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EDWIN G. KREBS
1918–2009

A Biographical Memoir by
EDMOND H. FISCHER

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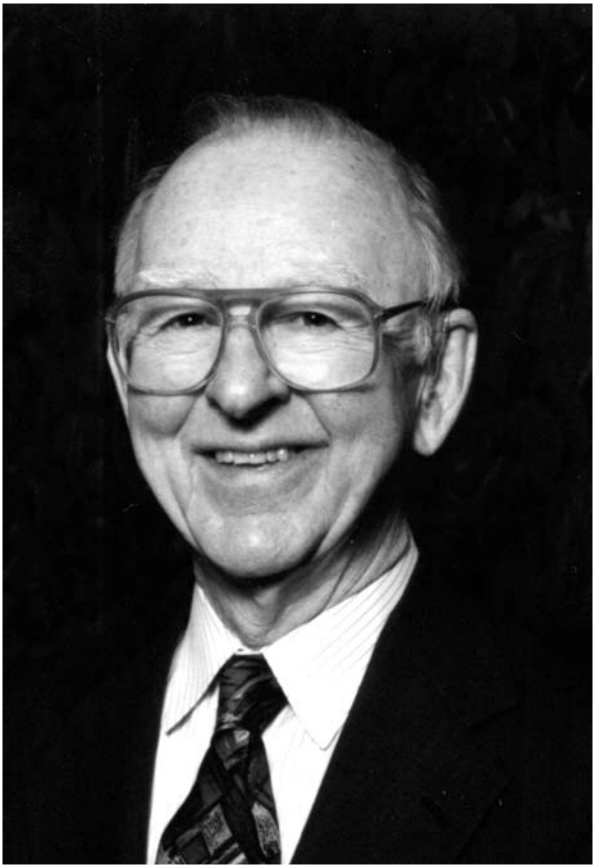
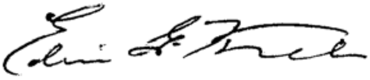
Biographical Memoir





EDWIN G. KREBS

June 6, 1918–December 21, 2009

BY EDMOND H. FISCHER

ED KREBS DIED ON DECEMBER 21, 2009, after a long and increasingly debilitating illness. For me, it marked the end of an extraordinary era and the end of a lifelong and marvelous friendship. I first met Ed early in 1953 in Los Angeles when Hans Neurath was recruiting me for a position in the Department of Biochemistry at the University of Washington in Seattle. When I joined the department, a few months later, he was the one who really took care of me. I arrived at a very turbulent time—at the heights of the McCarthy era (or perhaps more appropriately, the McCarthy inquisition)—and everybody was up in arms. Having recently arrived from the Old Continent and seen what had happened over there 20 years earlier, I was pretty upset and disturbed by what was going on. Well, Ed was the one who calmed me down and showed me what America was really like. He made it a point to educate me about the ways of the department and the university and patiently unraveled for me the complexities of the American academic system.

Ed was a person of solid judgment, insightful, down-to-earth, and straightforward. He also had a dry sense of humor. He was enormously respected, admired, and liked by his students; he never tried to impose his ideas on them but let them fend by themselves. He loved to read, particularly

history books about the Civil War and the settling of the West, and related adventure stories. We enjoyed exchanging good and trashy mystery novels; he also liked to take care of his garden. He was an avid antique collector; over the years he must have accumulated about 600 lampshades and took as much pleasure from meticulously photographing and cataloging them as he did from buying them.

EARLY YEARS AND EDUCATION

Ed Krebs was born on June 6, 1918, in Lansing, Iowa, the third of four children of William Carl Krebs, a Presbyterian minister, and Louise Helen (Stegeman) Krebs, who taught school until she got married. As was common in ministers' families, they moved several times, first to Newton, Illinois, and when Ed was six, to Greenville, Illinois. As a young man he enjoyed the outdoors (hiking, fishing, and sandlot sports), stamp collecting, and eventually ham radio.

