NATIONAL ACADEMY OF SCIENCES

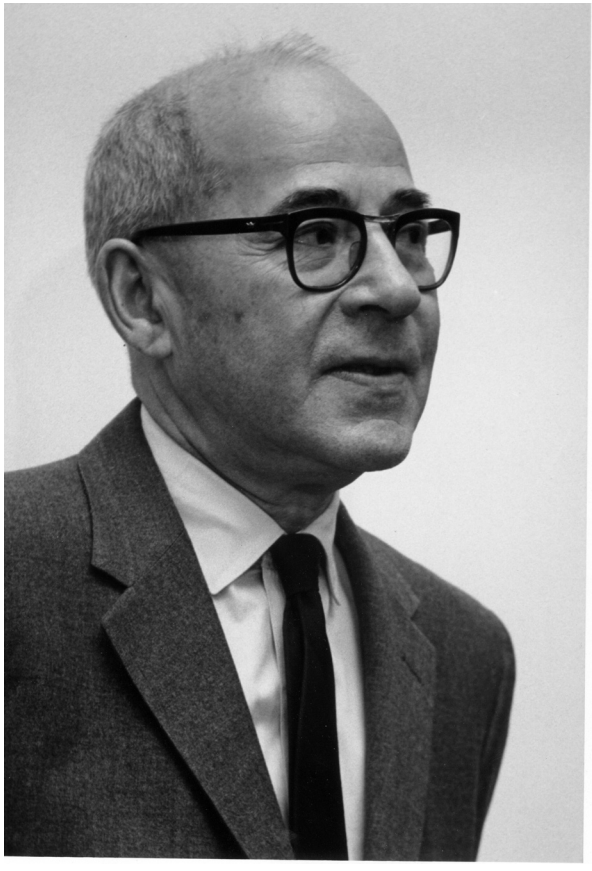
# KARL MEYER
1899—1990

*A Biographical Memoir by*

VINCENT C. HASCALL AND ENDRE A. BALAZS

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

*Biographical Memoir*



Karl Meyer

# KARL MEYER

*September 4, 1899–May 18, 1990*

BY VINCENT C. HASCALL AND ENDRE A. BALAZS

At the time Karl Meyer initiated his pioneering research on hyaluronan, previous relevant work had been done that he no doubt knew of and found useful in placing his work in its proper context. French chemist Portes reported in 1880 that a mucin isolated from vitreous differed from similar preparations from cornea and cartilage in its behavior in acid solutions, and he called it a "hyalomucoid," a precursor to hyaluronic acid, the name coined by Karl Meyer in the 1934 paper by Meyer and Palmer that was featured as a *Journal of Biological Chemistry* Classic (McDonald and Hascall, 2002). Subsequent work by Carl Morner in Sweden in 1884 confirmed Portes' results and showed that hyalomucoid had considerably less sulfur than the mucoids isolated from two other tissues. In 1918 P. A. T. Levene's laboratory, a dominant carbohydrate chemistry group at that time, isolated a polysaccharide that contained glucosamine, glucuronic acid, and sulfate, which they named "mucoitin sulfuric acid." This was probably primarily hyaluronan, although Meyer showed later that hyaluronan does not contain any sulfate groups. This prior work set the stage for the 1934 paper.

In 1917 at the age of 17, Karl Meyer was drafted into the German army and served the last year of the war on the western front in Flanders and central France. It is quite

possible that his experiences during this cataclysmic conflict were important factors in his decision to redirect his studies from the classics toward medicine.

I was born on September 4, in Kerpen, Cologne, Germany as the fourth child and only son of Ludwig and Ida Meyer. Kerpen was then a village of about 4,000 people. I grew up in a simple rural household where from early childhood on, I, with the rest of the family had my assigned duties in the house, garden and fields. My first reading instruction at 4 years of age was in Hebrew. At 5-1/2 years I joined the Jewish School of Kerpen and at 10 transferred to the Höhere Schole in Kerpen. This was a private Catholic gymnasium with almost exclusive emphasis on Latin and Greek (Karl Meyer, National Academy of Sciences, 1967).

After demobilization, Karl Meyer entered medical school and received his M.D. in 1924 from the University of Cologne. He worked as a clinician for the last time during his final months of internship at Cologne in the division of infectious diseases, where he treated women terminally ill with tuberculosis and was at considerable risk for contracting this, at the time, dread disease.

