *Protein Science*, a journal of the Protein Society, and he served as its editor-in-chief until 1998. Furthermore, he edited the most comprehensive treatise on proteins, *The Proteins*.



A handwritten signature of Hans Neurath in black ink, written in a cursive style.

By Edmond H. Fischer  
and Earl W. Davie

**H**ans was an avid mountain climber and skier and a first-class pianist. He will be remembered as the person who contributed the most to the field of serine proteases and zymogen activation and, in collaboration with Bert Vallee, to the field of metallo-protein research.

## Early years in Vienna (1909–1935)

Hans Neurath was born in Vienna, Austria, in 1909, the youngest of a family of four children. His father was a pediatrician and associate professor of pediatrics at the University of Vienna while his mother volunteered for the Red Cross during World War I. When he was very young, he was already attracted to chemistry and chose that field as his main subject in school.

Hans attended the University of Vienna, working toward a PhD in chemistry. When it came time to select a thesis advisor, rather than continuing in the area of physical chemistry in which he had previously been trained, he selected Wolfgang Pauli, Sr. (the father of the Nobel laureate physicist Wolfgang Pauli), who headed the Institute of Colloid Chemistry, which was housed in an old apartment building in the back of the university's Institute of Biochemistry.

“Colloids” in those days denoted suspensions of fine particles in a continuous medium that included proteins. His interest in proteins was stimulated while proofreading the monograph by Pauli and Valko entitled *Die Kolloidchemie der Eiweisskoerper* that appeared in 1933, a forerunner of the book by Cohn and Edsall, *Proteins, Amino Acids, and Peptides as Ions and Dipolar Ions*.

This was an era that preceded the recognition of proteins as macromolecules of defined amino acid sequence, as well as the recognition of their three-dimensional structure. As all protein chemistry text books published in those days show, understanding was limited to the physical chemistry of amino acids and peptides, their ionization, solubility, denaturation, viscosity, etc., and therefore, proteins were of minor interest to biochemists.

After completing his doctorate in 1933, Hans spent a year as a voluntary assistant in Pauli's institute before joining Frederick Donnan's group in the Chemistry Department at the University of London, supported by a loan from the Academic Assistance Council. With N. K. Adams, he worked on the surface properties of proteins and fatty acids as models of biological membranes, measuring the surface pressure and potential of serum and egg albumin when spread as a thin film.

He returned temporarily to Vienna as a way station before emigrating to the United States, a decision spurred by the increasing black clouds that loomed on the horizon due to the imminent Anschluss of Austria by Hitler's Germany.

### **Early years in the United States (1935–1950)**

Once in the United States, and with the help of Henry Bull, he obtained a research fellowship that allowed him to join the department of Ross A. Gortner, head of the Division of Agricultural Biochemistry at the University of Minnesota in St. Paul. On the way to Minnesota, Hans visited the laboratories of E. J. Cohn at Harvard, where he met John Edsall, Jesse Greenstein, and Larry Oncley, all top scientists in the field of proteins and lipoproteins. In Bull's laboratory, Hans worked on the surface denaturation of proteins including egg albumin, which he had to prepare himself.

Hans's starting research budget contributed by the department at Duke was \$200, but his experimental work received a major boost when he was awarded an annual grant of \$3,000, which was initially for three years and subsequently increased and extended to five and then ten years.

In 1936, he received a two-year appointment as a George Fisher Baker fellow and instructor in the Chemistry Department at Cornell University in Ithaca, New York. As he recalled: "These two years at Cornell were among the most stimulating experiences of my academic and scientific career in an environment that brought me in contact with many famous and distinguished chemists." Indeed, it is there that Hans met people like Linus Pauling, Peter Debye, N.V. Sidgwick of Oxford University, and Karl Landsteiner of the Rockefeller Institute for Medical Research.

His prime responsibility at Cornell was to carry out research on topics of his own choosing, which happened to be the hydrodynamic properties of proteins of particular interest: their size and shape and how the parameters obtained might be altered by their denaturation. Among other proteins, he worked on tobacco mosaic virus protein and bushy stunt virus protein, both provided by Wendell Stanley and his graduate assistant Howard Schachman, who were then at the Rockefeller Institute at Princeton University.

Through a distant friend, Hans even had the exciting experience to pay a visit to Albert Einstein at his home in Princeton, New Jersey. He had been using Einstein's equation to calculate the molecular weight of proteins and had an opportunity to discuss this with Einstein. He considered this visit one of the most memorable events in his life.

