BIOGRAPHICAL MEMOIRS

Bengt I. Samuelsson

May 21, 1934–July 5, 2024
Elected to the NAS, 1982

A Biographical Memoir by Lawrence J. Marnett and Jesper Z. Haeggström

Throughout his long, distinguished career, Bengt Ingemar Samuelsson discovered multiple series of biologically active, naturally occurring lipid mediators derived from polyunsaturated fatty acids, especially arachidonate. Specifically, he determined the chemical structures, mechanism of formation, and metabolism of prostaglandins, thromboxanes, and leukotrienes, the first members of the family of bioactive lipids called eicosanoids. His research at the interface of chemistry and biology enabled the development of drugs that have provided a major benefit to human health. In recognition of his achievements, Samuelsson was elected to the National Academy of Sciences in 1982, the same year he shared the Nobel Prize for Physiology or Medicine.

Bengt Samuelsson was born on May 21, 1934, in Halmstad, a town on the southwest coast of Sweden. He was the youngest of the three children of Kristina and Anders Samuelsson. His father was a merchant in Halmstad, and his mother kept the home. He attended public school and then went to Lund University to study medicine. He met his wife, Karin Bergstein, while in medical school, and they married in 1958. They would have three children—Elisabet (who died in 1996), Astrid, and Bo.

At Lund, Bengt began doing research on steroid metabolism in the laboratory of Sune Bergström. The Bergström laboratory was also investigating a vasoactive substance of unknown structure that the physiologists Raphael Kurzrok and Charles Lieb, M.W. Goldblatt, and Ulf von Euler had independently discovered in the 1930s.[1,2,3] Von Euler had named this factor prostaglandin (PG) because he mistakenly assumed it originated in the prostate gland. Samuelsson eventually joined the team working on PG identification and, when Bergström moved to the Karolinska Institute in 1958, he moved with him. Bengt received his Ph.D. in biochemistry in 1960 and his M.D. in 1961 and then joined the faculty at the Karolinska as an assistant professor of medical chemistry. He spent 1961-62 as a research fellow in chemistry in the laboratory of Elias J. Corey at Harvard University. This period offered Bengt close interactions with other prominent chemists, including Konrad E. Bloch and Robert B. Woodward, and had a profound impact on Bengt's future research work. Each of these Harvard chemists was an eventual Nobel laureate.

NATIONAL ACADEMY OF SCIENCES

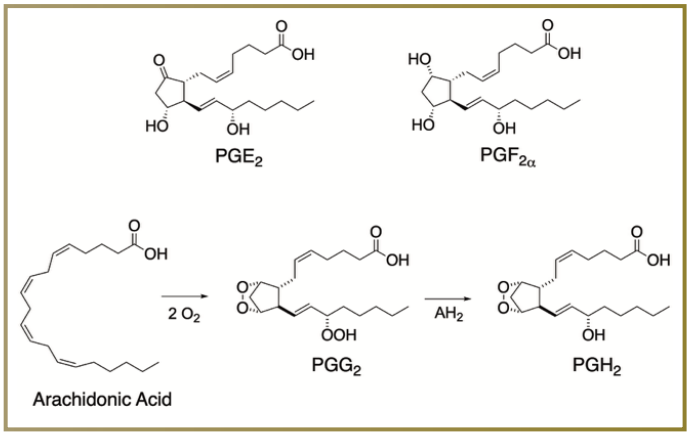

Figure 1 Top, structures of PGE_2 and $PGF_{2}\alpha$. Bottom, cyclooxygenase enzymes (COX-1 or COX-2) oxygenate arachidonic acid to PGG_2 and reduce PGG_2 to PGH_2.

The structural efforts in Stockholm were enhanced by a collaboration with Ragnar Ryhage, who had come to the Karolinska in 1950 and later invented the first gas jet interface connecting a gas chromatograph (GC) to a mass spectrometer (MS).[4] The Bergström team isolated and elucidated the structure of the ketonic E and non-ketonic F classes of PGs in 1962 (Figure 1, top).