Dr. Meyer then went to Berlin to take a one-year course in medical chemistry. There he met several promising young scientists embarking on distinguished careers, including Hans Krebs, Fritz Lipmann, and Ernst Chain, among others. At this major crossroad in his life, Meyer decided to obtain further training in chemistry, eventually enrolling as a graduate student in Otto Meyerhof's laboratory at the Kaiser-Wilhelm Institute. His thesis work on the enzymatic formation of lactic acid in muscle tissue and in yeast fermentation showed that the reaction required a heat-stable coenzyme, later identified as ADP, and launched him on his research career path.

In 1927 Dr. Meyer was awarded his Ph.D. degree in chemistry in Berlin, and received a Rockefeller Foundation Fellowship to study with Professor Kuhn at the Swiss Federal Institute of Technology in Zürich; he spent almost three

years at the institute studying the ability of heme complexes to catalyze the oxidation of unsaturated compounds. In 1930 he accepted an offer from Herbert Evans to work on anterior pituitary hormones as an assistant professor at the University of California, Berkeley. In April he and his new bride, Martha, whom he had met in Zürich, embarked on an ocean liner for New York City. At Ellis Island they found that he had been issued a tourist visa rather than a work permit. A sympathetic immigration officer suggested that they have a nice vacation on their way to California, and instructed him to go to a U.S. consulate in either Mexico or Canada to obtain the appropriate documents. After a daunting two days in Tijuana, Meyer succeeded in doing so and was then able to accept his position at the University of California, Berkeley.

Dr. Meyer attended a conference in Europe in 1932 and faced another major crossroad. He learned at the conference to his dismay that Evans was terminating his position at the University of California, Berkeley. Evans recommended that Meyer stay in Germany, but Meyer decided to return to the United States, perhaps sensing the storm clouds of World War II on the horizon. After his arrival in New York, Hans Clarke at Columbia University provided him with an interim fellowship until he received a position as assistant professor in the Department of Ophthalmology at Columbia University in 1933. Under some pressure to work on relevant tissue, Meyer initiated studies on lysozyme in tears and sought another source for a mucoid substrate for the enzyme. He considered the highly viscous vitreous humor as a likely candidate. The discovery of hyaluronan quickly followed.

From the vitreous humor of cattle eyes a polysaccharide acid of high molecular weight has been obtained…As constituents there have been recognized a uronic acid, an amino sugar . . . It appears to be a substance unique in higher animals, and may be best compared with some of the specific polysac-

charides of bacteria . . . we propose, for convenience, the name "hyaluronic acid," from hyaloid (vitreous) + uronic acid (1934).

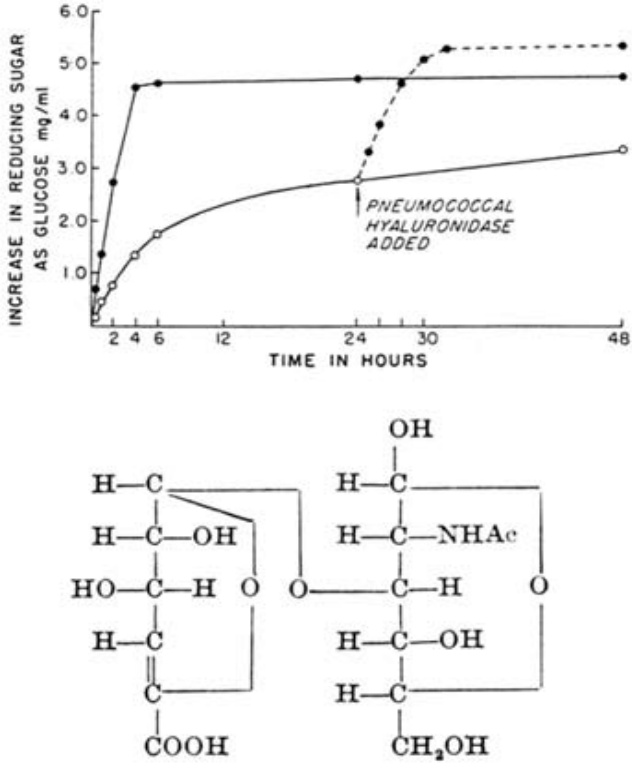



FIGURE 1 Hydrolysis of hyaluronic acid by hyaluronidases. *Top:* Kinetics of hyaluronan hydrolysis by testicular hyaluronidase (open circles) and pneumococcal hyaluronidase (closed circles). From Rapport et al. (1951), reproduced with permission. *Bottom:* "Bacterial" disaccharide—the unsaturated uronide product of pneumococcal hyaluronidase treatment of hyaluronan. From (1954,3), reproduced with permission.

