NATIONAL ACADEMY OF SCIENCES

HANS JOACHIM MÜLLER-EBERHARD
1927–1998

A Biographical Memoir by

ALEXANDER G. BEARN

Biographical Memoirs, VOLUME 79

PUBLISHED 2001 BY
THE NATIONAL ACADEMY PRESS
WASHINGTON, D.C.

Photo by Robert Smull, San Diego, California

HANS JOACHIM MÜLLER-EBERHARD

May 5, 1927-March 3, 1998

BY ALEXANDER G. BEARN

HANS JOACHIM MÜLLER-EBERHARD was born in Magdeburg, Germany, on May 5, 1927. There were no scientists in his family; his father, Adolph Müller, was a successful businessman. Two years after the outbreak of war, Hans's brother, Eberhard, was killed on the Russian front at the age of 21. Hans's father changed his family name to Müller-Eberhard after World War II to memorialize his son.

Although the atmosphere in the Müller-Eberhard household was not academic, there was much discussion of religious and political matters. His father was distinctly anti-Nazi and frequently propounded his conviction that a clique of criminals had assumed control of the government. He warned young Hans that he should not tell others about his views on Hitler, or he would be sent to a concentration camp. Hans was the only member of his class not to join the Hitler youth. When in later years a classmate asked him why he did not join, he said, simply, that he had no wish to associate with criminals.

Hans's class at school was sent to an anti-aircraft battery on the outskirts of Magdeburg where they replaced regular army units. These military activities decreased the time allowed for a normal education. At the age of 17 he was drafted into the army and sent to Hungary to serve on the

eastern front. Toward the close of the war he was captured by the Russians. He managed to escape the Russians, who were marching him eastward, by hiding in a ditch during the day and traveling by night through forests. He ultimately reached the Danube, where he was captured by the U.S. armed forces. He eventually rejoined his family in Altenau in the Harz Mountains, to which they had fled to avoid being in the Russian zone.

Although it was always Hans's intention to become a physician, he undertook formal studies to become a painter. While in Altenau, he also began studying with increasing pleasure textbooks of chemistry and physics. He augmented his meager financial resources by climbing fir trees to harvest the cones, a very hazardous occupation since the best seeds were frequently at the top of trees 10 to 15 meters tall. A number of Hans's fellow climbers were killed in falls.

In the spring of 1948 Hans entered the University of Göttingen to study medicine. His entry to medical school was contingent on his passing an examination, and so to further his education, he took classes at the Robert Koch Gymnasium in Clausthal-Zellerfeld, the birthplace of Robert Koch. It was a matter of quiet pleasure to Eberhard that some 40 years later he received the Robert Koch Medal in gold at the University of Bonn for a lifetime of achievement in medical research.

While in Altenau, Eberhard read widely in philosophy as well as science. By chance he read *Man the Unknown* by Alexis Carrel and first learned of the existence of the Rockefeller Institute for Medical Research. The intellectual atmosphere of Göttingen was of a high order. Hans's entry examination to the medical school had required an essay on the integration of Rutherford's model of the atom and Planck's quantum theory. In addition to his medical studies, he attended lectures given by major scientists at the univer-

sity. He was also greatly influenced by neo-Kantian Nicolai Hartmann, who lectured on philosophy. His reading companions included books by Hartmann, Heidegger, Jaspers, and the poetry of Rainer-Maria Rilke. In this way, the young Eberhard became a well-rounded intellectual, as well as a physician. To the regret of his friends, he seldom sketched or painted after becoming a physician. Nevertheless, on rare occasions he could be induced to sketch his colleagues, which he accomplished with great sensitivity and accuracy. A self-portrait was brilliantly executed in a fashion resembling the works of Augustus John.

During a medical tour of the United States, Eberhard's medical teacher Fritz Hartmann visited Henry Kunkel at the Rockefeller Institute, who in the course of conversation suggested that Hartmann might like to send one or two of his students to work at the Rockefeller in a postdoctoral capacity. Interestingly, Eberhard was not the first student recommended by Hartmann; his first recommendation was Hartwig Cleve, who declined but later came to work with Alexander G. Bearn at the Rockefeller Institute and became professor of human genetics at Munich. At the time, Kunkel was interested in the pathogenesis of liver disease, but was already focusing his lifelong attention on the gamma globulins of serum.