Comparison of the structures of PGE_1, PGE_2, and PGE_3, which differed only in the number of double bonds, suggested that their precursors were polyunsaturated fatty acids. Following a reciprocal exchange of materials with David A. van Dorp at the Unilever Research Group in the Netherlands, both the Dutch and the Swedish groups verified in 1964 that tritium-labeled arachidonic acid was converted into PGE_2 by homogenates of sheep vesicular glands.[5,6]

Bengt initiated an independent research program and, in 1965, published the results of an $^{18}O_2$ labeling experiment that established molecular oxygen as the source of the oxygen atoms in PGE_1. When his lab carried out incubations in mixtures of $^{18}O_2$ and $^{16}O_2$, the pattern of oxygen labeling demonstrated that the oxygen atoms at C-9 and C-11 in the five-membered ring were derived from the same molecule of O_2. A subsequent series of elegant isotopic labeling experiments enabled Bengt to propose a detailed mechanism for the conversion of polyunsaturated fatty acids into PGs. He proposed that a key intermediate in the transformation contained a 5-membered cyclic peroxide group between C-9 and C-11 (Figure 1, bottom). At the time, such a bicyclic peroxide was an unprecedented structure in a natural product from either the plant or animal kingdoms.

In 1967, Bengt moved from the Karolinska Institute to become a professor of medical chemistry at the Royal Veterinary College, also in Stockholm. While there, he studied the metabolism of PGs and the factors that regulate their synthesis. He returned to the Karolinska as a professor and chair of the Department of Physiological Chemistry in 1972 and shortly thereafter reported the isolation of the endoperoxide intermediate he had proposed earlier. There were actually two endoperoxides—one with a hydroperoxide at C-15 and another with an alcohol at C-15. He named the hydroperoxide PGG_2 and its reduction product PGH_2 (Figure 1, bottom). This work completed the picture of the enzymatic oxygenation of arachidonic acid, establishing that PGH_2 was the ultimate product. The responsible enzyme, named cyclooxygenase (COX) or prostaglandin G/H synthase, was isolated in 1976 by Hayaishi and colleagues.[7] PGH_2 diffuses off the COX enzyme and is a substrate for additional enzymes that convert its endoperoxide (1,2-dioxolane bridge) into different functional groups present in the biologically active PGE and PGF series, as well as other products.

The availability of PGG_2 and PGH_2 enabled Bengt to test a hypothesis advanced by John R. Vane to explain the identity of a highly vasoconstrictive material produced on antigen challenge of guinea pig lung. Vane reported in 1969 that this short-lived material, which he called rabbit aorta contracting substance (RCS), was also generated from arachidonic acid, but it was much more potent at constricting the rabbit aorta than then known PG species.[8] Vane had suggested that RCS might be an endoperoxide intermediate, although at the time the endoperoxides had not yet been isolated. Bengt was able to repeat Vane's findings, but discovered that, although vasoactive, the endoperoxides were less potent than RCS and longer-lived. RCS exhibited a half-life of 30 s under conditions where PGG_2 and PGH_2 had half-lives of ~5 min. Interestingly, experiments with washed human platelets suggested that PGH_2 could be converted to RCS.

With these observations as background, Bengt undertook what may have been the most impressive work of a long, extremely productive career. With Mats Hamberg, he found that guinea pig lung homogenates and platelet homogenates converted arachidonic acid to a novel metabolite in much higher concentrations than PGE_2 and $PGF_{2\alpha}$. This metabolite contained a dihydroxyoxane ring that had arisen from the rearrangement of the endoperoxide ring of PGH_2. In contrast to RCS, this novel metabolite was chemically stable and exhibited no muscle-contracting activity. By conducting short-term incubations with rapid quenching into methanol, they were able to trap an unstable intermediate as the methoxy adduct (Figure 2). This led them to propose that the intermediate was an oxetane oxane that they named thromboxane A_2 (TxA_2) because it originated in thrombocytes and contained an oxane ring. Hydrolysis of TxA_2 yielded the chemically stable and biologically inert compound they initially identified, which they named TxB_2. Like the endoperoxide structures before it, the structure

