Retrospective: Edwin G. Krebs (1918 – 2009)

Our Beloved "Reluctant" Biochemist

BY JOHN D. SCOTT

Edwin G. Krebs, a giant of biochemistry in the 20th century, died Dec. 21 in Seattle. He was 91. His discovery of protein phosphorylation as a regulatory mechanism (with Edmond Fischer) touched all aspects of biomedical science and profoundly influenced therapeutic approaches now widely used in clinical care. Ed's life story epitomizes his commitment to family and colleagues, excellence in research and service to the biochemical community.

Ed Krebs was born in Lansing, Iowa, on June 6, 1918, the son of a Presbyterian minister and a schoolteacher. His father died suddenly when Ed was 15 and, at the height of the Great Depression, the family moved to Urbana, Ill., for financial reasons. It was there that Krebs completed high school and earned a degree in chemistry from the University of Illinois in 1940. As an undergraduate, he became enamored with organic chemistry but eventually chose to become a physician, largely because he won a scholarship to attend Washington University School of Medicine in St. Louis.

The principal responsibility of a medical school during the war years was to train physicians for the armed forces. However, Krebs also was encouraged to participate in "medical research." After graduating from medical school in 1943 and doing 18 months of residency training in internal medicine at Barnes Hospital in St. Louis, Krebs went on active duty as a medical officer in the Navy. After being discharged from the Navy in 1946, Krebs returned to St. Louis with plans of becoming an academic internist. However, all of the hospital positions were filled by returning veterans, and, as a temporary measure, Krebs was advised to study basic science as a postdoctoral fellow at Washington University. Largely because of his background in chemistry, he was accepted into the laboratory of future Nobel laureates Carl and Gerty Cori in the department of biochemistry. After two years in the Cori lab doing research on the interaction of protamine with rabbit muscle phosphorylase, Ed became so captivated with biochemistry that this intially reluctant biochemist never returned to internal medicine. The next step was to find a permanent faculty position.

During his naval service, Ed's ship had gone to Seattle. The tranquil waters of the Puget Sound and the natural beauty of the city left a lasting impression. So, in 1948, he happily accepted a position as assistant professor of biochemistry in the fledgling University of Washington School of Medicine. Under the capable leadership of Hans Neurath, the department of biochemistry was being expanded to incorporate expertise in protein chemistry and enzymology. This included the recruitment of Edmond Fischer in 1953 — a talented and charismatic Swiss biochemist with experience in the enzymatic analysis of potato phosphorylase. Thus, a lifelong friendship and a formidable research partnership was forged.

Together, Ed (Krebs) and Eddy (Fischer) determined the mechanism by which 5'-AMP served as an activator of phosphorylase *b*. They found that ATP was required for phosphorylase activation, and, in a somewhat unusual experiment, discovered that calcium, leaching from filter paper used to clarify the extract, was an important co-factor. By using gamma-^{32}P-labeled ATP, they demonstrated that phosphate was incorporated into a specific serine residue of phosphorylase, thereby yielding the activated phosphorylase a form. This landmark paper was published in the Journal of Biological Chemistry in 1955

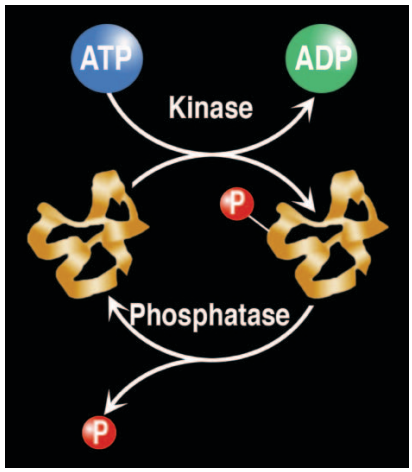
(1). Subsequently, Krebs, Fischer and colleagues confirmed that this phosphorylation is mediated by a phosphorylase b kinase, which is itself controlled by a cAMP-responsive kinase, leading to the idea of a kinase cascade. In 1968, Krebs purified this cAMP-dependent protein kinase (PKA).