It would take almost 25 years before his studies would correctly link the two sugars identified in the classic 1934 paper to form the hyaluronan disaccharide. Along the way a series of classic studies with hyaluronidases would prove essential in defining the structure. The experimental results

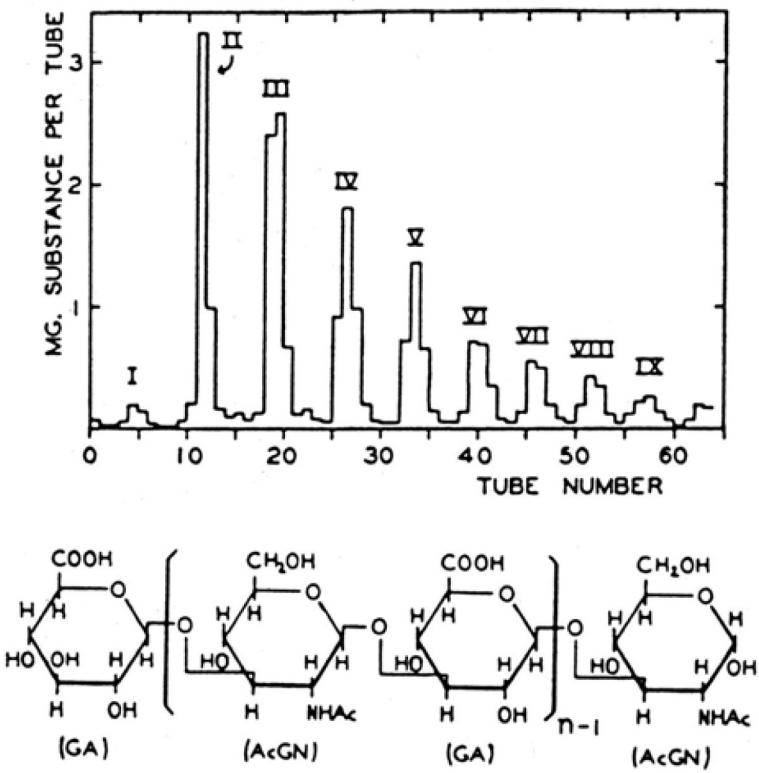



FIGURE 2 Ion exchange separation of hyaluronan oligosaccharides. *Top:* Human umbilical cord hyaluronan oligosaccharides, prepared using testicular hyaluronidase, were resolved using a Dowex 1 formate ion exchange column eluted with a formic acid gradient. *Bottom:* Representation of the hyaluronan oligosaccharides produced. From (1954,1), reproduced with permission.

depicted in Figure 1 (top) led to the correct interpretation that the limit digests by testicular hyaluronidase yielded mainly tetrasaccharides that could be cleaved to smaller disaccharides by the bacterial hyaluronidase (Rapport et al., 1951). The structure of the disaccharide (Figure 1, bottom) was defined in a gem of a small paper published in *Nature* in 1954, clearly indicating that the bacterial enzymes are eliminases (1954).

Those of us who have worked hard to isolate hyaluronan oligosaccharides of defined sizes can only admire the profile in Figure 2, showing baseline resolution through 18-mers in fractions from an ion exchange column, collected in 1954 without the benefit of a fraction collector (1954).

By the late 1950s Meyer's work was gaining recognition, no doubt prompting the following comment: "It is my opinion that the mucopolysaccharides will never be a highly popular field in biochemistry, but they probably will not be relegated again to the insignificance and disregard in which they were held not so long ago" (Karl Meyer, Chair, American Society of Biological Chemists Symposium on Acid Mucopolysaccharides of Animal Origin, 1958).

Hyaluronan was his first love, but Dr. Meyer by no means ignored other glycosaminoglycans. Early work published in 1937 used calcium chloride solutions to extract chondroitin sulfate from cartilage.

