My husband, Carl B. Camras, MD (chairman of the Department of Ophthalmology and Visual Sciences, University of Nebraska Medical Center, Omaha), died at age 55 years in 2009. His dying wish was to be remembered for being the first to hypothesize that prostaglandins lower intraocular pressure and had potential as a medication to treat glaucoma. I reviewed the research he performed as an undergraduate at Yale University (New Haven, Connecticut), as a medical student at Columbia University (New York, New York), and on the faculty at Mount Sinai School of Medicine (New York, New York), which confirmed his hypothesis and led to the development of latanoprost. This article summarizes his contributions to glaucoma research, his role in the development of latanoprost, and the error of omission that prevented his recognition as its coinventor. Carl is best remembered as an ethical scientist, a gifted clinician, and a beloved teacher, who inspired the medical community and the next generation of ophthalmologists.

In 2009, my husband, Carl B. Camras, MD, died at age 55 years of irradiation-induced congestive heart failure. During an internship in 1979, he had been diagnosed as having Hodgkin disease and was treated with radiation therapy. Despite his health issues, he devoted his life to research and medicine. His dying wish was to be remembered for being the first to hypothesize that prostaglandins lower intraocular pressure (IOP) and had potential as a medication to treat glaucoma. His ideas and research led to the development of latanoprost, the first-line treatment for open-angle glaucoma. I honored Carl’s wish by reviewing his letters, notes, and publications and by interviewing his professors, colleagues, and former students. This article summarizes what I learned and how his research, clinical work, and teaching are remembered.

Carl’s passion for research began as an undergraduate. During the 1974-1975 academic year, his senior research project for the molecular biophysics and biochemistry major involved evaluating the possibility of treating glaucoma by attaching epinephrine to glass beads. He studied under the direction of his research adviser, Ted W. Reid, PhD, and the chairman of ophthalmology, Marvin L. Sears, MD, at Yale University, New Haven, Connecticut. Because one treatment for glaucoma at this time was topically applied epinephrine, which caused severe irritation and for some patients intolerable adverse effects, Drs Reid and Sears were interested in finding a permanent solution to lowering IOP with epinephrine-coated glass bead injections. They thought that epinephrine covalently attached to these microscopic glass beads would remain biologically active; therefore, if they could be placed in the eye adjacent to their site of action and remain near that site, they potentially could control IOP forever. Their initial work demonstrated that epinephrine covalently bound to glass was not biologically active. The activity that previously had been shown to occur by other research groups was due to epinephrine that had been noncovalently absorbed on the glass surface and was being slowly released. Because the epinephrine on the glass sur-
face would be depleted eventually, it could not offer a cure for elevated IOP after a single injection; however, the slow release of epinephrine demonstrated a localized contraction effect on the dilator muscle of isolated iris–ciliary body preparations from rabbits. The researchers reasoned that they could use epinephrine on glass as a probe to determine the intraocular site of action of epinephrine.

Next, Carl and Dr Reid showed a pronounced and sustained (for several weeks) reduction of IOP after injections of the epinephrine on glass into the anterior chamber of rabbit eyes. Based on Carl’s suggestion about using the proper controls, they later found that glass beads without epinephrine produced an identical IOP reduction.

Dr Reid thought that the experiment was a failure, but Carl was intrigued by this glass bead–induced IOP reduction. The process of providing glass beads into the anterior chamber of rabbit eyes through a large-bore needle and the positioning of the beads in the eye produced intraocular inflammation, as evidenced by a breakdown of the blood-aqueous barrier and an anterior chamber cellular response.1 Carl firmly believed that prostaglandins were involved in this inflammatory response and wondered whether the prostaglandins also could be mediators of the prolonged IOP reduction. In speaking with Dr Reid about these events, he recalled with joy: “The tables turned, and this kid began teaching me!”

Carl thoroughly reviewed the literature, reading everything that was available on prostaglandins. In support of his hypothesis, he found a 1971 publication by Starr2 that showed the reduction of IOP after an initial rise following intracameral delivery of prostaglandins into the cannulated eyes of anesthetized rabbits. He also found 4 publications3-6 that showed a prostaglandin-induced increase in outflow facility. The increased outflow facility in these studies was measured during the initial prostaglandin-induced increase in IOP and was thought to represent pseudofacility. Despite this information, Carl believed that prostaglandins would reduce IOP and represented an explanation for glass bead–induced sustained reduction of IOP.