At this point in his career, interests in teaching and certain aspects of administration motivated Krebs. In 1968, he was attracted by the opportunity to become the founding chairman of the department of biological chemistry at the University of California, Davis, and stayed for a period of eight years. Ed also embarked on his long association with the American Society for Biochemistry and Molecular Biology, initially by joining the editorial board of the Journal of Biological Chemistry. In 1972, he became associate editor for the journal and remained in this position for more than 20 years. He also served as the president of ASBMB in 1985. In 1977, he returned to the University of Washington as chairman of the department of pharmacology. What he liked most about both positions, he said, was the responsibility of selecting good faculty members for the departments. At UW he was also appointed an investigator in the Howard Hughes Medical Institute.

After achieving his goals as department chair in 1983, Krebs refocused his efforts on research and training junior scientists. At this later stage in his career, he set his sights on solving new problems in signal transduction. His laboratory contributed to the analysis of phosphotyrosine signaling events and published key findings that were instrumental in the discovery of a new phosphorylation cascade— the MAP kinase pathway.

Krebs received many major scientific awards for his insights into the principles governing cellular regulation in health and disease. Among those honors were election to the National Academy of Sciences (1973), the Passano Foundation Award (1988), the Horwitz Prize (1989), the Lasker Research Award (1989), the 3M Life Sciences Award (1989) and the Welch Award in Chemistry (1991). At age 74, he and Edmond Fischer were honored with the 1992 Nobel Prize in Physiology or Medicine for the discovery they made almost 40 years before and its ongoing influence in many scientific and biomedical fields.

In 1997, Ed finally closed his lab but remained a fully committed ambassador for biomedical research at the University of Washington. He was frequently spotted wandering the halls of the medical center on his way to hear the latest and greatest results in a research seminar. Ed is survived by his wife of 64 years, Virgina (Deedy) Krebs, children Sally, Robert and Martha and several grandchildren.



This iconic image depicts the protein phosphorylation-dephosphorylation process as elucidated by Edwin Krebs and Edmond Fisher in their seminal 1955 Journal of Biological Chemistry paper (1).

Edwin G. Krebs will certainly be remembered for his keen intellect, astonishing research productivity and iconic status within the biomedical research community. He was a beloved mentor to numerous students and postdoctoral fellows. Those who were privileged to work closely with him will remember him fondly as a kind and gentle mentor who passed on extraordinary insights in a quiet and dignified manner. The legacy of this self-proclaimed "reluctant biochemist" should be a wonderful inspiration to the next generation of our profession.

Below, we offer reflections from several of Krebs' friends and colleagues.

I was very saddened by the passing of Ed Krebs. Even though I had not seen Ed for several years, I still considered him a close friend.

We are all familiar with his monumental work on protein phosphorylation. Less known is his importance to biochemistry as a member of the Editorial Board and as an Associate Editor of the Journal of Biological Chemistry. His influence on the development and operations of the JBC was particularly important during this period of rapid expansion for the Journal. We always depended on his advice and thoughtful consideration both on the overall operation of the Journal and on the review of specific manuscripts. Authors often commented on the thoroughness and fairness of his reviews.

We had many wonderful interactions over the years, due in large part to his commitment to the JBC. Ed was a superb scientist and a nice person, and I— and all of the Associate Editors— feel lucky to have known and worked with him.

Herbert Tabor
Editor
Journal of Biological Chemistry

I enjoyed working with Ed Krebs for five years as an associate editor of JBC. I had known him when he was a faculty member of the department of biochemistry at the University of Washington School of Medicine in Seattle,

but I saw him in a new role with JBC. He always had good advice in matters we considered at our associate editor meetings.

