RETROSPECTIVE

# A tribute to Eddy Fischer (April 6, 1920–August 27, 2021): Passionate biochemist and mentor

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Edmond (Eddy) Fischer was one of the great biochemists of the 20th and 21st centuries. He was also a gifted pianist, an avid mountain climber, and a pilot, a true man of the world who lived on three continents and spoke many languages fluently. Having spent his childhood in China and Europe, Eddy was formally schooled in Switzerland and began his studies at the University of Geneva in 1939, just as Hitler was invading Poland. After receiving his doctorate in Chemistry at the University of Geneva, he went to the California Institute of Technology, but was then quickly recruited to the fledgling Department of Biochemistry at the University of Washington in 1953 by Hans Neurath, where the mountains as well as the biochemistry were a big attraction. Seattle remained his home for the rest of his life, but the world was his home and his impact radiated across many continents.

In Seattle he met Edwin Krebs, who had been recruited in 1948, and in the next few years these two young scientists changed the course of history for all of us. They laid the foundation for a community of scholars that extended across the world and Eddy, in particular, became a friend and mentor to all of us. His sphere of influence extended well beyond those who trained directly in his laboratory. In the 1950s, Ed and Eddy built quickly on the foundation that was laid at Washington University in St. Louis by Gerty and Carl Cori, two other earlier transplants from Europe, and made a discovery that changed the world of biology and won them the Nobel Prize in Physiology or Medicine in 1992 (1). They discovered that proteins in cells are dynamically regulated by the covalent addition of a phosphate moiety from ATP, and that two enzymes catalyze the reversible addition and removal of the phosphates: a kinase and a phosphatase. Specifically, they showed that the activity of glycogen phosphorylase, the enzyme that breaks down glycogen by releasing a glucose-1-P moiety at each step, was activated by the addition of a single phosphate by an enzyme they called phosphorylase kinase. This discovery nucleated a family of enzymes that includes over 500 protein kinases that control much of biology, and this family has become a major target for drug discovery.

The three of us represent a community of scholars who were not directly trained by Eddy, but whose lives and careers were profoundly influenced by this extraordinary man. Here, we explore Eddy's world when he was 50 years old; this was 1971, the midpoint of his life. Fifteen years earlier he had made the discoveries that would earn him the Nobel Prize. In the following decade, he was busy raising his young family and traveling to Europe and Israel, but he was also training a group of young international postdoctoral fellows who would set the world stage for the next generations. This included Philip Cohen, Ludwig Heilmeyer, and Shmuel Shaltiel. So where were we in 1971, and what lay ahead for Eddy Fischer in the next 50 years?

At the time of the discovery of protein phosphorylation as a regulatory mechanism, many new scientific concepts were emerging around the world. The Department of Biochemistry at the University of Washington, in addition to being the birthplace of protein phosphorylation, was a mecca for protein chemistry and protein sequencing. Across the Atlantic, at the Laboratory of Molecular Biology (LMB) in Cambridge, England, in addition to discovering the DNA double helix, we were learning about the structure and function of the proteins that are encoded by the DNA, while the Biochemistry Department at Cambridge University was focused on protein synthesis. Two Nobel Prizes in 1962 went to LMB scientists: Jim Watson and Francis Crick received the Nobel Prize for Physiology or Medicine for their discovery of the double helix, while Max Perutz and John Kendrew received the Nobel Prize in Chemistry for their crystal structures of myoglobin and hemoglobin. In 1962 the LMB, which was laying the foundation for molecular biology, had just moved from the Department of Biochemistry in Cambridge University to their new home on Hills Road. At the same time, in Paris, the concepts of protein allostery were being

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born. And in the early 1960s a completely new university, the University of California at San Diego, as well as the Salk Institute for Biological Studies, were founded in La Jolla, California. By the end of the 1970s these worlds converged in a profound way that was woven together by Eddy Fischer and Ed Krebs, and this network would continue to grow over the ensuing decades. Protein phosphorylation emerged as a major field that regulates biological function in all cells, and Eddy and Ed, the founders, continued as the undeniable leaders. Eddy's impact continued well into the 21st century, reaching far beyond those who trained directly in his laboratory.