The environment was greatly to Eberhard's liking. For him, emerging from war-torn Germany, it was an effervescent community of scholars, both young and old. His initial studies at the Rockefeller concerned the carbohydrate component of gamma globulin; he discovered that the carbohydrate content of gamma globulin was entirely represented by the 19S component. This observation demolished the previous belief that 19S gamma globulin was merely an aggregate. This component of gamma globulin was later designated IGM. Eberhard also went on to prove that rheu-

matoid factor commonly present in the blood of patients with rheumatoid arthritis is a 19S antibody to 7S gamma globulin.

Returning to Göttingen after three years with Kunkel, Eberhard found the Department of Medicine lackadaisical and uninspiring. While at the Rockefeller, he had met Gunnar Wallanius of Sweden. Learning of Eberhard's mood upon his return to Germany, Wallanius invited him to spend some time with him in the Department of Clinical Chemistry in Uppsala, where he was alone in the laboratory and left to follow his own interests. In Uppsala Eberhard turned his attention to the nature of complement and determined the future direction of his research. While at Rockefeller he had reviewed the pertinent literature on complement, because complement, ill defined as it was, had in common with RF its combination with antigen-antibody complexes, as Michael Heidelberger had shown when he measured protein nitrogen.

In Uppsala the cardinal question, therefore, was: Can the serum protein be identified that combines with antigen-antibody complexes? In the 1950s Pierre Grabar at the Pasteur Institute in Paris had introduced immunoelectrophoresis as a new method to analyze complex mixtures of proteins. He decided to use this method to compare the pattern obtained of untreated human serum with that of serum incubated with an immune precipitate to activate complement. Careful inspection reproducibly revealed an electrophoretic shift of a minor component within the β-globulin region of the treated serum that was not occurring when the incubation was performed in the presence of chelating agent EDTA. He decided that the only way to elucidate the nature of the complement pathway was to identify in molecular detail the protein components that constitute the pathway. He called the component beta-1C globulin and its product B1A. After the isolation of both components, he obtained convincing

evidence that B1C-globulin was an essential constituent of the hemolytic complement system. Beta-1C was subsequently named C3c and the major physiological degradation product of C3 was called C3c. Working with C3, Eberhard identified an active enzyme called C3gb convertase, responsible for C3 activation. Later evidence indicated that C3 was involved in immunological mechanisms, and he showed that although the absence of C3 in the blood of individuals predisposed them to recurrent infections, surprisingly, such individuals do not develop autoimmune disease. Eberhard's studies on C3 were not universally accepted, but its existence was beyond doubt.

After two productive years in Uppsala, Eberhard rejoined Kunkel in 1959 at the Rockefeller University, where he stayed for the next four years. He returned briefly to Uppsala to defend successfully his Ph.D. thesis, and subsequently became the first docent of immunochemistry in Sweden. Using immunoelectrophoresis, Eberhard investigated the pattern obtained from normal serum with serum incubated with an immune precipitate to activate complement. After electrophoresis on a supporting median, which Eberhard did much to develop, a minor component in serum became evident. This shift in mobility was abolished by a chelating agent. The principal fragment was named BA and the fragment BC, later to be called C3 and C3A, respectively. Eberhard isolated and purified these proteins. The first demonstration and purification of a specific protein in the complement system, this was a critical event, for it was the beginning of a series of molecular identifications of the proteins of the complement system. As Maclyn McCarty noted in 1971 on presenting him the Helen Hay Whitney Duckett Award, "You have lifted complement out of its primordial slime."

Working with C3, Eberhard identified an active enzyme called C3B convertase, which converts C3 to C3A. Later

evidence indicated that C3 was involved in immunological mechanisms. He further showed that absence of C3 in the blood of individuals predisposed them to recurrent infections, although surprisingly, such individuals do not develop autoimmune disease.