Robert L. Hill
James B. Duke professor of biochemistry
Duke University

Ed Krebs and Ed Fischer were two icons in the field of reversible phosphorylation. When my laboratory group started its work on protein phosphatases, they were both very welcoming to me and to members of my group. Their personalities made the field better, and they set the standard for exemplary scientific behavior. I also had the privilege of giving the Ed Krebs Lecture a few years ago, an event I still remember very fondly and treasure to this day.

Jack Dixon
Professor of pharmacology, cellular and molecular medicine and professor of chemistry and biochemistry
University of California, San Diego

I was so sad to hear of the passing of Ed Krebs. He was one of the true gentlemen in science. I owe any success that I have had to his willingness to take on a young and very naïve scientist from Wyoming as a postdoctoral fellow. His lab was a place where you could propose and pursue your own projects under his subtle, but always insightful, guidance. I remember once returning from an interview for a faculty position that I was not offered, probably due in part to my inherent laconic personality. Ed gently pulled me aside, put his arm around my shoulders and said "Bob, the next time you go on a job interview, take some amphetamines."

Robert Geahlen
Professor of medicinal chemistry and molecular pharmacology
Purdue University

My fondest memories of Ed involved our annual laboratory research retreats. These were held over a couple of days and nights in a place called Pack Forest, a conference center that was owned by the University of Washington's School of Forest Resources. It was not the Hilton. It was a former logging camp where you slept in bunkhouses, showered in a communal bathhouse, gave your research presentations in a big log cabin heated by a stone fireplace and ate hearty food in a rustic cafeteria. Away from the office, the phone, etc., Ed doffed his coat and tie and donned his jeans and flannel shirt. He joined us for hikes, softball (he broke his hand one year) and Frisbee. There, he'd let his guard down a little and share stories about life. The one that sticks in my mind was the awkward moment when he arrived in Seattle to start work at the UW in the late '40s. There, he was greeted by several reporters wishing to get the first interview with the son of Sir Hans Krebs...

When I arrived as a postdoc in Seattle, I was thoroughly intimidated by this great man. Even the most innocuous conversations were awkward as I tried to get to know him. Then, one evening when the lab was quiet, I was just finishing a cartoon I had drawn that depicted one of my fellow postdocs, Don Tinker, dressed in a tutu, wielding a magic wand. Ed walked past me on his way out. Behind me, I heard him softly repeat the words of the caption — "Tinker Bell" — followed by a quiet chuckle. I had discovered Ed's dry but wicked sense of humor.

Peter Kennelly
Professor and head of biochemistry
Virginia Polytechnic Institute and State University

My postdoctoral experience with Ed Krebs molded my scientific career. Ed was a very kind gentleman. He had a special knack for telling you that your ideas or interpretations were wrong in an unobjectionable way. He was careful to not overtly dictate any of his ideas to his scientific group, but he made suggestions and nourished his thoughts carefully in order to guide young scientists toward the right goals. Sometimes, I was proud to have a good idea, but I came to realize later on that the idea actually came from Ed. I remember just a few times that he was persistent in directing my research toward a specific direction, but, even then, he did it in a congenial manner, and he was practically always right.

Ed will be sorely missed in the scientific world, especially in the field of signal transduction. I miss my wonderful mentor and good friend.

Jackie D. Corbin
Professor of molecular physiology and biophysics
Vanderbilt University Medical Center

For me, Ed was a hands-off adviser. He gave people tremendous freedom — there was certainly ample opportunity to sink or swim in his lab. Ed had a heavy journal editor role, so we did not see a lot of him in the laboratory, but every now and then he would drift in for coffee. The one time Ed came into the laboratory on a Saturday, we were so pleased to see him and be noticed for our diligence, but it came with an unexpected cost. He was there to centrifuge some terrible homemade wine, and we had to taste it in little glass beakers.

