NATIONAL ACADEMY OF SCIENCES

MANFRED MARTIN MAYER

1916—1984

A Biographical Memoir by

K. FRANK AUSTEN

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June 15, 1916–September 18, 1984

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WHAT IS THE LEGACY of a scientist? A pioneer in the field of immunochemistry, Manfred Mayer almost singlehandedly established the discipline of complement. He contributed the one-hit theory of immune hemolysis. He uncovered the first indications of the enzymatic cleavage of one complement protein by another, leading to our eventual understanding of the sequential interaction and function of the eighteen proteins of the complement system. He appreciated that cytolysis by complement is due to the insertion of hydrophobic complement peptides into the lipid bilayer of biomembranes and formation of transmembrane channels. Finally, on a different tack, he and Robert Nelson developed the *Triponema pallidum* immobilization test for syphilis. As a teacher and mentor, his impeccable methodology and the care he lavished on the members of his laboratory produced many distinguished intellectual descendants. Finally, Manfred Mayer will always remain the model of a life lived by the highest values, scientific and personal.

EDUCATION AND EARLY LIFE

Manfred was born in Frankfurt-am-Main, Germany, on June 15, 1916, and died in Baltimore, Maryland, on September 18, 1984. He received his primary and secondary school-

ing in Germany but was forced to leave that country in 1933, at the age of seventeen, because of political events. He worked his way through the City College of New York, receiving a B.S. in 1938, then entered a doctoral program at Columbia University. His doctoral thesis was on the chemical and immunologic properties of phosphorylated serum albumin. He received the Ph.D. degree in 1946.

From 1938 through 1942, Manfred supported himself working as a laboratory assistant to Dr. Michael Heidelberger—a founder of the discipline of immunochemistry—at Columbia University. His background in physical chemistry fit well with Heidelberger's organic chemical background and approach, and he was very comfortable in this laboratory that also contained Forest Kendall and had just trained Elvin Kabat. During his four years there, Manfred progressed from laboratory assistant to the role of distinguished graduate student. He worked on both the cross-reactions to Type III pneumococcal capsular polysaccharides and the fixation of the activity in immune complex reactions known as "complement." By 1946 Manfred was an accomplished immunochemist with two unique interests of his own that would occupy his subsequent scientific career: quantitative assessment of the complement system and its components, and the elucidation—in biochemical terms—of the reaction sequence.

The same year that Manfred received his Ph.D., Thomas B. Turner, chairman of the Department of Bacteriology at the Johns Hopkins School of Medicine, asked Michael Heidelberger to recommend someone in immunology. Heidelberger praised Mayer highly, and he was offered the position of assistant professor. With his wife, Elinor, Manfred proceeded to Baltimore, and within two years his contributions as a teacher and investigator had earned him promotion to associate professor. In recognition of the quality of his scholarship and his balanced approach to departmental

issues, he was chosen acting head of the Department (though not yet a full professor) when Thomas Turner left to become dean. He served throughout 1957, when Barry Wood arrived to take over the chairmanship, and was appointed full professor in 1960.

SCIENTIFIC CONTRIBUTION

Working with Elvin Kabat from 1942 to 1945, long before his arrival at Hopkins, Mayer had completed *Experimental Immunochemistry* (1948,1), though this most important volume did not appear in print until 1948. During that era, everyone in the field of immunochemistry had been instructed by Michael Heidelberger, either personally or through his distinguished disciples, Elvin Kabat and Manfred Mayer. The Heidelberger school had developed techniques for conducting quantitative precipitin reactions and agglutination determinations, and Kabat and Mayer decided it was critical for the future of research in the field to produce a textbook of quantitative immunochemistry that was both conceptual and practical in content. For a number of years, Elvin Kabat and Manfred Mayer met virtually every weekend in one another's apartments to read aloud and revise every word of the proposed text. Heidelberger also read it and ultimately prepared the introduction to the volume. These were difficult times for the wives of immunochemists, but Elinor supported Manfred throughout while at the same time proceeding with her own substantial interests.

By 1945 the unique and historically critical volume was complete, only to be delayed three years by the publishers—allegedly because of a paper shortage. The authors, however, used the delay to revise the manuscript extensively and produced a volume that went through three printings without revision over the next ten years. In 1958 the authors began work on a second edition in which Mayer's contribution on

the complement system was greatly expanded, largely due to the findings of his laboratory. This edition (1961,5) went through four printings before going out of print in 1984.

