

Review

## Complement: A nostalgic journey The Hans J. Müller-Eberhard Memorial Lecture, Honolulu, June 14, 2004

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### Abstract

The scientific career and research contributions of Hans J. Müller-Eberhard to the field of complement research are presented in historical context, and interpreted with regard to the state of the field and the research technologies available when the contributions were made.  
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It is a great honor and personal pleasure to be invited to give the inaugural Hans J. Müller-Eberhard lecture. I am grateful to Drs. Irma Gigli and Carl-Wilhelm Vogel and the International Complement Society for selecting me as the first lecturer.

During his 40-year career in biological research, Hans Joachim Müller-Eberhard (Fig. 1) and his colleagues made a series of fundamental, often seminal contributions to the understanding of the components and functions of the complement system. He and his co-workers first identified many of the factors of the system as proteins and characterized their reaction mechanisms, control processes and biological actions in molecular terms. More important, Hans Müller-Eberhard and his colleagues showed that limited proteolytic events and the sequential generation of protein–protein complexes yield products with *de novo* biological activities and thus represent the basic mechanisms by which biological activity is generated during activation of the complement system. These findings were unique and highly controversial at the time of their presentation. Since then, these processes have been shown to represent fundamental biological principles governing many complex multistep reactions.

Hans Müller-Eberhard achieved much recognition for his numerous contributions. He was elected to membership in the

National Academy of Sciences and the American Academy of Arts and Sciences. He received many honors, including the Parke Davis Meritorious Award of the American Society for Experimental Pathology, the Squibb Award for Excellence of Achievement in Infectious Diseases of the Infectious Diseases Society of America, the T. Duckett Jones Memorial Award of the Helen Hay Whitney Foundation, the Karl Landsteiner Memorial Award of the American Association of Blood Banks, the Annual International Award of the Gairdner Foundation, the Emil von Behring prize of the Philipps-Universität, and the Robert Koch Medal in Gold among others.

How did this man, growing up in a non-academic family in Nazi Germany, and who was responsible as a schoolboy for manning an antiaircraft battery attempting to shoot down American bombers, become an accomplished, respected and highly acclaimed American scientist? I would like to try to identify some of the factors involved, which are also crucial to the formation of any creative person. Clearly it is important to begin with a good mind, and to be in the right place at the right time. These were true for Hans Müller-Eberhard. But there are a number of other very important additional factors, including good mentoring, intellectual curiosity, collegiality, trust, and the ability and courage to deviate from the accepted patterns of scientific investigation. I think it is instructive for all of us to consider these aspects in our own roles as emerging mentors, colleagues and teachers.

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Fig. 1. Hans J. Müller-Eberhard.

I also want to give some sense of the time when Hans Müller-Eberhard began his career, since scientific contributions are generally only interpretable in relation to contemporary knowledge of the subject at the time the discoveries are made. For this reason, I will describe and interpret some of Müller-Eberhard's contributions in the context of current knowledge of complement at the time he began his studies in the late 1950s. I also want to give a feeling for the scientific questions considered important at the time, and the approaches and "tools" available to answer these questions.

Finally, I hope to give you a feeling for him as a person. A very few of you worked with him, some of you knew him, but most of you, I think, knew him only as a name on published papers. Maybe some of you have no knowledge of his contributions at all, since as systems become well understood, name identification becomes lost as the principles appear as citation-less contributions in textbooks.

Although I will be talking about Hans Müller-Eberhard, I do not mean to suggest that he was the only person studying the complement system at the time he began his studies. Several other investigators used similar or other approaches and made important contributions. Hans Müller-Eberhard's career in complement research was, however, unique in several ways. First, he and his coworkers made an unusually large number of important, often seminal findings. Second, he and his colleagues had a very long and productive 30-year career in the complement field. Third, he had a leadership role in building a large group of investigators, of whom I was one, who functioned independently, but shared an abiding interest in fundamental studies of the complement system. Finally, his laboratory was a global training site for

complement as a result of the large number of postdoctoral fellows from around the world who were trained there. Most of these individuals returned home and began their own complement research groups.

Hans Joachim Müller-Eberhard was born as Hans Joachim Müller on May 5, 1927 in Magdeburg, Germany, the third child of an upper middle class family. None of his extended family members were physicians, scientists or academicians, rather, they were merchants, craftsmen, farmers and civil servants. His father, a successful small businessman, was not a supporter of the Nazi party and frequently expressed his disapproval within the home of the "clique of criminals" who controlled the government. Although the intellectual life of the family was limited to discussions of politics and religion, young Müller learned during these formative years that intelligent thought and truthful expression were important values, even in a society engulfed by totalitarianism, enforced conformity fear and hysteria. Hans Müller was the only member of his class not to join the Hitler youth.

The family became enveloped by the war almost immediately after it began in 1939. His older brother Eberhard was drafted and assigned, after training, to the Eastern front. He was killed during the siege of Stalingrad in 1941. That same year, when young Hans Müller was 14, his school class was assigned to man a Flak anti-aircraft battery near Magdeburg so that regular army troops could be relieved and sent to the Eastern front. The students' job was to shoot down Allied planes during their ever more frequent bombing raids. Sporadic schooling continued in the vicinity of the Flak battery when military duties permitted. At age 17, Hans Müller was drafted into the regular German army and sent to Hungary on the Eastern front manning a Flak battery attempting to destroy Russian tanks. Shortly after the end of fighting in May of 1945, he was captured by the Russian army. While being marched East by the Russians, young Müller dropped into a ditch and slowly worked his way west, hiding by day and traveling through the forests by night. He reached the U.S. zone and was quickly released. Hans Müller rejoined his parents and older sister in Altenau, where they had fled, after leaving everything behind, to avoid capture by the Russians. His father changed the family name to Müller-Eberhard to honor Eberhard, the son who had died in Stalingrad.

During the next two years, Müller-Eberhard did odd jobs to help the family survive. This was a period of self-examination and self-motivated extensive reading in many topics, but especially chemistry and physics, as well as philosophy. His lifelong deep interests in science, philosophy, as well as in all forms of art were born during this time in decimated postwar Germany. It was during this period of time that he decided to become a physician. In order to enter medical school, he had to pass the national maturity examination, or Abitur, as well as the specific medical school entrance test. Despite Müller-Eberhard's extensive studies on his own, these were challenging, especially as his education in high school was not comprehensive. He took classes to remedy the defects in his education in Clausthal,

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