In 1938, Hans was offered an assistant professorship in the Biochemistry Department at Duke University School of Medicine in Durham, North Carolina, which he joined at about the same time as Phil Handler. The two men soon became competitors and friends.

Hans's starting research budget contributed by the department at Duke was \$200, but his experimental work received a major boost when he was awarded an annual grant of \$3,000, which was initially for three years and subsequently increased and extended to five and then ten years.

During the following twelve years, Hans established a research program in physical chemistry of proteins, first supported by the Rockefeller Foundation and later also by

the National Institutes of Health, which had just started an extramural grant program. He was awarded \$12,000 to purchase an air-driven ultracentrifuge. Together with Frank Putnam, who joined him as a postdoctoral fellow (and later became a recognized authority in immunology), and with several graduate students, he undertook his well-noted studies on protein denaturation. With funds from the Lederle division of the American Cyanamid Company, he equipped his laboratory with the latest scientific instruments, including diffusion and electrophoresis apparatus. He rose through the ranks to professor of physical chemistry.

Then came the war years. He was requested to continue the education of medical students and his group was selected to participate in a multi-laboratory project to develop methods for the elimination of false-positive reactions in the serologic diagnosis of syphilis, a problem of concern to the military. Indeed, false-positive reactions were often associated with malaria, leprosy, and other bacterial and viral infections.

The method he ultimately developed was tested on hundreds of samples supplied by military installations and was eventually published as a series of articles in the American Journal of Syphilis and Venereal Diseases. The method was subsequently superseded by a more specific immunological procedure.

It is at Duke that, besides performing some chamber music (including giving with Ernest Nelson, professor of history, a piano four-hands concert that was open to the public and served as a precursor to the chamber music series of Duke), he presented experimental proof with Frank Putnam that Linus Pauling was in error in proposing that antibodies and normal globulins differed in shape rather than in chemical structure. But then, realizing that antibodies were not defined well enough to be used as models for studying the structure-to-function relationship of proteins, he turned his attention toward proteolytic enzymes, because they were available in large quantities and in high purity.

Indeed, Northrop, Kunitz, and Herriott had just crystallized trypsin, chymotrypsin, and carboxypeptidase; and Bergman, Fruton, and Niemann had discovered that low-molecular-weight synthetic peptides could serve as substrates for these enzymes. This provided a quantitative method to measure their enzymatic activity and relate their chemical structure to their biological function.

Hans had just initiated studies with this method and had moved into a new house (designed and built according to his specifications) when he received an offer to chair the newly established Department of Biochemistry at the University of Washington in Seattle.

**Department of Biochemistry,  
University of Washington (1950–1975)**

There is no question that the next fifty years he spent at the University of Washington were the most exciting and scientifically productive of his entire academic career. Using the most recent methods of protein chemistry that had been developed, he undertook a seminal study of the pancreatic serine proteases trypsin, chymotrypsin, and carboxypeptidase, focusing in particular on the mechanism by which the zymogens (the inactive precursors of the enzymes) were activated.

Indeed, with a few exceptions, zymogen activation requires the cleavage of primary peptide bonds. This allows the separation of a peptide, which, when removed, leads to the activation of the enzyme.

With Earl Davie, he isolated and determined the sequence of the hexapeptide that masks the activity of trypsinogen and, a couple of years later, elucidated the mechanism of activation of chymotrypsin. Such types of consecutive zymogen activations are involved in the initiation and regulation of complex pathways such as the blood coagulation cascade, as demonstrated later by Davie at Case Western Reserve University. The amino acid sequence of the catalytic sites of both trypsin and chymotrypsin was determined after labeling the enzymes with diisopropyl-phosphorofluoridate.

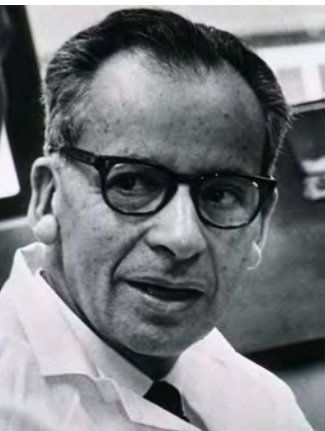
When Hans initiated his studies on pancreatic carboxypeptidase, it was thought that magnesium might be the cofactor for the enzyme. But a collaborative study undertaken with Bert Vallee of Harvard showed that the enzyme was actually a zinc-metalloexopeptidase. Indeed, Vallee had constructed a flame-spectrometer that allowed him to detect and measure trace quantities of metals in biological preparations. The establishment of this novel family of proteases marked the opening of an entire new field of investigation: that of the zinc-metalloproteases.