## Jean-Pierre and the Birth of Allostery

In the spring of 1964, I (J.-P.C.) was finishing my doctoral thesis at the Pasteur Institute in the laboratory of Jacques Monod, who was then head of the Service de Biochimie Cellulaire. One day, Jacques opened the door of his office into the laboratory with a distinguished and cheerful gentleman, and said to me, "May I introduce your neighbor in the lab for the next few months?" This was my first encounter with Eddy and the beginning of a lifelong friendship. Indeed, Jacques had the idea to place Eddy's desk "in a sort of telephone booth from where Jean Pierre was carrying out his research on threonine deaminase" (2). There were a few such "cubicles" in his laboratory, which were specifically designed for private scientific discussions. We took advantage of this opportunity to begin an endless debate about the chemical and molecular mechanisms of protein regulation, a debate that lasted many decades until Eddy's death in 2021. At the time I knew, of course, Eddy's work with Ed Krebs on the regulation of glycogen phosphorylase by phosphorylation/dephosphorylation, and his main motivation to visit our laboratory was, as he says, "to understand how this enzyme was activated by AMP." A change in the conformation was needed to account for its indirect, allosteric, effect on the protein! But what was it? A change of the state of aggregation of the protein or something else? Possible examples supporting the aggregation–dissociation scheme were the dimerization of phosphorylase b into phosphorylase a, already reported by Eddy himself and similar to the dissociation of glutamate dehydrogenase into subunits provoked by NADH, as reported earlier by both Carl Frieden and Gordon Tomkins (3).

Jacques initially was supporting, yet with caution, the association–dissociation scheme. I was firmly opposed to it. I had never noticed any change in sedimentation velocity of threonine deaminase in the presence of its feedback inhibitor isoleucine or any deaminase ligand (4). A conformational change had to be involved, but more subtle than a change of aggregation. But what was it? In the discussions with Eddy, it took time for me to suggest to him what I had in mind! I had observed that in the presence of urea, threonine deaminase reversibly split into subunits and that inhibitors like isoleucine protect against dissociation, while activators like valine or allothreonine did the opposite: they enhance the dissociation. Thus, the idea emerged that a change in conformation would take place between discrete states of a common oligomeric aggregate, yet with differences in the strength of interaction between the constitutive subunits (without change in aggregation) (4). A given ligand would then selectively stabilize one of the states thereby mediating signal transduction (5, 6).

Eddy wanted to know how general the suggested model was. How might it apply to the phosphorylase system not only to the addition of a ligand, but also to the covalent addition of a phosphate? He later wrote, "we (with Ed Krebs) had to wait five or six years for the Pasteur group to come up with their allosteric model of enzyme regulation" (2). I may say that I was very pleased by what happened later, and in particular to discover the picture of Eddy and Ed standing together with a poster illustrating the mechanism of action of protein phosphorylation on phosphorylase (Fig. 1), which shows some similarities with the original diagram of my thesis work. After all, these discussions in the Pasteur cubicles had been rather fruitful. Of course, this was not the end.

Our friendship lasted decades. Both of us were for years on the Board of Scientific Governors of the Scripps Research Institute in La Jolla. This was a unique opportunity for us to meet regularly every year, to further discuss allostery, in particular in the brain, and to speak French together. Aware of the many difficulties the Pasteur Institute had to face—and still faces—Eddy was also systematically trying to find a manner, always elegant, to help us. Perhaps some kind of memorial of his 1964 visit? He remained a passionate and lifelong advocate for the Pasteur Institute.

Nothing was missing in our extraordinary friendship, which was a constant fight for good science, a deep free-thinking open humanism, and an eternal sense of French–Swiss humor. Unforgettable.

## Tyrosine Phosphorylation, Cancer Biology, and Tony Hunter

I (T.H.) first met Eddy Fischer in December 1979 at a meeting on protein phosphorylation and bioregulation in Basel, where I had been invited to speak about our recent discovery of tyrosine phosphorylation, a new type of protein kinase activity associated with viral transforming proteins that can switch normal cells into cancer cells. In fact, in October that year, I had visited Seattle and spoken about tyrosine phosphorylation at a meeting between the groups at the Salk Institute and the Fred Hutchinson Cancer Research Center working on mechanisms of tumor virus transformation, but no one from the University of Washington was present. Of course, prior to 1979 I was well aware of the seminal work that Krebs and Fischer had done some 20 years earlier, which had shown that phosphorylation of glycogen phosphorylase stimulates its catalytic activity. Indeed, as a graduate student in the Department of Biochemistry in Cambridge in the mid-1960s, I had taught this

