Letter to the Glyco-Forum

The Karl Meyer Award for glycoconjugate research

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Editor’s Note: The Society for Complex Carbohydrates, the forerunner of the Society for Glycobiology, initiated the Karl Meyer Award for Glycoconjugate Research in 1991, a year after the death of Dr. Meyer at the age of 90. The society has conferred the award on 12 eminent Glycobiologists since that time:

- 1991: Vincent Hascall and Ulf Lindahl
- 1993: Gilbert Ashwell and Saul Roseman
- 1995: Sen-itiroh Hakomori
- 1997: Minoru Fukuda
- 1998: Harry Schachter
- 1999: Stuart Kornfeld
- 2000: Phillips Robbins
- 2001: Robert Hill
- 2002: Jacques Baenziger
- 2003: Pamela Stanley

As time has passed, knowledge of the seminal contributions of Dr. Meyer to glycobiology and the burgeoning area of proteoglycan research have become less familiar to those in the field. In this issue, Glycobiology is pleased to reproduce a perspective on Dr. Meyer prepared by one of the first awardees, Dr. Vincent Hascall.

How well I remember my confusion in 1991. I was presenting Dr. Ulf Lindahl to the Society for Complex Carbohydrates as the first Karl Meyer awardee when I learned, quite unexpectedly, that there were to be two awards granted. I felt very honored when I understood that the second award was for me! In the intervening years since Lindahl and I became the first awardees for our work with glycosaminoglycans and proteoglycans, the award has been granted to a stellar series of researchers who have established the breadth and depth of what is now glycobiology.

Karl Meyer (see Figure 1) is often considered the father of glycosaminoglycan research. 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, and it is very appropriate for the society to honor his work and his memory through the award that bears his name.

The perspective that follows was first presented as a poster at Hyaluronan 2000, an international meeting held in Wrexham, Wales (Kennedy et al., 2002). It provides an overview of Meyer and his work in the context of his time. It focuses on hyaluronan, the simplest of the glycosaminoglycans, and the molecule that continues to amaze those of us who work with it for its diversity and importance in a wide variety of normal and pathological processes. On behalf of the recipients of this singular honor, I hope you will enjoy this perspective and pause to reflect on Meyer’s seminal contributions at the annual Society for Glycobiology meeting each year when the new honoree receives the Karl Meyer Award.

At the time that Meyer initiated his pioneering research on hyaluronan, previous work had been done in the area that he no doubt knew of and found useful in placing his work in its proper context. A 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
Karl Meyer: discoverer of hyaluronan

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)

In 1917, at the age of 17, 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.

After demobilization he 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 dread disease.

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 Lippman, 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 a Ph.D. in chemistry in Berlin and received a Rockefeller Foundation Fellowship to study with Professor Kuhn at the Federal Swiss Institute of Technology in Zurich, where he spent almost 3 years 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 Assistant Professor at the University of California, Berkeley. In April, he and his new bride, Martha, whom he had met in Zurich, embarked on an oceanliner for New York City. At Ellis Island, they found that he had been issued a tourist visa, rather than a work permit. However, 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 2 days in Tijuana, Meyer succeeded in doing so and was then able to accept his position at the university.

Meyer attended a conference in Europe in 1932 and faced another major crossroad. To his dismay, he learned at the conference that Dr. Evans was terminating his position at the University of California, Berkeley, and recommended that he stay in Germany. However, Meyer decided to return to the 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 lysosome 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 (Meyer and Palmer, 1934):

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 polysaccharides of bacteria. . . .

We propose, for convenience, the name “hyaluronic acid,” from hyaloid (vitreous) + uronic acid.

It took almost 25 years before his studies linked the two sugars identified in the classic 1934 paper together correctly to form the polymer that captures our interest today. Along the way, a series of classic studies with hyaluronidases proved essential in defining the structure.

The experimental results depicted in Figure 2 (top) led to the correct interpretation that the limit digest 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 2, bottom) was defined in the gem of a small paper published in Nature in 1954 clearly indicating that the bacterial enzymes are eliminases (Linker and Meyer, 1954).

Those of us who have worked hard to isolate hyaluronan oligosaccharides of defined sizes can only admire the profile in Figure 3, showing baseline resolution through 18-mers in fractions from an ion exchange column, collected without the benefit of a fraction collector in 1954 (Weissmann et al., 1954).

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, Chairman, American Society of Biological Chemists Symposium on Acid Mucopolysaccharides of Animal Origin, 1958).
Hyaluronan was his first love, but Meyer by no means ignored other glycosaminoglycans. Early work published in 1937 used calcium chloride solutions to extract chondroitin sulfate from cartilage (Meyer and Smyth, 1937):

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 CaCl₂ seems advantageous. The major portion of the cartilage is a protein salt of chondroitinsulfuric acid.

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 Meyer in 1958, work primarily in Max Schubert’s laboratory refuted this hypothesis by unmasking the core protein and laying the foundation for research on proteoglycans.

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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)
Though chondroitin sulfate had been known for almost a century by this time, 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 (Meyer et al., 1953).

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.

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, and 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 9-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 article, published in 1983, returned to the eye, in this case a study of the glycosaminoglycans in the vitreous humor of a fish (Armand et al., 1983). Karl Meyer died May 18, 1990, at the age of 90.

References


Meeting Announcements

7th Jenner Glycobiology & Medicine Symposium

Exeter College, Oxford, UK
September 5–8, 2004

The conference will bring together specialists exploring the biological roles of glycoconjugates in health and disease using different approaches. Its goal is to present the state of the art in the field to young and established investigators. The following aspects will be highlighted: glycosylation-dependent bacterial and viral infections, lectin- and proteoglycan-dependent interactions in leukocyte homing processes to lymphoid tissues and inflamed tissues, congenital defects in glycosylation of glycoproteins and glycolipids, and role of carbohydrates in tumour development and neuropathology, including Creutzfeldt-Jakob disease. Each of eight sessions will be introduced by a keynote speaker.

Topics: Glycosylation dependent bacterial infections, Inflammation, Glycopathology, Glycosylation-dependent viral infections, Congenital defects in glycosylation and glycoimmunology

Organizing committee: John Axford, UK; Pauline Rudd, UK; Ghislain Opdenakker, UK; Jim Van Dijk, The Netherlands; and Claudine Kieda, France.

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