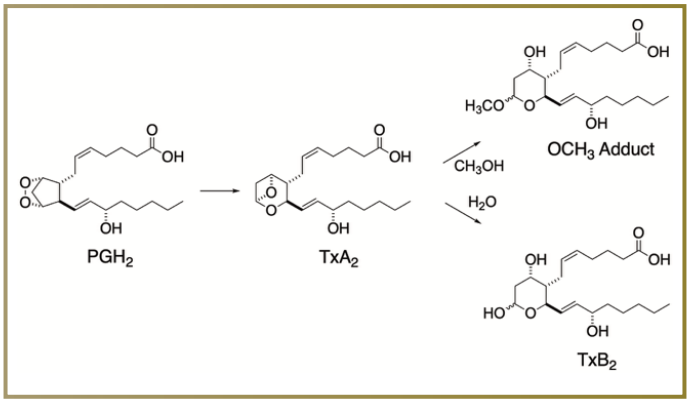

Figure 2 Thromboxane synthase-catalyzed conversion of PGH_2 to TxA_2. TxA_2 hydrolyses to form TxB_2 but can be trapped using CH_3OH to form the methoxy adduct.

of TxA_2 was without chemical precedent when Bengt proposed it. In fact, it was ten years before a synthetic chemist—W. Clark Still at Columbia University—could synthesize TxA_2.[9] The synthetic product had identical chemical and biological properties to the biosynthetically generated material.

Such rapid progress led to tremendous foment and excitement in the field around this time. John Vane had demonstrated that non-steroidal anti-inflammatory drugs, such as aspirin and indomethacin, inhibited PG formation and proposed it as the mechanism of action of these ubiquitously used drugs. Thus, pharmaceutical companies were focusing intense attention on the arachidonic acid cascade. The availability of substantial quantities of PGs prepared at the Upjohn Company by total organic synthesis enabled a rapid and comprehensive elucidation of their physiological and pathophysiological activities. To highlight these exciting discoveries, the first International Conference on Prostaglandins and Related Compounds was held in 1975 in Florence, Italy. Bengt gave the opening lecture and for the first time described the experiments that led to the identification of the structure of TxA_2. It was a stunning revelation that electrified the more than 1,000 attendees.

The second International Conference on Prostaglandins and Related Compounds was held in 1979 in Washington, DC, and again Bengt gave the opening lecture. This time he unveiled a completely new family of lipid mediators—the leukotrienes—products of the lipoxygenase pathway of arachidonic acid metabolism (Figure 3). Lipoxygenases are a family of enzymes that add an oxygen molecule to a polyunsaturated fatty acid to form a hydroperoxide. They are named on the basis of the carbon atom of the fatty acid to which the oxygen is added. Originally discovered in plants, these enzymes were only demonstrated to exist in animals in 1975 when a 12-lipoxygenase was reported in human platelets.[10] Then, a 5-lipoxygenase was discovered in 1976.

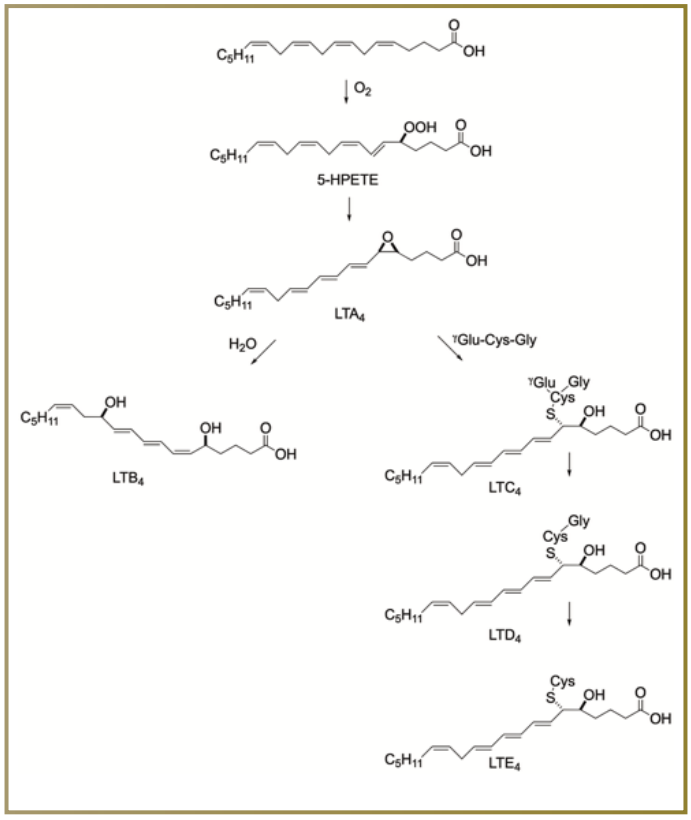

Figure 3 Biosynthesis of leukotrienes. Arachidonic acid is oxygenated by 5-lipoxygenase to 5-HPETE, which is further oxidized by 5-lipoxygenase to LTA_4. LTA_4 is hydrolyzed by LTA_4 hydrolase to LTB_4, or it is conjugated with glutathione by LTC_4 synthase to form LTC_4. LTC_4 is hydrolyzed to LTD_4, which is hydrolyzed to LTE_4. Slow-reacting substance of anaphylaxis (SRS-A) is a mixture of LTC_4, LTD_4, and LTE_4.