In an e-mail in which he recalled his reaction, Dr Sears wrote about Carl’s new hypothesis: “You are speculating without any scientific basis, and that IOP reduction that you observed with glass beads was due to aqueous hyposcretion resulting from the inflammation.” Like most experts working in the field at this time, Dr Sears believed that prostaglandins raised IOP and contributed to or caused inflammation and was opposed to experiments that demonstrated a possible prostaglandin-induced IOP reduction. He recommended that Carl should concentrate on confirming the ability of epinephrine on glass to reduce IOP.

But Carl’s instincts told him otherwise, as he continued to evaluate his hypothesis. He performed paracentesis in rabbits and monitored the long-term effect on IOP. Previous investigations had shown a prostaglandin-mediated initial rise in IOP and a breakdown of the blood-aqueous barrier after paracentesis. Carl demonstrated a subsequent reduction of IOP after paracentesis lasting at least 1 week, which he attributed to paracentesis-induced stimulation of endogenous synthesis of prostaglandins. He hypothesized that prostaglandins might mediate the reduction of IOP often seen during acute ocular inflammation and speculated about its usefulness in the treatment of glaucoma.

Before graduating from Yale University with honors a semester early, Carl wrote up his experiments and submitted his senior thesis, entitled Hypothesis to Account for the Glass Beads’ Ability to Produce a Long-term Reduction of IOP.7 His hypothesis was as follows:

Intracameral injections of glass beads into rabbit eyes cause vasodilation in both the iris (iridal hyperaemia) and conjunctiva (conjunctival hyperaemia) and the release of plasmoid proteins into the aqueous humor (aqueous flare) due to disruption of the blood-aqueous barrier. This inflammatory response is characteristic of acutely traumatized mammalian eyes and may be mediated by [prostaglandins].7

During Carl’s review of the literature, he had become familiar with the research by László Z. Bito, PhD, and Kenneth E. Eakins, PhD. When Carl began his first year at Columbia University College of Physicians and Surgeons, New York, New York, he had anticipated the continuation of his research with one or both scientists to further develop his hypothesis. Carl introduced himself to Dr Bito and then shared with him his ideas and his senior thesis. Dr Bito was receptive to Carl’s ideas about the possible hypotensive effects of prostaglandins.

Throughout medical school, Carl continued his research with Dr Bito. In 1977, they presented their findings at the Association for Research in Vision and Ophthalmology Annual Meeting. Beforehand, Dr Bito had written to Ann S. Peterson, MD, the dean of student affairs, requesting financial support. In his March 8, 1977, letter, Dr Bito wrote: “I must say that I was very impressed with Mr. Camras. His endurance during the past summer was remarkable considering that many experiments had to be attended to virtually around the clock. I was even more impressed with his ability to integrate the findings of many investigators and come up with not only new ideas but also with workable protocols to test various hypotheses.” Their first coauthored article, “Reduction of intraocular pressure by prostaglandins applied topically to the eyes of conscious rabbits,”8 was published in the same year.

Together, Dr Bito and Carl designed (and Carl performed) experiments in rabbits and owl monkeys that were described from 1977 through 1983 in a series of publications.6,10 Based on his undergraduate experience at Yale University, Carl was familiar with handling rabbits and the technique of pneumotonometry, which he had used routinely and painstakingly documented in his laboratory notebooks. Dr Bito and Carl showed that a pronounced and prolonged reduction of IOP could be achieved after topical application of prostaglandins in rabbits and monkeys.

Based on the results of their rabbit investigations, Carl and Dr Bito suggested that exogenous administration of low doses of certain pros-
taglandins or their analogues would aid in the treatment of ocular hypertension; however, they ran into difficulty when they observed tachyphylaxis of the hypertensive response with successive dosing. Their initial findings published in 1977 had failed to demonstrate any tachyphylaxis of the hypertensive response when they applied prostaglandins at intervals of 1 to 3½ hours.8 However, their results in rabbits did not temper Carl's faith in the possible clinical usefulness of prostaglandins for glaucoma therapy9 or his desire to continue the experiments in monkeys. As a result of this work, Carl and Dr Bito9 showed in a 1981 publication that periodic, successive topical application of prostaglandins reduced IOP in normotensive owl monkeys. They described how topical application of certain prostaglandins to normotensive or hypertensive primate eyes can cause a long-lasting and highly significant decrease in IOP and suggested that prostaglandins or their analogues might aid in the therapeutic control of ocular hypertension and glaucoma. Unpublished but recorded in Carl's original laboratory notebook is the fact that he and Dr Bito had also shown a maintained reduction of IOP by successive, periodic topical application of prostaglandins in a glaucomatous primate eye model.9