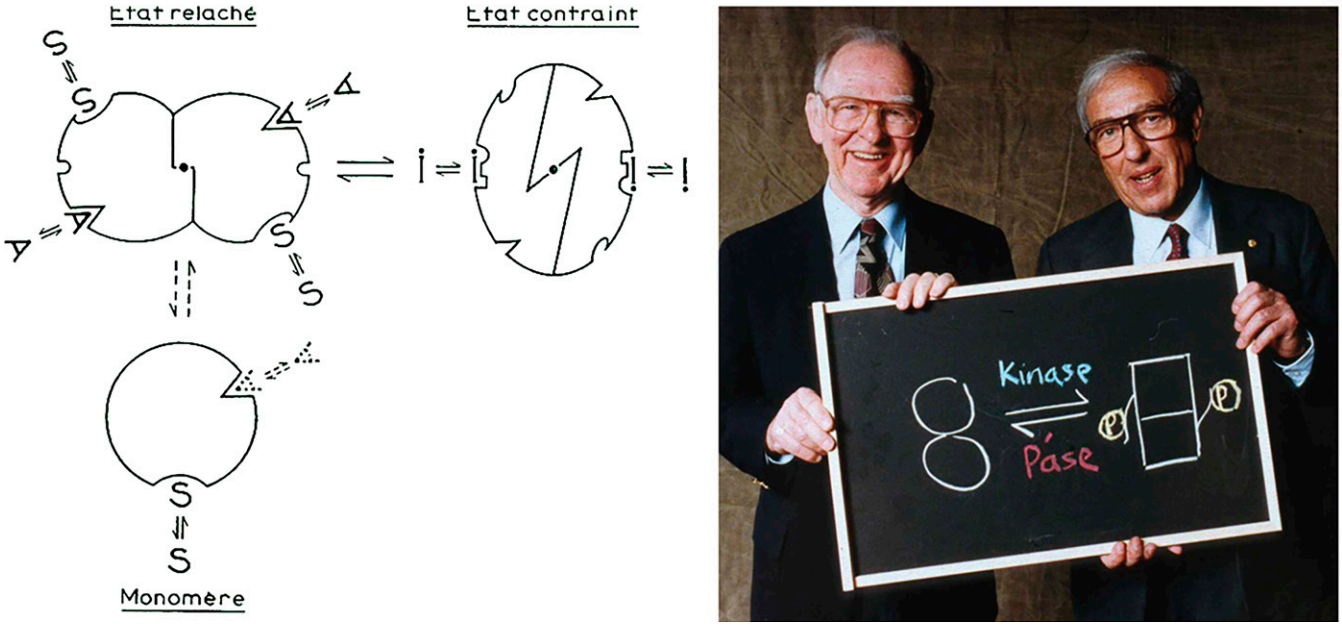


**Fig. 1. Allosteric transitions. (*Left*) A page from Jean-Pierre Changeux's thesis. Image credit: Changeux family. (*Right*) Eddy Fischer and Ed Krebs, decades later, speculating on the conformational changes that are induced by adding a phosphate. Image credit: American Society of Biochemistry and Molecular Biology.**

key regulatory principle to the biochemistry undergraduates I supervised. At the Basel meeting, Eddy spoke about his work identifying two phosphorylation sites in the catalytic (C) subunit of cAMP-dependent protein kinase (PKA) (7). This was just 2 years before he reported the complete sequence of the PKA C-subunit, assembled the old-fashioned way, by protein sequencing (8). This sequence was the Rosetta stone that unlocked the basic design of all protein kinases, and its sequence became the template that allowed sequence gazers, like me, to demonstrate that nearly all eukaryotic serine/threonine kinases and tyrosine kinases are closely related in their catalytic domains, possessing a series of key conserved motifs that are essential for phosphate transfer (9).

From 1980 on, following the discovery that tyrosine residues, as well as serine and threonine residues, could be phosphorylated by a protein kinase (10), our paths crossed on innumerable occasions at meetings on protein phosphorylation and dephosphorylation at venues around the world. At one particularly memorable meeting, held in 1988 in Titisee, Germany, Eddy's postdoctoral fellow, Nick Tonks, talked for the first time about his biochemical purification and characterization of the first phosphotyrosine-specific protein phosphatase (PTP), which led on to the discovery of a huge family of related PTPs (11, 12). It was typical of Eddy to let his postdoctoral fellow present the work, rather than taking the credit himself for this breakthrough discovery. From then on, and even after he had to close his laboratory in 1991, Eddy's research was focused on the exciting new field of PTPs, and altogether he published 49 PTP papers, a fitting bookend to an amazing career. Even after he finally retired, Eddy was a fixture at phosphorylation meetings, keeping up with latest developments in the field. When he was 90, I asked Eddy to write the Foreword for a multiauthored book on signal transduction that I was coediting, and back came a lucid and thought-provoking piece on the history of the signal transduction field, but, more importantly, the problems still left to be solved (13).

Eddy was indeed a remarkable scientist, who inspired a whole generation of biochemists and cell biologists to work on protein phosphorylation.