With Ken Walsh and Ralph Bradshaw, Hans set up a remarkably effective protein-sequencing laboratory with which they could determine the primary structure of a variety of proteins. Under Walsh's leadership and with the help of first-class collaborators such as Ko Titani, this unit became the basis for many collaborative projects undertaken with various groups within the department.

By extending those studies to proteases obtained from lower species, Hans and his group could provide experimental proof that the various serine proteases were structurally related and, therefore, had derived from a common origin. This firmly established the



concept of structural homology that exists among these enzymes, stimulating further his interest in the evolution of proteins and their complex organization into functional domains.



Hans Neurath,  
undated photo.

Mapping the course of their evolution allowed classification of proteins into defined sub-groups by David Blow and Brian Hartley. The detailed structural characteristics of proteins and their mechanism of action involving a substrate-binding pocket and a “charge relay system” were then established with the help of the x-ray crystallographers such as Robert Huber.

After twenty-five years of service as head of the department, Hans reached administrative retirement in 1975 and assumed the part-time position of scientific director of the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, while continuing his research program on proteins and proteolytic enzymes at the university. He recruited a number of outstanding basic scientists at the FHCRC, some of whom, in the meantime, reached positions of eminence at the center and elsewhere.

### **German Cancer Research Center (Deutsches Krebsforschungszentrum) (1980–1981)**

At age 70, Hans reached mandatory retirement, as was the case in those days. He became professor emeritus, thereby losing the privilege of applying for his own salary and research grants. Even though the faculty of the Department of Biochemistry, supported by many friends, including several Nobel laureates, had recommended unanimously to the university administration that his employment be continued as a research professor, this request was denied on the grounds that it would create a precedent that the university was unwilling to establish. This lack of support from his own university must have been a contributing factor for him to accept a position that was offered abroad.

Following an international meeting Hans attended in Heidelberg, Germany, in 1979, he was offered the position of scientific director of the Deutsches Krebsforschungszentrum (DKFZ) in Heidelberg. In spite of many words of caution from friends who were well aware of the internal discord and strife that plagued the center, he accepted the challenge. His nomination became highly controversial because he did not belong to the

inner clique of the center and he was unwilling to compromise his standards of scientific quality and merit.

The discord came to a boil when the director of the Institute for Nuclear Medicine (a man who had also been his predecessor as scientific director of DKFZ) tried to introduce neutron radiation for the treatment of cancer, even though he knew that there was no experimental evidence to justify this kind of therapy. Hans ordered that this procedure be discontinued for lack of evidence validating its effectiveness. This triggered an avalanche of protests and a cabal of vicious accusations in the press, to such an extent that the incident became the subject on an inquiry by the German Parliament's committee on research.

As a result, the person involved was forced to resign, but Hans, who by that time felt that enough was enough, tendered his resignation. However, he did feel satisfied that his personal efforts and frustrations had not been in vain because the Federal Ministry for Research and Technology appointed an international blue ribbon commission that recommended a total overhaul of the center. Today, the DKFZ has become a world-class scientific institution under the sure guidance of Harald zur Hausen, whose work on the relationship between the human papillomavirus and cervical cancer earned him the Nobel Prize in Physiology or Medicine in 2008.

**Scientific editing:  
*The Proteins* (1953–1982),  
*Biochemistry* (1961–1991),  
 and *Protein Science* (1992–1998)**

Upon first joining the Department of Biochemistry at the University of Washington, one of the first things Hans did was to assume, together with Kenneth Bailey of the Department of Biochemistry at the University of Cambridge, the editorship of *The Proteins*, a four-volume treatise that presented a comprehensive and integrated account of the chemical, physical, and biological properties of proteins. The first volume, with chapters provided by the top experts in the field, appeared in 1953. The second edition, edited by Hans alone after the untimely death of Kenneth Bailey, contained five volumes; while the third and last edition, edited with Robert L. Hill, was published between 1975 and 1982. These books represented an up-to-date and authoritative overview of protein structure and function and undoubtedly contributed to Hans's worldwide fame in this area of research.