After six years in the Kunkel laboratory, Eberhard was recruited by Frank Dixon to join the Scripps Clinic and Research Foundation in La Jolla. While at Scripps, Eberhard dissected still further the complement reaction and described its mode of action in exquisite molecular detail. His elegant Harvey Lecture in 1970 was one of the best and clearest summaries of the biology of complement at that time. His review in *Annual Reviews of Biochemistry* on the complement system also revealed the rigorous clarity of thought that was an essential feature of Eberhard's scientific papers, both oral and written. Eberhard, during his studies on complement, did much to elucidate the alternate pathway, identifying its initiating mechanisms and control. Eberhard was always generous in attributing certain aspects of the complement cascade to other workers in addition to himself.

At Scripps Eberhard was appointed to the Cecil H. and Ida M. Green Chair in Medical Research in 1972 and became chairman of the Department of Immunology in 1972 and associate director of research in 1978. He was also appointed adjunct professor in the Department of Pathology at the University of California at San Diego.

While in La Jolla, Eberhard was frequently invited to accept senior positions in molecular biology in Switzerland and Germany. Although tempted, he decided to remain at Scripps, where he was soon to be associate director of the institute as well as head of the Department of Immunology. One opportunity intrigued him, however; for more than two years he discussed the possibility of returning to Germany to head the Bernhard Nocht Institute for Tropical Disease in Ham-

burg, a distinguished institute that had not taken advantage of new developments in science. Eberhard had been given to understand that he would succeed Frank Dixon at the Scripps Institute, but this did not happen. Moreover, the new administration took the extraordinary action of removing him, without any discussion, from his named professorship. In 1988, with an atmosphere at Scripps increasingly hostile, he returned with mixed feelings to Germany, where he quickly invigorated the almost defunct Bernard Nocht Institute. The reinvigoration of this historically important institute was a formidable task. In reviving the institute, Eberhard showed administrative capabilities of a high order. The institute required considerable structural change, and Eberhard took a close interest in these architectural changes and brought to the table his sound aesthetic judgment. During his tenure, Eberhard obtained funds to create a new and modern library, a modern auditorium, and many major alterations in the existing laboratories.

Before Eberhard arrived there was very little communication between the institute's clinical and investigative sides. Indeed, there was much unprofitable bickering. This Eberhard was determined to change. His arrival resulted in a marked increase in morale and closer and more effective working relationships. The recruitment of young molecular biologists, virologists, protein chemists, and individuals well versed in DNA research was rapidly and successfully accomplished. Soon the institute became admired by colleagues in the field throughout the world. In addition, he greatly impressed the German government, which provided generously for the institute. The Federal Ministry of Research and Technology provided ample sums allowing for 30 "hard" money positions for scientists. In 1987 there were some 250 scientists; in 1995 there were more than 380. In addition, there were 61 students working for the Ph.D. degree.

Two research programs were particularly effective. The first dealt with the protozoan disease invasive ameobiasis, which is caused by *Entamoeba histolytica.* Only 10 percent of about 5 million individuals infected with the organism develop the disease. This was explained by Eberhard, who discovered marked DNA differences between pathogenic and nonpathogenic isolates of *E. histolytica*. Further work in his laboratory demonstrated the differences in both structure and function in the gene products that confer pathogenicity. Research on another disease, onchocerciasis, for which 80 million people are estimated to be at risk, centered on the identification of larval antigens that provide immunoprotection. This program could be carried out only by using the institute's newly created research facilities in Liberia. The civil war in Liberia endangered the program, but with tact and persuasion Eberhard initiated contacts with other African nations and the continuity of the work was maintained. Eberhard's success in revitalizing the institute was remarkable, and he received many awards during his time there. It is worth emphasizing that he was always concerned with human disease and, although not primarily a physician, his interest in the welfare of the patients was a major concern.

In 1990 the Bernhard Nocht Institute observed its ninetieth anniversary. In the year 2000, the institute celebrated its centenary. It is greatly to be regretted that Eberhard died before the celebration of this milestone in the life of the institute.

