

RETROSPECTIVE

Edwin G. Krebs (1918–2009)

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Edwin G. Krebs, a giant of biomedical science in the 20th century, died on 21 December from congestive heart failure in Seattle at the age of 91. His discovery (with Edmond H. Fischer) of protein phosphorylation as a regulatory mechanism touched all aspects of biomedical science and profoundly influenced therapeutic approaches now used in clinical care. Ed's life epitomizes commitment to family, excellence in research, and academic service.

Edwin G. Krebs was born in Lansing, Iowa, in 1918, the son of a Presbyterian minister and a schoolteacher. His father died suddenly when Ed was 15 and, at the height of the Depression, the family moved to Urbana, Illinois, where Ed 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 study medicine at the Washington University School of Medicine in St. Louis, Missouri. Although the principal responsibility of a medical school during World War II was to train physicians for the armed forces, Ed also participated in medical research. After medical school and residency training at Barnes Hospital in St. Louis, he went on active duty as a medical officer in the Navy. Following his discharge in 1946, he returned to St. Louis and was accepted as a postdoctoral fellow in the laboratory of Nobel Laureates Carl and Gerty Cori in the Department of Biochemistry. After 2 years of postdoctoral research on the interaction of protamine (a small sperm protein) with rabbit muscle phosphorylase, Ed became so captivated with biochemistry that he never returned to clinical medicine.

During his naval service, Ed enjoyed a brief visit to Puget Sound, so he happily accepted a position as assistant professor of biochemistry in the fledgling University of Washington School of Medicine in 1948. Under the visionary leadership of Hans Neurath, the

Department of Biochemistry expanded in protein chemistry and enzymology, including recruitment in 1953 of Edmond Fischer, a talented and charismatic Swiss biochemist studying potato phosphorylase. Thus, a life-long friendship and a formidable research partnership were forged.

Together Ed (Krebs) and Eddy (Fischer) determined the mechanism by which adenosine 5'-monophosphate (AMP) served as an activator of phosphorylase b in skeletal muscle. They found that adenosine 5'-triphosphate (ATP) was required for phosphorylase activation, and in an unusual experiment discovered that calcium, leaching from filter paper used to clarify the muscle extract, was an important cofactor. They demonstrated that phosphate was incorporated into a specific serine residue of phosphorylase b, thereby yielding an activated form called phosphorylase a. Their landmark paper was published in the *Journal of Biological Chemistry* in 1955. Subsequently, Krebs, Fischer, and colleagues confirmed that this phosphorylation is mediated by another enzyme (phosphorylase b kinase), which itself is controlled by yet another enzyme, a cyclic AMP (cAMP)-responsive kinase. This finding led directly to the concept of kinase cascades. In 1968, Ed purified the cAMP-dependent protein kinase (protein kinase A). The recognition that protein kinase A is the primary cellular effector for cAMP signaling placed protein phosphorylation in a central position in hormone action and broadened the importance of this protein modification in cell biology, physiology, and pharmacology.

At the same time as his discovery of protein kinase A, Ed's interests in teaching and academic administration led him to seek new opportunities and challenges as founding chair of the Department of Biological Chemistry at the University of California, Davis. He also embarked on a long association with the American Society for Biochemistry and Molecular Biology as associate editor of the *Journal of Biological Chemistry* for 20 years and as president of the American Society

Defining how protein phosphorylation is regulated led to an explosion of knowledge about most cellular processes.

for Biochemistry and Molecular Biology in 1985. In 1977, Ed returned to the University of Washington as investigator of the Howard Hughes Medical Institute and chair of the Department of Pharmacology, where he inaugurated a major new research direction in molecular pharmacology. What he liked most about both of his chair positions, he said, was the responsibility of selecting outstanding faculty members for the departments.

After achieving his goals as department chair in 1983, Ed refocused his efforts on research, training junior scientists, and solving new problems in cell signaling. His laboratory studied signaling events that involved the phosphorylation of proteins on tyrosine residues. His lab was also instrumental in the discovery of the mitogen-activated protein kinase pathway, a sequence of protein kinases that respond to extracellular stimuli and regulate a wide range of cellular processes including gene expression and cell growth, differentiation, and survival.

Krebs received many major scientific awards for his insights into the principles governing cellular regulation in health and disease, including election to the National Academy of Sciences (1973), the Passano Foundation Award (1988), the Horwitz Prize (1989), the Lasker Medical 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 their discovery of protein phosphorylation. In 1997, Ed finally closed his lab but was frequently spotted wandering the halls of the University of Washington Medical Center on his way to hear the latest research seminars. Ed is survived by his wife of 64 years Virginia (Deedy) Krebs, three children, and several grandchildren.

Edwin G. Krebs will be remembered for his keen intellect, astonishing research productivity, and iconic status within the research community. 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.