His father died suddenly at the end of his first year in high school, when he was 16, which made it very difficult for a family with limited income. They therefore decided to move to Urbana, Illinois, where his two older brothers were already enrolled at the University of Illinois. They rented a large house so they could rent one of the rooms to help with the expenses. From 1933 to 1940 Ed completed the last three years of high school and carried out undergraduate work at the University of Illinois. Because these were depression years, on thinking about various professions, he gravitated toward a scientific career, not so much because of a deep attraction toward the field but because there was security in becoming a scientist. He decided to enter the University of Illinois in 1936 with the idea of majoring in some branch of science related to chemistry. He had an opportunity to carry out some undergraduate research in the laboratories

of Harold Snyder and Charles Price, which he enjoyed very much.

By the beginning of his fourth year, Ed narrowed his choice to organic chemistry or medicine, for which he would require financial help. This became available in the form of a scholarship to attend Washington University School of Medicine in St. Louis. Ed's university experience was not all academic. When he graduated, he went all the way down the Mississippi River in a small boat with two of his classmates (one of whom was Andy Anderson who became professor of chemistry at the University of Washington).

His stay at Washington University played a decisive role in his scientific career; besides providing him with classical medical training, it opened his appreciation of medical research. Basic science courses were solid and the equivalent of graduate courses, and students were encouraged to participate in laboratory projects. This he did, first under Dean Philip A. Schafer and later under Arda A. Green, a faculty member associated with Carl and Gerty Cori. It is there that for the first time he heard about glycogen phosphorylase, an enzyme that Arda Green had crystallized and shown to exist in two interconvertible forms referred to as phosphorylase *b* and *a*. Phosphorylase *b* had an absolute requirement of adenylic acid (AMP) for activity whereas phosphorylase *a* was active without this nucleotide.

His medical school years, 1940-1943, were war years, and his main objective was to become a physician who could serve in the armed forces. He spent 18 months in residency training at the Barnes Hospital in St. Louis. It is there that he met Deedy Frech, a student nurse, whom he married before going on active duty as a medical officer in the navy. The navy was the only time he really practiced medicine and, in fact, enjoyed the experience to such an extent that when he was discharged in 1946, he returned to St. Louis to continue his

residency with the idea of becoming an academic internist. But since all hospital residency places were already taken, he was advised to continue his studies in a basic science department. He selected biochemistry and was lucky enough to be accepted as a postdoctoral fellow with Carl and Gerty Cori (who received the Nobel Prize in Physiology or Medicine in 1947). For two years in their laboratory he studied the interaction of protamine with rabbit muscle phosphorylase. He became so fascinated with biochemistry that he decided to remain in that field rather than returning to internal medicine.

UNIVERSITY OF WASHINGTON

THE ORIGIN OF REVERSIBLE PROTEIN PHOSPHORYLATION

In 1948 Ed was offered an assistant professorship in the Department of Biochemistry at the University of Washington. He accepted enthusiastically because during his active duty in the navy, his ship had put into Seattle and he had been greatly impressed by the beauty of the city. In 1950 Hans Neurath took on the leadership of the department and began to build what was to become one of the foremost biochemistry departments in the country. Neurath worked on proteolytic enzymes and zymogen activation, so the main emphasis of the department was on protein chemistry and enzymology. This provided an excellent environment for Ed to pursue and develop his field of investigation, which, at that time was directed toward a study of yeast glyceraldehyde-3-phosphate dehydrogenase, and a reduced derivative of diphosphopyridine nucleotide of unknown function that he temporarily termed "DPNH-X."

Ed and I became involved with the problem of glycogen phosphorylase in 1953 when I joined the Department of Biochemistry at the University of Washington. As indicated above, Ed worked on muscle phosphorylase as a postdoc-

toral fellow with the Coris in St. Louis. I obtained my Ph.D. degree with Kurt H. Meyer at the University of Geneva, Switzerland, where, among other things, we had isolated potato phosphorylase. Having worked on the same enzyme, we naturally spoke a lot about phosphorylase and its possible mode of regulation. It must be remembered that in those days, half a century ago, one knew essentially nothing about the mechanism of enzyme regulation, and terms such as signaling or signal transduction that are used so commonly today in biochemistry did not even exist.