Carl repeated treatment in the glaucomatous eye of the owl monkey with prostaglandins to maintain an IOP reduction. The pronounced and prolonged reduction of IOP achieved with prostaglandin F2α in owl monkeys9 could not be reproduced in 2 rhesus monkeys (only one of which is described in the 1983 publication10). The IOP reduction was maintained during 24 hours after a single application of a prostaglandin in owl monkeys (demonstrated in their published study9 and in the unpublished data from Carl's laboratory notebook), but the magnitude and duration were less in rhesus monkeys after 1½ to 1½ hours,10 as would eventually be discovered in humans.

Carl and Dr Bito discovered that the hypertensive effects of prostaglandins in owl monkeys, but not in rhesus monkeys, closely mimicked the effects in humans (effective for ≥24 hours when applied daily). This finding that prostaglandin-induced reduced IOP in owl monkey eyes, instead of rhesus monkey eyes compared with human eyes, could not have been predicted a priori.

During his ophthalmology residency at the Jules Stein Eye Institute, University of California, Los Angeles, from 1980 to 1983, Carl looked into the possibility of continuing his work by further evaluating the effect of successive doses of prostaglandins in monkeys, but this was incompatible with his clinical training. Next, he considered a clinical study to evaluate the effects of topically applied prostaglandins in humans. He obtained permission and encouragement to pursue such studies from Bradley R. Straatsma, MD, JD, chairman of the Department of Ophthalmology, but Dr Bito thought that the concept was premature for clinical studies. Instead, Carl continued his research on the effect of prostaglandins in the eye by performing and later publishing the results of investigations on the role of prostaglandins in treating surgically induced (or trauma induced) miosis and in mediating the reduction of IOP produced by topically applied epinephrine in humans.11

After residency, Carl returned to New York City for glaucoma fellowship training under the mentorship of Steven M. Podos, MD, chairman of the Department of Ophthalmology at the Mount Sinai School of Medicine. With support from Dr Podos, he continued his prostaglandin research with Dr Bito in monkeys and humans. In mid-1983, Carl began work (which was later published) to scientifically establish for the first time that periodic topical application of prostaglandins could maintain an IOP reduction without any evidence of tachyphylaxis in nonhuman primate eyes.11-13 Before these investigations, evidence supporting the lack of tachyphylaxis had been anecdotal from the experiments in owl monkeys by Carl and Dr Bito and in the 2 rhesus monkey studies14,15 led by Dr Bito.

Taking the lead in what became known as the PG [Prostaglandin] Project, Dr Bito retired from Columbia University after doing the legal work to patent the idea and performing all the legwork to get Pharmacia, Inc, to license the patent and continue the research and development needed to bring the drug to market. Although Carl had collaborated with Dr Bito during medical school and throughout his physician training and later became a consultant for Pharmacia, Inc, he was not named as coinventor on the latanoprost patent.

How could that be? When interviewing Carl's Yale University research advisers, Dr Sears and Dr Reid, I asked, "Was it Carl's idea that PGs reduced IOP back at Yale?" Dr Sears responded yes and later e-mailed: "Carl was the most important clinician in all this, and, without him, I doubt the chemistry and physiology would have come to fruition as it did." Dr Reid added: "Carl was the driving force for the whole idea of using PGs for glaucoma. His ideas, his innovation and perseverance made this project work. László contributed to this project, but for him to get all the credit and none for Carl was a true tragedy and a gross mistake." Carl believed that this was an error of omission.

Without being coinventor, Carl was nevertheless a driving force keeping the PG Project moving forward until (and after) the correct analogue for human use was developed by Johan Stjernschantz, MD, PhD.14 At meetings around the world, Carl taught scientists and physicians about prostaglandins. During our telephone interview, Dr Bito said:

One of Carl's greatest contributions to the success of latanoprost was his enthusiastic and well-argued support of it in forums, conferences, and in scientific journals. He consistently encouraged finding answers through research and long-term studies and served as a principal investigator of the US phase 3 multicenter clinical investigations. In a further demonstration of his belief in the benefits of latanoprost, Carl made a convincing, if not the most convincing, presentation at the FDA [Food and Drug Administration] hearing which led to its approval as Xalatan.