During the late 1940s and early 1950s Manfred had begun to assemble an outstanding group committed to immunochemistry in general and to complement research in specific—with startling results. During those years Lawrence Levine demonstrated that the introduction of diisopropyl fluorophosphate (DFP) would block enzymatic activity in the first component of complement—a critical step in the recognition of the biochemical events in the complement cascade. Keith Cowan was studying how carbowax acted as a substitute for specific antibody in mediating the hemolytic action of complement. Al Marucci, with Manfred's guidance, had begun to evaluate the use of radiolabeled antibody as an analytic tool in defining immunochemical events. Finally, Herbert Rapp was analyzing the different functions of rabbit antibodies of different immunoglobulin classes and, with Manfred, was beginning to develop a mathematical basis for the analysis of the reaction sequence. Their work resulted in the conclusion that the "third component of complement" was not a single substance but, based upon its behavioral characteristics as defined in mathematical terms, represented multiple substances—a conclusion subsequently substantiated by the identification of five component proteins.

Manfred's definition of the cofactor functions of calcium and magnesium made possible the singularly important demonstration that the functional interactions of the components of the complement system met the "one-hit" model of interactions. By preparing, with his students, specific intermediates, he broke the reaction down into sequential events and initially purified the components being analyzed. This "one-hit" analysis permitted the measurement of complement components—or proteins—in molecular terms with a level

of sensitivity that enabled the researchers, working with both guinea pig and human sources, to isolate each individual protein.

Effective molecule titration proved useful again some years later when the alternative complement pathway—or properdin system—was rediscovered as a non-antibody-dependent mechanism for recruiting the terminal capabilities of the complement system. On this occasion, the method's sensitivity and specificity enabled the researchers to isolate and characterize the activating proteins rapidly.

The work of Mayer's laboratory on effective molecule titration of the components of the complement system also led to the initial recognition that certain of the components had multiple biologically-active sites. In the case of the second complement component, these studies showed, the binding site to the fourth component was clearly distinguished from the catalytic site, resulting in the cleavage activation of the third component.

Mayer later turned his attention to the mechanism by which the sequentially reacting proteins (at one time termed "C3") produced "holes" in the membrane of a target cell destined to undergo lysis. He established that lysis was caused by a pentamolecular complex of the terminal five components, C5–9, which formed a transmembrane channel identified (in earlier studies by English electron microscopists) as discontinuities with an elevated border.

In addition to his unique contributions to the understanding of the sequential interaction and function of the eighteen proteins of the complement system, Mayer and his colleague Robert Nelson developed the *Triponema pallidum* immobilization test for syphilis—an important contribution to clinical medicine capable of eliminating false-positive reactions. At that time the conventional test for syphilis yielded false-positive results in individuals with gamma globulin abnor-

malities, including those with autoimmune diseases who did not have the antibody specific to the spirochete.

Dr. Mayer's contributions to the immunochemistry and biochemistry of the complement field were recognized in 1969 by an honorary degree in medical science from the Johannes Gutenberg University of Mainz, Germany; in 1974 by the Karl Landsteiner Award of the American Association of Blood Banks; in 1979 by election to the presidency of the American Association of Immunologists; and in 1982 by the Gairdner Foundation International Award. In 1953 he shared with Robert Nelson the Kimble Award for Methodology for the development of the *T. pallidum* immobilization test. He was elected to the National Academy of Sciences in 1979.

TEACHER AND MENTOR

Most teachers of science provide their students with basic skills and knowledge, but few can instill that additional ingredient: confidence to meet the challenges of independent research. Manfred Mayer was an inspiring scholar who—by example, instruction, and wisdom—made independent researchers of many of his students. Well aware that Mayer's own vision had uncovered the immunochemistry of complement (today a significant portion of the discipline of immunology), they used his laboratory as the reference point for all aspects of the field of complement research and the model for addressing—with technical resourcefulness and appropriate critical analysis—all difficult scientific questions.

Dr. Mayer, politely but firmly, demanded technical mastery of all the relevant immunologic methodologies before he would trust a member of his laboratory to deal with critical research questions. Technical competence, he maintained, was the essential prerequisite for personal creativity. He examined each experiment with an open mind, exploring the

established results and their implications. Several times a day he would go with colleagues to the blackboard to discuss which data were secure and which required more work. He frequently suggested an alternative hypothesis that required the development of a new methodology. If the new methodology took months but was the only way to obtain an answer, that was the direction the research took. Mayer's committed belief that correct methodology was the prerequisite for meaningful research meant that his laboratory's methodologic development was continually in flux. His science was state-of-the-art.