In 1961, Hans was invited by the editorial committee of the American Chemical Society (ACS) to become the founding editor of a new journal in the field of biochemistry. The ACS was already publishing 20 chemical journals, but none in biochemistry. The new journal could serve as an alternative to the *Journal of Biological Chemistry*, placing greater emphasis on the chemical aspects of proteins and enzymology. After some hesitation about adding editorial responsibilities to his already heavy duties as chairman of the department at the university and leader of a relatively large research program, but with the possibility of introducing innovations into scientific publications, he accepted the position.

The new journal was simply named *Biochemistry*. Much of the success of the journal came from the fact that the editorial office was installed within the Department of Biochemistry and that the editor-in-chief and all five associate editors were in the same department. Therefore, they could review all incoming manuscripts day-by-day (they met daily from 1:00 to 2:30 pm) and could jointly reach editorial decisions.

Hans retired from his editorship in 1991 and the editorial office moved to Duke University when Gordon Hammes became editor-in-chief. The journal had grown from 1,200 pages published in the first volume (1962) to 9,200 pages when Hammes took over.

A year later, in 1992, the Protein Society decided to publish its own journal and asked Hans to become its founding editor, which he agreed to do. This gave him an opportunity to combine his lifelong interest in the study of proteins with his experience in scientific publication. The new journal was called *Protein Science* and it immediately acquired considerable success, increasing the Protein Society from approximately 1,800 to 3,000 members.

## Epilogue

In the last few years, in spite of an increasingly debilitating disease, Hans came to his office every day. He was still keenly interested in the affairs of the department and followed the research literature like a hawk. Every once in a while he would call us, saying, "I have something important to discuss. May I see you?" And we would reply, "Hans, our door is always open. Please come down anytime." And he would arrive, look around, take a chair, and say, "So, what's new?"

**ACKNOWLEDGEMENTS**

Most of this biographical memoir has been derived from various works written by Hans Neurath himself. These include:

- Reflections of an editor. (1986) *Chemtech* 16:87–91.
- Proteolytic enzymes past and present: the second golden era. (1994) *Protein Science* 3:1734–1739.
- “The Golden Years of Protein Science” (Banquet address at the first European symposium of the Protein Society in Davos, Switzerland, May 30, 1995). Published in *Protein Science* (1995) 4:1939–1943.
- From colloids to proteases. (2000) *Biochim. Biophys. Acta* 1477:7–15.
- From proteases to proteomics. (2001) *Protein Science* 10:892–904.

Essentially, then, the account presented here has been written as much as possible on the basis of Hans’s own words.

## SELECTED BIBLIOGRAPHY

- 1936 The influence of denaturation on the spreading of proteins on a water surface. *J. Phys. Chem.* 40:361–368.
- 1939 With A. M. Saum. The denaturation of serum albumin, diffusion and viscosity measurements of serum albumin in the presence of urea. *J. Biol. Chem.* 128:347–362.
- 1940 With G. R. Cooper. The apparent molecular shape and molecular weight of proteins, from viscosity and diffusion measurements. *J. Am. Chem. Soc.* 62:2248–2249.
- 1944 With J. P. Greenstein, F. W. Putnam, and J. O. Erickson. The chemistry of protein denaturation. *Chem. Rev.* 34:157–265.
- 1946 With F. W. Putnam. Chemical and enzymatic properties of crystalline carboxypeptidase. *J. Biol. Chem.* 166:603–619.
- 1948 With G. W. Schwert, S. Kaufman, and J. E. Snoke. The specific esterase activity of trypsin. *J. Biol. Chem.* 172:221–239.
- With J. E. Snoke and G. W. Schwert. The specific esterase activity of carboxypeptidase. *J. Biol. Chem.* 175:7–13.
- 1949 With S. Kaufman and G. W. Schwert. The specific peptidase and esterase activities of chymotrypsin. *J. Biol. Chem.* 177:793–814.
- With J. E. Snoke. Structural requirements of specific substrates for chymotrypsin. I. The contribution of the secondary peptide bond. *Arch. Biochem.* 21:351–362.
- 1950 With G. W. Schwert. The mode of action of the crystalline pancreatic proteolytic enzymes. *Chem. Rev.* 46:69–153.
- With J. E. Snoke. The proteolytic activity of striated rabbit muscle. *J. Biol. Chem.* 187:127–135.
- 1953 With E. W. Davie. Identification of the peptide split from trypsinogen during autocatalytic activation. *Biochim. Biophys. Acta.* 11:442.
- 1954 With F. R. Bettelheim. Tyrosine-O-sulfate in a peptide from fibrinogen. *J. Am. Chem. Soc.* 76:2838–2839.
- With B. L. Vallee. Carboxypeptidase, a zinc metalloprotein. *J. Am. Chem. Soc.* 76:5006–5007.