The novel leukotriene metabolites reported by Samuelsson in 1979 are products of the 5-lipoxygenase pathway. Bengt and Pierre Borgeat had initially identified a dihydroxy compound as a novel metabolite of arachidonic acid in rabbit polymorphonuclear leukocytes. As with his early studies of the mechanism of PG and thromboxane biosynthesis, Bengt used isotopic oxygen labeling studies and mass spectrometry to define the chemistry of its generation. He showed that arachidonic acid is oxygenated by 5-lipoxygenase to produce a 5-hydroperoxy derivative that is further oxidized by the enzyme to ultimately yield a highly reactive epoxide, leukotriene A_4 (LTA_4) (Figure 3). Hydrolysis of this intermediate yields the dihydroxy metabolite, LTB_4, that he and Borgeat had previously discovered.

The discovery of the leukotriene biosynthetic pathway shed new light onto the formation of a biological activity called "slow-reacting substance of anaphylaxis" (SRS-A). SRS-A, a powerful bronchoconstrictor generated during anaphylactic shock, had been discovered in 1938 by Australian medical researcher Charles H. Kellaway and co-workers.[11] Subsequent research from many laboratories over the next

forty years suggested that it was produced from arachidonic acid and contained cysteine, but attempts to identify such a peptido-lipid had been unsuccessful. Bengt proposed the hypothesis that SRS-A was a peptide conjugate of LTA_4. He, Robert Murphy, and Sven Hammarström used cultured mouse mast-cell tumor cells to produce enough SRS-A for chemical characterization and confirmed its identity as a glutathione conjugate of LTA_4 that they named LTC_4. The biosynthetic material was identical chemically and biologically to authentic standards synthesized by the E. J. Corey laboratory. Subsequent research revealed that LTC_4 was hydrolyzed to LTD_4 then LTE_4 (Figure 3) and that the biological activity of SRS-A was a composite of the three. Thus, in a span of four years, Bengt's laboratory had identified a completely new family of arachidonic acid metabolites with powerful roles in inflammation and allergic hypersensitivity.

Bengt was only forty-six years old at the time he unraveled the chemistry of SRS-A biosynthesis, and he continued to expand the field of bioactive lipids throughout the rest of his career. Among his many discoveries were definition of the in vivo metabolism of PGs (with Elisabeth Granström and Krister Gréen), initial characterization of the G-protein-coupled PG receptors (with Sven Hammarström), definition of the biosynthesis of lipoxins (with Charles Serhan), exploration of the regulation of 5-lipoxygenase (with Takao Shimizu, Carol Rouzer, and Olof Rådmark) and the inducible prostaglandin E synthase (with Per-Johan Jakobsson), and characterization of LTA_4 hydrolase (with Jesper Haeggström). Bengt used whatever tools were necessary to solve a problem, whether it was GC/MS, LC/MS, protein purification, structure determination, molecular biology, generation of animal models, or innumerable bioassays. He was never limited by a technique.

His approach was characterized by chemical ingenuity, analytical rigor, and high-quality biology. He used biology as a filter to identify the most important chemistry to study, and he used chemistry to define the structures and pathways for production of important biological mediators. This reciprocal relationship ensured that he focused on the most important problems and solved them expeditiously. As a practitioner of true chemical biology, he was an inspiration to many.