Eberhard had one more move in his scientific career, which was unfortunately brought to a premature close by his early death. He was asked by the University of Texas at Houston to develop a new institute to be called the Institute of Molecular Medicine for the Prevention of Human Diseases. His recruitment to Houston was largely due to the

efforts of James Willison, who helped provide the initial resources that Eberhard required. Somewhat surprisingly, Eberhard proved to be an effortless but highly successful fundraiser within the Texan business world.

It was greatly to the disadvantage of the institute and to the misfortune of his many friends that carcinoma of the prostate was diagnosed even before his arrival in Houston. His courage during this illness was an example to his many friends. He did not flag in his enthusiasm for the institute despite the increasing pain of bone metastases. Despite aggressive medical therapy, during which Eberhard considered but did not elect to have a therapeutic immunological approach, he died at the age of 70 in 1998.

Until the end of his life, Eberhard kept the future of the institute in the forefront of his mind. Even while in the hospital he continued to work on plans for the future and took his briefcase wherever he went. Sadly, toward the end of his life he had not the strength to open it. Müller-Eberhard was married three times and leaves two daughters from his first marriage to Ursula Flech Müller-Eberhard, who had been a fellow medical student at Göttingen. Irma Gigli, his wife of 15 years and a distinguished immunological dermatologist, shared his scientific interests and was assistant director of the institute in Houston. She provided a warm and graceful home environment that he loved and that enabled him to refresh and flourish.

This generous and brilliant medical investigator greatly influenced the field of immunology; he was as imaginative and talented in the laboratory at the age of 70 as he was as a young man in his thirties. In addition to his love of science, his knowledge of art and philosophy enlarged his intellectual horizon and entranced his friends. His courage and defiance of the Nazi regime was but one indication of his unwavering determination to live a life in which loyalty

and concern for his friends never flagged, even during the last painful months of his life.

Hans Müller-Eberhard was of medium height with kind but piercing blue eyes; he was always impeccably dressed in suit and tie, reserving blazer and sports jacket for the weekend. He never yielded to the casual life in California. He was a charming and excellent host at his home, where he regularly entertained colleagues from the laboratory and many visitors from overseas. Guests and friends knew they would enjoy with him his exquisite taste in music and the wines of California.

He worked in the laboratory with his own hands and on his own projects until the end of his life. In the laboratory he exuded confidence and exhibited great technical skills. His office was never cluttered; his door always open. He was as tidy in administrative matters as he was in the lab. His interest in his students was steadfast and even after they left his laboratory he took much pleasure in their successes. Although he had many admiring acquaintances throughout the world, he made only a few deep and enduring friendships, but for them no request went unheeded, and he spent many vacations and holidays with them. His loyalty followed the advice of Polonius, “The friends thou hast, and their adoption tried, grapple them unto thy soul with hoops of steel.” He did indeed.

THIS MEMORIAL greatly benefited from its thoughtful review by Dr. Irma Gigli.

SELECTED BIBLIOGRAPHY

1956

With H. G. Kunkel. The carbohydrate of γ-globulin and myeloma proteins. *J. Exp. Med.* 104:253.

1960

With U. Nilsson and T. Aronsson. Isolation and characterization of two β_1-glycoproteins of human serum. *J. Exp. Med.* 111:201.

With U. Nilsson. Relation of a β_1-glycoprotein of human serum to the complement system. *J. Exp. Med.* 111:217.

1966

With U. Nilsson, A. P. Dalmasso, M. J. Polley, and M. A. Calcott. A molecular concept of immune cytolysis. *Arch. Pathol.* 82:205.

1967

With W. S. Rodman, R. C. Williams, Jr., and P. J. Bilka. Immunofluorescent localization of the third and the fourth component of complement in synovial tissue from patients with rheumatoid arthritis. *J. Lab. Clin. Med.* 69:141.

With M. J. Polley and M. A. Calcott. Formation and functional significance of a molecular complex derived from the second and the fourth component of human complement. *J. Exp. Med.* 125:359.

1968

With M. J. Polley. The second component of human complement: Its isolation, fragmentation by C′1 esterase and incorporation into C′3 convertase. *J. Exp. Med.* 128:533.

1969

With P. Perlmann, H. Perlmann, and J. A. Manni. Cytotoxic effects of leukocytes triggered by complement bound to target cells. *Science* 163:937.