- 1955 With E. W. Davie. Identification of a peptide released during autocatalytic activation of trypsinogen. *J. Biol. Chem.* 212:515–530.
- With B. L. Vallee. Carboxypeptidase, a zinc metalloenzyme. *J. Biol. Chem.* 217:253–261.
- With W. J. Dreyer. The activation of chymotrypsinogen, isolation and identification of a peptide liberated during activation. *J. Biol. Chem.* 217:527–529.
- 1956 With P. J. Keller and E. Cohen. Purification and properties of procarboxypeptidase. *J. Biol. Chem.* 223:457–467.
- 1958 With G. H. Dixon and D. L. Kauffman. Amino acid sequence in the region of diisopropyl phosphoryl binding in dip-trypsin. *J. Am. Chem. Soc.* 80:1260–1261.
- 1960 With B. S. Hartley. Proteolytic enzymes. *Ann. Rev. Biochem.* 29:45–72.
- 1961 With J. R. Brown, D. J. Cox, R. N. Greenshields, K. A. Walsh, and M. Yamasaki. The chemical structure and enzymatic functions of bovine procarboxypeptidase A. *Proc. Natl. Acad. Sci. U.S.A.* 47:1554–1567.
- 1962 With E. Wintersberger and D. J. Cox. Bovine pancreatic procarboxypeptidase B. I. Isolation, properties, and activation. *Biochemistry* 1:1069–1078.
- 1964 Mechanism of zymogen activation. *Fed. Proc.* 23:1–7.
- 1969 With R. A. Bradshaw, L. H. Ericsson, and K. A. Walsh. The amino acid sequence of bovine carboxypeptidase A. *Proc. Natl. Acad. Sci. U.S.A.* 63:1389–1394.
- 1970 With R. A. Bradshaw. Evolution of proteolytic function. *Acc. Chem. Res.* 3:249–257.
- 1972 With K. Titani, M. A. Hermodson, L. H. Ericsson, and K. A. Walsh. Amino-acid sequence of thermolysin. *Nat. New Biol.* 238:35–37.
- With M. A. Hermodson, R. W. Kuhn, K. A. Walsh, N. Eriksen, and E. P. Benditt. The amino acid sequence of monkey amyloid protein A. *Biochemistry* 11:2934–2938.
- 1975 With K. Titani, L. H. Ericsson, and K. A. Walsh. Amino-acid sequence of bovine carboxypeptidase B. *Proc. Natl. Acad. Sci. U.S.A.* 72:1666–1670.

- 1977 With L. E. Anderson and K. A. Walsh. Bovine enterokinase: Purification, specificity, and some molecular properties. *Biochemistry* 16:3354–3360.
- With K. Titani, A. Koide, J. Hermann, L. H. Ericsson, S. Kumar, R. D. Wade, K. A. Walsh, E. H. Fischer. The complete amino acid sequence of rabbit muscle glycogen phosphorylase. *Proc. Natl. Acad. Sci. U.S.A.* 74:4762–4766.
- 1978 With K. Titani, A. Koide, L. H. Ericsson, S. Kumar, J. Hermann, R. D. Wade, K. A. Walsh, and E. H. Fischer. Sequence of carboxyl-terminal 492 residues of rabbit muscle glycogen phosphorylase including the pyridoxal 5'-phosphate binding site. *Biochemistry* 17:5680–5693.
- 1981 With S. Shoji, D. C. Parmelee, R. D. Wade, S. Kumar, L. H. Ericsson, K. A. Walsh, G. L. Long, J. G. Demaille, E. H. Fischer, and K. Titani. Complete amino acid sequence of the catalytic subunit of bovine cardiac muscle cyclic AMP-dependent protein kinase. *Proc. Natl. Acad. Sci. U.S.A.* 78:848–851.
- 1984 Evolution of proteolytic enzymes. *Science* 224:350–357.

---

Published since 1877, *Biographical Memoirs* are brief biographies of deceased National Academy of Sciences members, written by those who knew them or their work. These biographies provide personal and scholarly views of America's most distinguished researchers and a biographical history of U.S. science. *Biographical Memoirs* are freely available online at [www.nasonline.org/memoirs](http://www.nasonline.org/memoirs).