In addition to the national conferences, Carl attended meetings in 35 countries and 50 foreign cities. While at a 1992 meeting in Italy, I
met Dr Sears for the first time, as he shook hands and congratulated Carl for proving his hypothesis. Although Dr Sears had disagreed with him, he was sufficiently impressed to have kept Carl’s laboratory notebook (which included raw data from his research studies) and thesis, and Dr Sears then sent them back to Carl after the meeting.

When I interviewed Dr Bito about Carl’s contributions to the PG Project, he said:

Carl had independently concluded that the role of PGs in ocular inflammation is primarily a hypotensive (low pressure) one. Carl showed a keen ability to analyze and critically evaluate relevant publications, as well as to defend his viewpoints vigorously and effectively—virtues he never compromised over the years.

Carl’s training and research led us to live on both coastlines, and we then settled down on a Midwestern farm during 1991, after Michael E. Yablonski, MD, PhD, recruited Carl to be vice-chairman of the Department of Ophthalmology and Visual Sciences at the University of Nebraska Medical Center, Omaha. When Dr Yablonski left the department in 2000, Carl became the chairman, with a vision for building an eye institute with international recognition.

Although Carl’s health began to fail in December 2006, he continued to work for as long as he could, doing as much as he was able for his students, patients, and the growing Department of Ophthalmology and Visual Sciences. He was greatly admired by those he taught, mentored, and inspired, as was made evident at Carl’s memorial service, when he was paid the following tribute:

John F. Golan MD, dean of the University of Nebraska School of Medicine, said:

With his international recognition, Carl was responsible for elevating University of Nebraska Medical Center’s ophthalmology department to national prominence. He was the model chair.

Researcher Carol B. Toris, PhD, said:

Everything changed when Carl became chairman because of the way he supported research. Carl’s leadership abilities were most admirable. He took the time weekly to attend the conferences on basic research articles. Carl was an incisive and critical reader, with an amazing memory for past articles. He was frequently skeptical of studies from pharmaceutical company laboratories and would become quite animated when he found misrepresentation or misinterpretation of some results.

Thomas W. Hejkal, MD, PhD, now chairman of the Department of Ophthalmology and Visual Sciences, memorialized:

Carl always demanded precision in drawing conclusions in the form of scientific studies. His scientific integrity was beyond reproach. Carl’s greatness was not in his genius. He just happened to have that gift. It was what he did with his gift that made him great.

Former fellow Dan L. Eisenberg, MD, described his experience of training with Carl in terms of editing:

Writing a paper with Carl was both wonderful and excruciating. His knowledge of the literature was so vast that even a simple statement might receive 7 citations, and because we had many projects going simultaneously, we routinely met deadlines with just minutes to spare. . . . Carl was a perfectionist with a capital P. His ethic would not tolerate inaccuracy; every statement had to be correct. Ultimately, he wanted to bring research back to the clinic, where patients could benefit. He conducted investigations because he needed to find answers, and he published his results because he wanted to share his knowledge with others, not to satisfy his ego or better his professional standing.

Staff ophthalmologist James W. Gigantelli, MD, remembered:

In the clinical arena, Carl was compulsive. The world wants evidence-based medicine. Carl taught us evidence-based medicine before the phrase was conceived. He taught us [that] to provide patient care is not enough. To walk in Carl’s shoes, you truly had to care about the patients. In the clinic there were no geographical or socioeconomic boundaries. A patient without a penny for their care still received care, care that in no way could be different from a patient who could choose to fly anywhere in the world to receive their care from the specialist that the experts called a best doctor. He taught us to educate thyself thoroughly, but don’t succumb to dogma. He taught us to challenge conventional wisdom. Ask the questions, and, if possible, work tirelessly to answer them.

I witnessed how Carl maximized his short life by working tirelessly and accomplishing more in his 55 years than seemed humanly possible: he was a member of 26 eye societies, served on 4 editorial boards, published more than 286 papers in the literature, and received 69 honors and awards (still counting). I believe that the world is a better place because Carl was here. His teachings will live on and continue to inspire the next generation of ophthalmologists in the Carl B. Camras Clinical Research Center inside the new Stanley M. Truhlsen Eye Institute at the University of Nebraska Medical Center. Our 2 daughters and I are proud of Carl and grateful for all our time together. We will miss him forever.

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