Between his hearing aide and my Australian accent, I am not sure he understood a thing I said for the first six months. When I first met Ed, I was struck by his being so low key and devoid of any "brilliant façade," but then I

came to realize that nothing but clear thinking and common sense ever parted from his lips. While somewhat remote, he was immensely likeable, someone whose value just kept growing on you.

His weekly laboratory meetings were of tremendous value and provided the real mentoring environment. Ed was keenly interested in politics and the U.S. economy. He was a strong critic of the infamous U.S. Sen. William Proxmire and his "Golden Fleece" awards. Perhaps the best illustration of his political interests was at a plenary lecture at a Gordon Conference, where he traced the development of the protein phosphorylation field over his long career and what was happening in politics in the U.S. at the time of each major scientific development.

We remember Ed with fondness and enduring thanks for the impact he had on science and our lives.

Bruce E. Kemp
Pehr Edman Fellow in protein chemistry and metabolism
St. Vincent's Institute of Medical Research

My time with Ed Krebs as a postdoc in the mid-1970s in both Davis and Seattle had a great influence on my scientific development. Ed had a "hands-off" approach to science that focused on providing resources for a large lab with mostly postdocs, each with a different, mostly self-directed project that had minimal overlap with other projects. This freedom had a broadening impact on postdocs, and, for myself, it formed the model for my own laboratory. Ed expected each person to have passion for his or her work, and once commented that he was disappointed to drive by the lab late on a Saturday evening and find no lights on. We postdocs then decided to leave the lights on 24/7.

Ed was a traditional "ice bucket biochemist" and enzymologist, and I was his first postdoc with a cell biology background. I think he was initially not sure what to make of "biochemistry without a license," but that skepticism vanished when we were quickly able to show by microinjecting protein kinase A into Xenopus oocytes that changes in kinase activity could fully account for all the in vivo actions of cAMP in an important biological process. For myself, I learned how to purify enzymes, beginning with phosphorylase kinase, from kilograms of tissue, and this experience served me well in later years when purifying mitotic enzymes (Cdks), whose characterization had eluded others for many years. It was an amazing time in science, because, although Krebs and Fischer had shown the critical importance of phosphorylation in glycogen metabolism, it was not thought to be of much importance for other aspects of biology. At the end of my postdoc, it was reported that the Src oncogene encoded a protein kinase— a finding that linked kinases to cancer and ultimately led the way to the current realization that protein phosphorylation controls virtually all biological processes. It was one of those rare times in science when one happens to be working on something that turns out to be much more important than initially believed.

Although Ed received many honors during his lifetime, his gentle nature was very unassuming, and he exhibited little interest in scientific politics or in going to meetings. He had a long-standing presence in ASBMB as associate editor of the JBC and felt that there was no need to search for "higher impact" journals if the work was sound. Throughout his life, he kept focused on key questions in glycogen metabolism, even after vastly increased support from Howard Hughes Medical Institute and winning the Nobel Prize. To the end, he felt that there were many questions still unanswered about the regulation of metabolism by protein phosphorylation, and he wanted to continue working on them.

James L. Maller
Professor of pharmacology
University of Colorado School of Medicine

I was fortunate to have Ed as my Ph.D. mentor from 1966 to 1970. Two specific pieces of advice that influenced my career come to mind. The first was when I was a student in Ed's lab and was concerned that another lab was working on the same project. Ed's advice was that any time you are working on an important project, there will be strong competition, so find some niche where you have an advantage and pursue that aspect. The second was as a professor at Vanderbilt (University) when we were both Howard Hughes investigators. There had been a change in Hughes leadership, and I was concerned about whether or not they would continue to fund my research. Ed told me to not worry about what Hughes wanted, just make sure my research was outstanding— if so, it would all work out. He was right! Ed's legacy will continue through the many young scientists he mentored.