The legacy of his body of work was massive. To put it in perspective, one must realize that before the demonstration that arachidonic acid was converted to PGs by an initial oxygenation step, fatty acid dioxygenases had only been reported in plants, and there were no known fatty acid dioxygenase-dependent metabolites reported in animals. Between 1964 and 1979, Bengt defined the biosynthesis of two large families of arachidonic acid metabolites and demonstrated them to be responsible for a diverse and powerful range of physiological and pathophysiological activities in humans. The field of arachidonic acid metabolism has evolved into a huge, diverse one that was largely defined in Bengt's lab. Furthermore, there are many drugs that are important treatments for human diseases that target arachidonic acid pathways. These include non-steroidal anti-inflammatory drugs, COX-2 inhibitors, low-dose aspirin for cardiovascular and cancer prevention, Montelukast™ for asthma and allergic hypersensitivity, prostacyclin analogs for pulmonary hypertension, misoprostol for gastric ulcers and labor induction, and bimatoprost for prevention of glaucoma.

In 1982, Sune Bergström, Bengt Samuelsson, and John Vane shared the Nobel Prize for Physiology or Medicine "for their discoveries concerning prostaglandins and related biologically active substances." It was the same year that Bengt was elected as a foreign member of the U.S. National Academy of Sciences. Prior to that, he had received many awards, including the Swedish Medical Association's Jubilee Award (twice), the Anders Jahres Award for Medical Research, the Louisa Gross Horwitz Prize, the Albert Lasker Basic Medical Research Award, the CIBA-Geigy Drew Award in Biomedical Research, the Heinrich Wieland Prize, the Canada Gairdner International Award, and the Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Research. He was elected as a foreign member to the American Academy of Arts and Sciences, the Académie des Sciences (Paris), and the Royal Society (London). In 1996, Sweden issued a stamp bearing his likeness in his honor.

Bengt played major leadership roles at the Karolinska Institute. He served as dean of the medical faculty from 1978 to 1983 and rector, or president, of the institute from 1983 to 1995. As rector, his goal was "to ensure that the Karolinska had the best faculty, best students, and best facilities."[12] To reach these goals, Bengt launched a complete structural and organizational makeover of the institute. Inspired by the U.S. academic system and realizing the importance of economic incentive, Bengt reduced the number of departments and department heads from 145 to thirty-two, introduced competition for faculty resources, and initiated a program for recruitment of only outstanding scientists as new faculty. These visionary and ambitious changes have been referred to as a "cultural revolution" at Karolinska, in which "100 kingdoms were removed" to promote efficiency, quality, and competitiveness. Meanwhile, Bengt enjoyed strong political support and was able to raise significant governmental resources to build new ultramodern facilities for basic experimental research.

Bengt was also very active in the Nobel organization, first as the chair of the committee for the Prize in Physiology or Medicine and then, from 1995 to 2005, as the chair of the

Nobel Foundation. The foundation's main responsibility is the financial management of the Nobel fortune, as well as maintenance and development of the Nobel brand in compliance with the will of Alfred Nobel. In this role, Bengt engaged in the creation of the Nobel Prize Museum in Stockholm and acquired funds to erect a new building, the Nobel Forum, as a worthy home and conference center dedicated to the Nobel work at Karolinska.

Despite these significant institutional responsibilities, Bengt maintained a keen interest in curiosity-driven research. He created a very welcoming environment in his laboratory, which was always an exciting place to work. As a result, his group was populated by outstanding faculty, students, and staff, and the laboratory was a magnet for talented collaborators from around the world, all of whom contributed significantly to his discoveries. Many went on to establish productive research laboratories that made major contributions to the bioactive lipid field.

As discovery followed discovery, there was a sense that the world was watching and that we were part of history in the making. Bengt's enthusiasm for research was infectious. He loved to talk about experiments and was excited by the results. He would always come by during the day to check on the progress of experiments, not to apply pressure, but from pure interest. He also had a very critical eye and was rigorous in his evaluation of data. Sven-Eric Dahlén, now a professor at the Karolinska, tells the story of his time as student representative while Bengt was Dean: "As the student rep, I needed to arrange a meeting with Bengt and I fixed a time with the secretary some three weeks later. But then I explained that I wanted to report on some tests in the lab and just ten minutes later I was able to walk in!"[13]

Bengt Samuelsson was a collaborator, mentor, and inspiration to generations of biomedical scientists. He is remembered as a low-key yet curious, enthusiastic, and humorous person with a razor-sharp intellect. In his private life, Bengt was a fan of opera, literature, and modern art as well as an avid sailor, skier, and golfer. His was a life extremely well lived. He died on July 5, 2024, at the age of ninety at his summer residence in Mölle, Sweden.

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