> It was observed that the chondroitinsulfuric acid salt of gelatin was soluble in a concentrated solution of calcium, barium, or strontium chloride. This observation was utilized in the extraction of chondroitinsulfuric acid from cartilage in neutral solution. Hitherto extraction with strong alkali has been employed for the preparation of chondroitinsulfuric acid. Since treatment with alkali might easily lead to decomposition, the present method of extraction by a neutral solution of $CaCl_2$ seems advantageous. The major portion of the cartilage is a protein salt of chondroitinsulfuric acid (1937).

This led to the hypothesis that the extracellular matrix was primarily a protein salt of chondroitinsulfuric acid, a concept that prevailed until the mid-1950s. However, as noted by Dr. Meyer in 1958, work primarily in Maxwell Schubert's laboratory refuted this hypothesis by unmasking the core protein and laying the foundation for research on proteoglycans.

It was known for quite some time that most of the chondroitin sulfates of the tissues do not occur as free polysaccharides, but rather as protein complexes. There have been many contributions to the literature of the protein complexes, including some of my own in 1936, which have now been proven wrong, namely, that the polysaccharide was bound to protein only by polar bonds. Dr. Schubert started some of the most fundamental studies on the protein complexes of chondroitin sulfate of cartilage" (Karl Meyer, Josiah Macy Jr. Foundation Conference 4: Chondroitin Sulfates, 1958).

While chondroitin sulfate had been known for almost a century, keratan sulfate remained to be discovered. Turning once again to tissue from the eye, this time cornea, Meyer isolated an unknown glycosaminoglycan. Initially he thought it might be a sulfated form of hyaluronan. However, it became clear that the sugar partner was galactose and not glucuronic acid, and he proposed the name keratosulfate.

From bovine cornea, three distinct mucopolysaccharide fractions were obtained. They have been identified as (1) chondroitin sulfate, (2) a fraction resembling hyaluronic acid, and (3) a sulfated mucopolysaccharide, composed of equimolar quantities of glucosamine, acetyl, galactose, and sulfate, for which we propose the name keratosulfate. The last represents approximately half of the total mucopolysaccharide fraction of the cornea (1953).

The same study proposed that hyaluronan was also present in cornea, a conclusion based on the observation that some of the glycosaminoglycans were undersulfated (chondroitin, as it turned out). By 1981 Meyer had received many awards,

including election to the National Academy of Sciences in 1967; his reputation as the father of glycosaminoglycan chemistry was firmly established.

> Looking back on my scientific career I have often wondered whether it was worthwhile to stick so tenaciously to a technically difficult and, conceptually, apparently unexciting field, while my colleagues and friends shifted over to more fashionable and rewarding areas. The reasons for my persistence are manifold: among them a distaste for jumping in on ground broken by others. Besides, I felt committed to problems such as the biological functions of the mucopolysaccharides of connective tissues, to their role in differentiation, in cell membranes and in inherited diseases (Karl Meyer, National Academy of Sciences, 1967).

At this time, he was back in the Department of Ophthalmology at Columbia as an emeritus professor, having returned there in 1976 at the invitation of Endre Balazs after a nine-year stint as professor of biochemistry at Yeshiva University. He continued to work in the laboratory for a few more years, into the late 1980s, before failing health made this impossible. Fittingly, his last paper, published in 1983, returned to the eye, in this case a study of the glycosaminoglycans in the vitreous humor of a fish (1983).

Karl Meyer died on May 18, 1990, at the age of 90.

The Society for Complex Carbohydrates, the forerunner of the current Society for Glycobiology, initiated the Karl Meyer Award for Glycoconjugate Research in 1991, a year after his death. Karl Meyer is often considered the father of glycosaminoglycan research, and his contributions to our knowledge of the structures of hyaluronan, chondroitin sulfate, and keratan sulfate (three of the four classes of glycosaminoglycans) certainly merit such consideration. Therefore, it is very appropriate for the society to honor his work and his memory through the award that bears his name.

THIS BIOSKETCH OF KARL MEYER is based on a poster "Karl Meyer—Discoverer of Hyaluronan" presented in 2000 at an international meeting "Hyaluronan 2000" in Wrexham, Wales (Kennedy et al., 2002) and on a version that was published in Glycobiology in 2004 to provide a perspective for why the Glycobiology Society established its annual Karl Meyer Award for outstanding glycobiology researchers (Hascall, 2004).

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The following list comprises 20 of Karl Meyer's most important publications. The first one is a one-page description of his work as a student with Otto Meyerhof. It was his second citation and his first in English. The last one is his last published work.

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1937

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