Ed and I were particularly intrigued by a problem that had not been solved regarding muscle phosphorylase, that is, the role AMP played in its activation. The Coris knew that the enzyme existed in two forms: form *a* that did not require AMP for activity while form *b* did, but they did not know how these two forms differed. Strange as it might seem today, they had actually dropped the problem. Ed, having come from the Coris, assumed like they did and like most people did that AMP played the role of some sort of coenzyme or prosthetic group. On the other hand, the potato phosphorylase we had isolated in Geneva showed no requirement whatsoever for AMP. Even though biochemistry was still in its infancy in the early 1950s, it was well established that coenzymes were conserved throughout all species. It therefore seemed unlikely that AMP would serve as a coenzyme for muscle phosphorylase but not for the potato enzyme. Accordingly, we decided to tackle this problem.

At first, Ed expressed some hesitation. In those days postdoctoral fellows, when they left a lab, did not work on the problem of their mentor; it was simply not done. But then, he thought that as there had been five years since he had left the Coris' lab, it should be permissible for us to work together on this problem. So we got started, just the two of us, side by side at a bench we had cleared off, working

much more as two close friends than as two colleagues in a department. As it turned out, we never solved the AMP problem either; for that, we had to wait six to eight years for Jacques Monod, Jeffrey Wyman, and Jean-Pierre Changeux to come out with their remarkable allosteric model for enzyme regulation. But we soon found out that in reality the activation of phosphorylase involved a totally different kind of mechanism.

To begin with, we had to prepare some pure phosphorylase using the Coris' classical procedure. It called for making a water extract of ground muscle, squeezing this gunk through cheesecloth and then filtering the very turbid extract through a huge battery of filter papers. The filters would get rapidly clogged up so the Coris would simply punch a hole in the filter and move to the next one. Gerty Cori always said that one had to work very fast, otherwise active phosphorylase *a* might be degraded to the inactive *b* form; it was not unusual for them to use 15 or 20 large filter papers. The method was very cumbersome, so we decided to replace the filtration procedure by a centrifugation. But then, when the extracts were centrifuged, no matter how carefully or how fast we worked, the preparations always failed. We could never obtain active phosphorylase *a*, only the inactive, so-called degraded, *b* form. Until finally, in desperation, we decided to follow the Coris' procedure to the letter, paper filtration and all, checking every step, analyzing every fraction from beginning to end.

To our total amazement, we found, first, that the original extract obtained from the muscle did not contain active phosphorylase *a,* as we had expected, but the inactive *b* form; second, that the inactive enzyme had been converted to the active *a* form during the filtration process.

Calling this a letdown would be putting it mildly. Of all the wonderful, sophisticated mechanisms one could dream

of to activate an enzyme, filtration through paper was really pathetic, simply the pits. But then we rapidly found that this conversion was not due to the filtration per se but to traces of calcium ions that contaminated the filter paper; enough were picked up during the multiple filtrations the Coris used to do the trick. We found next that the conversion also required Mg-ATP always present in fresh muscle extracts. If the extracts were aged for a while, ATP was hydrolyzed and no conversion occurred until ATP was re-added. This was really the reason why Gertie always said one had to work very fast. Unknown to her, it was because ATP was getting hydrolyzed by the multiple ATPases present in muscle extracts. If she had simply added some ATP, she would have reactivated her enzyme and this would have been the end of that. Anyway, this strongly suggested that we were dealing with a phosphorylation reaction.