Tom Soderling
Senior scientist, Vollum Institute
Professor of biochemistry
Oregon Health and Science University

Thinking of Ed always brings a smile to my face. While others will rightfully comment on his brilliant scientific insight, his administrative skills and his role as a mentor, what particularly stands out in my memory is Ed's unusual sense of humor. About 10 years ago, I brought a star-struck graduate student to meet Ed, who proceeded to talk to her about research that he had done "during World War I." Afterward, he professed to me his amusement that the student had not caught the

historical error. This, and many other incidents, always left me wondering whether Ed was kidding around in a given situation. He kept such a straight face that one could never tell. Once, during a whiskey-laced late-night card game at one of our Pack Forest retreats, Ed told me that I had a good poker face. Coming from him, this was quite a compliment!

I thank Ed for many things, including his anecdotes of agricultural pursuits, his tutelage in antique hunting and his mentoring in how to write manuscript reviews, but most of all I thank him for demonstrating how a great scientist can be a great human being.

Kathryn E. Meier
Director of program in nutrition and exercise physiology
Washington State University

It is a pleasure to remember Ed Krebs as a friendly and passionate teacher and science supervisor. His pioneering work on protein kinases as modulators of cellular functions served as a basis for my later investigations. He cordially shared his knowledge of biochemical methodology and readily participated in discussions on protein kinases and protein phosphatases. Much of what I and my colleagues were able to accomplish was made possible by his intuitive research.

Franz Hofmann
Emeritus professor of pharmacology
Technische Universität München

I was on a plane from Durham, N.C., to Seattle, Wash., to start my postdoc in Ed's lab when Mount St. Helens first erupted. It was an apt introduction to my time in Ed's lab. It was May 1980, and tyrosine phosphorylation of pp60src recently had been described. There followed a rapid explosion in our knowledge of protein tyrosine kinases, and Ed's lab was the ideal place to be during this revolution. Ed was supportive of his postdocs who ventured into this new area, and he helped us apply the knowledge he had acquired in decades of studies on protein kinases to these new members of the family. He was rigorous in his approach to data but kind and patient at the same time. He was a wonderful mentor to whom I always will be grateful.

Linda J. Pike
Professor of biochemistry and molecular biophysics
Washington University School of Medicine

When I began working with Ed, his only directive was "find a protein kinase cascade— I know it exists." This initiated studies that led to the discovery and characterization of MAP kinases and MAP kinase kinases. I could not have become a professor without Ed's generosity in accepting me in his lab when my options were limited.

One of the most important lessons that Ed taught us by example was how to conduct ourselves as citizens within the scientific community. Our work on various projects led to competitive interactions with scientists at other institutions and sometimes within our own lab. Ed maintained a balanced approach to scientific competition, treating whomever he met as a colleague and showing him or her great respect and kindness. There were very few people who Ed disliked, and he always was able to find strengths in every person. I recall sessions in his office when Ed pulled out letters and other documents from his past that illustrated in various ways "how to handle oneself with aplomb." Ed valued this deeply, and, in doing so, he set a high standard for fairness, collegiality and professional conduct, which continues to influence investigators throughout the field of signal transduction.

What I remember most fondly about Ed was his keen sense of humor. We'd have to pay close attention in order to pick up his hilarious observations, which were often delivered as soft, understated commentaries, as well as the occasional practical joke. The year was 1991 and Bill Clinton had generated controversy during the primaries with statements about his drug use. To kick off the annual Krebs & Fischer lab retreat at Mt. Rainier, Ed stood up and confessed to the group that "I too have used pot, but that was before I became a professor."

Natalie Ahn
Associate professor of chemistry and biochemistry
University of Colorado at Boulder

Ed Krebs was one of those people whose accomplishments were so numerous and so extraordinary that, paradoxically, they were easy to overlook because they formed such a huge part of our scientific world. But, every time we teach or do research on the regulation of pretty much anything that goes on inside the living cell, the chances are good that we are either talking about or building on his work.

Gregory A. Petsko
Gyula and Katica Tauber professor of biochemistry and chemistry
Brandeis University

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REFERENCE

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