With V. A. Bokisch and C. G. Cochrane. Isolation of a fragment (C3a) of the third component of human complement containing anaphylatoxin and chemotactic activity and description of an anaphylatoxin inactivator of human serum. *J. Exp. Med.* 129:1109.

Complement. In *Annual Review of Biochemistry,* vol. 38, ed. E. E. Snell, p. 389. Palo Alto, Calif.: Annual Reviews, Inc.

1970

With D. B. Budzko. Cleavage of the fourth component of human complement (C4) by C1 esterase: Isolation and characterization of the low molecular weight product. *Immunochemistry* 7:227.

1971

With M. J. Polley and J. D. Feldman. Production of ultrastructural membrane lesions by the fifth component of complement. *J. Exp. Med.* 133:53.

With O. Götze. The C3-activator system: An alternative pathway of complement activation. *J. Exp. Med.* 134:90s.

Biochemistry of complement. In *Progress in Immunology,* vol. I, ed. B. Amos, p. 553. New York: Academic Press.

1972

The molecular basis of the biological activities of complement. In *The Harvey Lectures,* series 66. New York: Academic Press.

With L. G. Hunsicker, S. Ruddy, C. B. Carpenter, P. H. Schur, J. P. Merrill, and K. F. Austen. Metabolism of third complement component (C3) in nephritis. involvement of the classic and alternative (Properdin) pathways for complement activation. *N. Engl. J. Med.* 287:835.

1973

With W. P. Kolb, J. A. Haxby, and C. M. Arroyave. The membrane attack mechanism of complement: Reversible interactions among the five native components in free solution. *J. Exp. Med.* 138:428.

1974

With V. A. Bokisch and F. J. Dixon. Complement—A potential mediator of the hemorrhagic shock syndrome (dengue). In *Advances in the Biosciences. Schering Symposium on Immunopathology,* vol. 12, ed. G. Raspé, p. 417. New York: Pergamon Press.

1975

Complement. In *Annual Review of Biochemistry*, vol. 44, ed. E. E, Snell, p. 697. Palo Alto, Calif.: Annual Reviews, Inc.

With W. P. Kolb. Neoantigens of the membrane attack complex of human complement. *Proc. Natl. Acad. Sci. U. S. A.* 72:1687.

1976

With E. R. Podack and W. P. Kolb. The C5b-9 complex: Subunit composition of the classical and alternative pathway generated complex. *J. Immunol.* 116:1431.

With O. Götze. The alternative pathway of complement activation. *Adv. Immunol.* 24:1.

1978

Molecular dynamics and regulation of the complement system. In *Versatility of Proteins; Proceedings of the International Symposium on Proteins*, ed. C. H. Li, p. 373. New York: Academic Press.

1982

With E. R. Podack and J. Tschopp. Molecular organization of C9 within the membrane attack complex of complement. Induction of circular C9 polymerization by the C5b-8 assembly. *J. Exp. Med.* 156:268.

1984

With R. J. Ziccardi and B. Dahlbäck. Characterization of the interaction of human C4b-binding protein with physiological ligands. *J. Biol. Chem.* 259:13674.

1987

With Z. Fishelson. Regulation of the alternative pathway of human complement by C1q. *Mol. Immunol.* 24:987.

1992

With M. Leippe, E. Tannich, R. Nickel, G. Goot, F. Pattus, and R. D. Horstmann. Primary and secondary structure of the pore-forming peptide of pathogenic *Entamoeba histolytica*. *EMBO J.* 11:3501.

1994

With M. Leippe and J. Andrä. Cytolytic and antibacterial activity of synthetic peptides derived from Amoebapore, the pore-forming peptide of *Entamoeba histolytica*. *Proc. Natl. Acad. Sci. U. S. A.* 91:2602-2606.

With M. Leippe, J. Andrä, R. Nickel, and E. Tannich. Amoebapores: A family of membranolytic peptides from cytoplasmic granules of *Entamoeba histolytica*: Isolation, primary structure, and pore formation in bacterial cytoplasmic membranes. *Mol. Microbiol.* 14(5):895-904.