In those days there was no radioactive ATP^{32}; the compound had to be synthesized. We knew that Art Kornberg had prepared some radioactive ATP, which he needed for his studies on the biosynthesis of DNA. We called Art, who was in St. Louis in those days, and he immediately sent us a sample of γ-labeled ATP^{32}. With this we could demonstrate that radioactivity had been incorporated into a protein fraction that turned out to be phosphorylase. Only then could we propose that the reaction proceeded according to the following scheme: that phosphorylase *b* was converted into phosphorylase *a* in a reaction that required Ca^{2+}, Mg^{2+}, and ATP, and an enzyme that we called phosphorylase kinase. Obviously, the reverse reaction had to be catalyzed by a phosphorylase phosphatase.

We sent the manuscript to the *Journal of Biological Chemistry*. In those days the editorial board of the JBC was very small. There were perhaps five or six people in the whole country who reviewed all the manuscripts submitted to the journal.

And we remembered well that when we submitted our first paper on phosphorylase, we were aware that Carl Cori was among the editors, so we knew he would be the one who would review it. But we had total faith that he would not take advantage of seeing the manuscript, and he did not. On the contrary, he was very excited by our data.

What would be viewed today as a most ordinary reaction, if not a trivial reaction, came nevertheless as an enormous surprise because at that time nobody could imagine that the phosphorylation of an enzyme could be involved in its regulation. In fact, one knew essentially nothing about phosphoproteins. Only two had been characterized—casein from milk and ovovitellin from egg yolk—and their only function was thought to be associated with the feeding of the young.

As soon as we started to purify the components of the system it became apparent that calcium did not participate directly in the conversion of phosphorylase *b* to *a* even though it was essential when crude muscle extracts were used. Obviously, calcium had to act at an earlier step. Could phosphorylase kinase also exist in an inactive and active form, and could calcium be required for that reaction? That hypothesis turned out to be correct. At this point it was clear that we were dealing with a cascade of two successive enzymatic reactions, of an enzyme acting on an enzyme, both activated through a phosphorylation reaction, to bring about the degradation of glycogen.

At the same time, Earl Sutherland and his group working on liver phosphorylase had arrived at a similar conclusion. An epochal finding that grew out of their studies was the discovery by Earl and Ted Rall of cyclic AMP (cAMP); they showed that it served as a second messenger—an intracellular messenger—for the action of adrenaline. By an unknown mechanism cAMP shifted the equilibrium between phos-

phorylase *b* and *a* toward the active form. After they provided us with a sample of cAMP, we could show that its action was directed toward the activation of phosphorylase kinase, either by accelerating its autophosphorylation or perhaps by acting on yet another kinase that at first we called a kinase kinase for want of a better term. The latter hypothesis was confirmed by the isolation of the cAMP-dependent protein kinase by Don Walsh and Ed Krebs four years later. Since, by that time Sutherland's group had elucidated the formation of cAMP at the membrane level by the hormone-dependent adenylate cyclase system, the entire cascade of enzymatic reactions responsible for the phosphorolysis of glycogen was established.

At the beginning Ed and I did not know whether the reversible phosphorylation of phosphorylase was a unique occurrence, a rare event restricted to the control of that enzyme only or perhaps of a few enzymes of glycogen metabolism. As luck would have it, reversible protein phosphorylation turned out to be one of the most prevalent mechanisms by which cellular events are regulated. It is involved, for example, in the control of metabolism and gene transcription and translation; the immune response; cell development, differentiation, and transformation; and cell cycle. In fact, it would be difficult to find a physiological process that is not directly or indirectly regulated by this kind of mechanism. It is implicated in innumerable hereditary diseases or pathological conditions, including diabetes, Alzheimer's, Parkinson's, and chronic myelogenous leukemia, viral diseases such as smallpox, and bacterial diseases such as cholera and plague. Better than 99.9 percent of all these phosphorylation reactions occur on serine and threonine. One of the most exciting developments in this field was the discovery by Tony Hunter at the Salk Institute, working on Rous sarcoma virus and polyoma middle T antigen 30 years

ago, that phosphorylation of proteins on tyrosyl residues was intimately implicated in cell transformation and oncogenesis, bringing into play a multitude of kinases of cellular or viral origin, or linked to growth factor receptors.