After a piece of work had been completed, the researchers had the remarkable experience of putting their results down on paper for critique by other members of Mayer's laboratory. Manfred always treated the literature of his field with integrity, while discussing his own data with great imagination and insight.

What more can be said of a giant who developed a whole scientific field not only in his personal research, but also through the training he so generously gave to others? His rocklike personal integrity became a part of his students' educational environment. Never forgetting his own early years as a refugee from Nazi oppression, he did all in his power for the displaced of any background. Truth—not politics—was his only goal, and in the search for truth he generously shared new hypotheses to be tested with every student, making sure that each had a part in the joy of discovery. His hypotheses further stimulated those about him, generating ever more definitive experiments. Not surprisingly, Mayer's laboratory produced a number of distinguished colleagues and students who carry on his own high standards in a variety of fields (immunochemistry, complement biology, cellular immunology), among them Teruko Ishizaka, Moon Shin, and Hyun Shin.

Manfred was equally committed to the development of new knowledge and to the education of those of us who interacted with him. He had no sense of status or rank, and the friendships he formed with colleagues and students were lifelong and meaningful. He felt the opportunity for a life in research a rare privilege that obliged the researcher to strive for the highest possible level of technical competence, resourcefulness, integrity, and commitment, both to research and to education—and he transferred these values to his students. Manfred was conspicuously more concerned about the development of the discipline of immunology and of complement immunochemistry than about his own personal fame.

Manfred's nonprofessional interests centered on his wife and four children. Born into a musical family, he maintained interests in music, languages, and art throughout his life. Both he and Elinor were accomplished amateur pianists, as well as collectors of art and archaeology.

An admirer of beauty in art, music, and science, Manfred Mayer was a true role model of the scientist-teacher. He developed a major area of immunology and, with the aid of his concepts and technologies, prepared those individuals who now pursue it. He is sorely missed by everyone who trained with him and or was influenced by his work. He will be remembered always as a scientist, a teacher, and the founder of the discipline of complement immunochemistry.

HONORS AND DISTINCTIONS

PROFESSIONAL AND ACADEMIC POSITIONS

1938–1942	Laboratory Assistant in Immunochemistry, Columbia University
1942–1945	Member of the Scientific Staff, Project of the Office of Scientific Research and Development, Columbia University
1946	Instructor in Biochemistry, Columbia University
1946–1947	Assistant Professor of Bacteriology, Johns Hopkins University School of Hygiene and Public Health
1948	Associate Professor of Microbiology, Johns Hopkins University School of Hygiene and Public Health
1957	Acting Chairman, Department of Microbiology, Johns Hopkins University School of Hygiene and Public Health
1960	Professor of Microbiology, Department of Microbiology, Johns Hopkins University of Medicine

LEARNED SOCIETIES

American Association for the Advancement of Science
American Association of Immunologists
American Chemical Society
American Society of Biological Chemists
Biochemical Society
National Academy of Sciences
Society for Experimental Biology and Medicine

HONORARY MEMBERSHIPS

Phi Beta Kappa
Sigma Xi
Collegium Internationale Allergologicum

OTHER PROFESSIONAL ACTIVITIES

Consultant, United States Public Health Service
Consultant, National Science Foundation
Consultant, Office of Naval Research
Consultant, Plum Island Animal Disease Laboratory, Department of Agriculture
Associate Editor, *Biological Abstracts*

Associate Editor, *Journal of Immunology*
Associate Editor, *Analytical Biochemistry*
Associate Editor, *Immunochemistry*
President, American Association of Immunologists
Editorial Board, *Journal of Immunology*

PRIZES AND AWARDS

1945 Citation, Columbia University, for work in the Division of War Research during World War II
1953 Kimble Award for Methodology
1957 Selman Waksman Lectureship Award
1969 Honorary Doctor of Medical Science, Johannes Gutenberg University, Mainz, Germany
1974 Karl Landsteiner Award, American Association of Blood Banks
1976 Albion O. Bernstein Award, Medical Society of the State of New York
1982 Gairdner Foundation International Award, Toronto, Canada

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1942

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