When it was later found that a single seryl residue had become phosphorylated during the phosphorylase *b* to *a* conversion, the reaction seemed so straightforward and simple that there was no doubt in our minds that it would represent the prototype for such kinds of interconversions. As it turned out, it was really the exception. It soon became evident that most other phosphorylation reactions followed a far more complicated path. For instance, whereas phosphorylase is phosphorylated by a single kinase on a single seryl residue, glycogen synthase is hit by no less than eight different protein kinases, all of course totally unknown at that time, and on at least seven different sites. Furthermore, these phosphorylation events must follow a most complicated program of successive reactions that must proceed in a strictly defined order. Had we started working on glycogen synthase, rather than on phosphorylase, we would have never, absolutely never been able to solve the problem.

UNIVERSITY OF CALIFORNIA AT DAVIS

At this point of his career Ed Krebs felt a desire to enlarge his interests in science and become more involved in teaching and academic administration. An opportunity to do so presented itself when he was offered the position of founding chair of the Department of Biological Chemistry in the newly established School of Medicine at the University of California in Davis. He accepted that offer and moved there in 1968. The eight years he stayed in Davis turned out to be most rewarding. He enjoyed the challenge of recruiting new collaborators and faculty members, and the interaction with colleagues in shaping the development of the school. He

recruited a superb group of collaborators, many of whom have had prestigious careers and now occupy professorships in various universities. It was also the time when he became actively engaged in a number of professional extracurricular activities. Aside from being on the scientific advisory board of various institutions, he joined the editorial board of different journals, including the *Journal of Biological Chemistry* in 1965, becoming associate editor in 1972. He held that position until 1993.

It was in Davis that he carried out his seminal work on the cAMP-dependent protein kinase (PKA) and phosphorylase kinase. He showed that PKA consisted of a catalytic subunit attached to a regulatory subunit that blocked its activity. Cyclic AMP would activate the enzyme by causing a dissociation of the complex.

In 1975 Ed spent a few months in Seattle as part of a sabbatical leave of absence, and I provided him with a little office next to mine. He did a lot of writing and, of course, participated in all our weekly seminars, as we had done before his departure. It was such a pleasure to have him around that we wondered how we could bring him back.

The opportunity arose when the chair of pharmacology at the University of Washington became open, and the Howard Hughes Medical Institute agreed to appoint him as an HHMI investigator. At first they hesitated at having an HHMI investigator saddled with the duties of the chair of a department. But they soon agreed to create an HHMI unit, which Ed would direct as chair of pharmacology. In fact, they financed the total remodeling of the sixth floor of the Biochemistry-Genetics Building, which then became an HHMI institute.

At first Ed had some second thoughts about accepting that position. He claimed he was not a "card-carrying pharmacologist" but primarily a research scientist who would not have

the necessary background to give a course in pharmacology and to participate actively in the teaching program of the department. We assured him that this was precisely the kind of person the school was looking for.

RETURN TO THE UNIVERSITY OF WASHINGTON

Ed Krebs returned to the University of Washington in 1977. He brought with him two of his collaborators (Joe Beavo and Stan McKnight) and, with a series of superb appointments, succeeded in transforming what had been a rather dormant Department of Pharmacology into one of the best in the country. In the next 30 years he carried out some of the most outstanding work of his research career, diversifying his interests from phosphorylase and related problems to a variety of aspects of cell signaling and regulation. He carried out extensive work on the highly complex structure, properties, and regulation of phosphorylase kinase and cAMP-dependent protein kinase; regulation of muscle contraction, including the tyrosine phosphorylation of the myosin light chain; hormonal regulation by cyclic AMP, cell cycle in oocytes; and cell signaling initiated by growth factors such as the epidermal and the platelet-derived growth factors. It was during these years that Ed opened up a brand-new mitogenic pathway known today as the MAP kinase pathway that plays an essential role in cell signaling down from growth factor receptors.

It was wonderful to be able to resume our weekly research conferences. Once a year, in early October, Ed's group and mine would meet for two days at Pack Forest, a former logging camp—owned by the University of Washington School of Forest Resources at the foot of Mt. Rainier—that had been converted into a rather primitive conference center. The program was prepared by the postdocs; everyone would discuss not what they had been doing but what they proposed to

work on in the coming year. It was a time for us to reassess our research programs and plan for the work ahead, see who might interact with whom, or decide whether we should go in a new direction. There was a huge stone fireplace in the conference room in which logs one-foot thick were burning. The afternoon was open, and I would accompany Ed when he was visiting antique (mostly junk) country stores in search of additional lampshades.

On October 12, 1992, it was announced that Ed and I had been awarded the Nobel Prize in Physiology or Medicine. After the usual celebrations, William P. Gerberding, then president of the University of Washington, planned for a big reception for the following Thursday. When he heard that we were supposed to have our annual Pack Forest retreat on that very day, he told us that it should be canceled. No way, we told him, and spent two very festive days with our students. They gave us T shirts on which was printed: PHOSPHORYLATION IS NOT AN ARTIFACT.

There is no question that Ed and I were blessed by having over the years a superb group of students, postdocs, and collaborators, without whom we could not have accomplished all that we did. And then, of course, countless scientists throughout the world contributed greatly to the development of the field. So, though Ed and I were singled out by the Nobel committee for getting the ball rolling, the award we received should be seen as recognition of all those who worked in this area.

We have often been asked whether we realized at the beginning that we were dealing with a ubiquitous and, therefore, very fundamental process. Absolutely not. We stayed with this system because we felt it was an exciting and obviously important one, but we never could have predicted the incredible developments that followed. In those days almost everybody felt that allostery was it, that it was the principal

mode of regulation of cellular processes. The question that seemed of concern to nearly everybody was whether the regulation of a particular enzyme followed the allosteric model of Jacques Monod or the induced-fit model of Daniel Koshland. It was clear to me, for instance, that Jacques Monod, who was a very close friend, never really believed that covalent regulation by protein phosphorylation could play any fundamental role in enzyme regulation. With his passing away 34 years ago, then that of Dany Koshland four years ago, and now that of Ed Krebs, we have witnessed the end of an extraordinary era.

Eraldo Antonini, a brilliant, charming, and captivating scientist who used to work on hemoglobin and died prematurely at age 53 while at the peak of his scientific and academic career, once told me, "You know, many people can be top scientists, but not that many can also be real gentlemen." Well, Ed was certainly both, a superb scientist and the absolute epitome of the gentleman.

Ed is survived by his wife, Deedy; his daughters, Sally (Mrs. Herman) and Martha (Mrs. Abrego); son, Robert; five grandchildren; and six great grandchildren.

SELECTED AWARDS AND DISTINCTIONS

American Academy of Arts and Sciences, 1971
Membership in the National Academy of Sciences, 1973
Gairdner Foundation Award, 1978
Passano Foundation Award, 1988
3M Life Sciences Award, Federation of American Societies for Experimental Biology, 1989
Albert Lasker Basic Medical Research Award, 1989
Louisa Gross Horwitz Award, 1989
Robert A. Welch Award in Chemistry, 1991
Steven C. Beering Award, 1991
Nobel Prize in Physiology or Medicine, 1992
L'Académie Royale de Médecine de Belgique, 1994
Lifetime Achievement Award, Miami Nature Biotechnology Winter Symposium, 2005

DOCTORATE HONORIS CAUSA

University of Geneva, 1989
Medical College of Ohio, 1993
University of Indiana, 1993
Universidad Nacional de Cuyo (Argentina), 1993
University of Illinois, 1995
Washington University, 1995
Iowa State University, 1997
University of Miami, 1998

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1991

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