## Building an International Network, Susan S. Taylor

Embedded within the early studies of Gerty and Carl Cori in the 1940s were two enzymes, the "converting enzyme," subsequently referred to as phosphorylase kinase, and the "phosphate removing (PR) enzyme," which became the protein phosphatase, and the students and fellows who joined Eddy in the 1960s spawned both fields. This world of protein phosphorylation was about to charge onto the world stage, and 1971 was a critical year of migrations (Fig. 2). Philip Cohen moved to the University of Dundee in 1971, having spent 2 years as a postdoctoral fellow in Eddy's laboratory. Tony Hunter, with his focus on protein synthesis, moved in 1971 from the Biochemistry Department in Cambridge to the newly formed Salk Institute. I (S.S.T.), with my focus on protein structure and function, came as a postdoctoral fellow from the LMB in Cambridge to Nate Kaplan's laboratory at the University of California, San Diego. Jack Dixon, who later became a part of this network with his discovery that the virulence factor in *Yersinia pestis* was a tyrosine phosphatase (14), also joined Nate Kaplan's laboratory as a postdoctoral fellow in 1971. Jack's discovery, along with Nick Tonks' discovery of

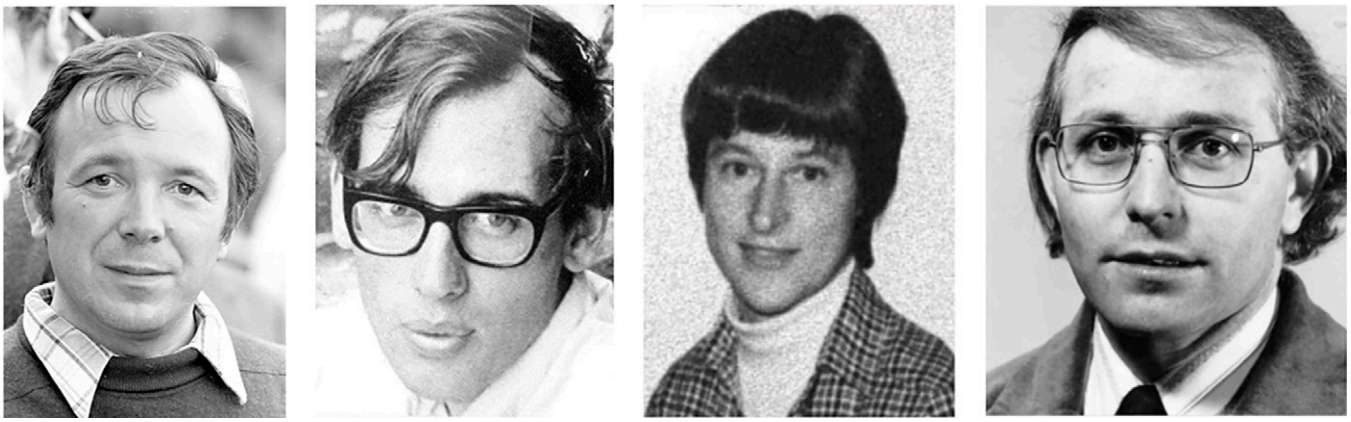

**Fig. 2. Laying the foundations for a network in 1971. From left to right: Jean-Pierre Changeux (Image credit: J.-P. Changeux, Emeritus professor Collège de France and Institut Pasteur, Paris, France), Tony Hunter (Image credit: Tony Hunter, University of Cambridge, Cambridge, United Kingdom), Susan Taylor (Image credit: MRC Laboratory of Molecular Biology, Cambridge, United Kingdom), and Philip Cohen (Image courtesy of Philip Cohen, University of Dundee, Dundee, United Kingdom).**

the PTPase (11), added an exciting new chapter to the last three decades of Eddy's life, and Jack and Eddy also became close friends. Neither Tony nor I knew much about protein phosphorylation, but that would quickly change. My world, however, changed abruptly and became indelibly intertwined with Eddy's and Ed's in late 1971, when Nate put a PKA paper by Fritz Lipmann on my desk (15). By the end of the 1970s and early 1980s, an international network was in place that would educate many future generations, and Eddy and Ed not only nucleated this network but became our mentors and role models.

Eddy was first and foremost a biochemist with extraordinary vision who used chemistry to discover the secrets that were embedded in proteins (16). Initially his passion remained focused on these two enzymes, the kinase and the phosphatase, as well as the protein kinase inhibitor (17), although eventually the phosphatases would dominate his world. Like Eddy, my focus was on protein chemistry and structure. While I looked at sites of covalent modification of the PKA C-subunit using affinity labeling (18), Eddy was mapping its phosphorylation sites (7). Eddy also worked closely with Ken Walsh and Ko Titani and, using classic and laborious protein chemistry, they sequenced not only the PKA C-subunit in 1981 (8) but also in rapid succession glycogen phosphorylase (19) and phosphorylase kinase (20). Eddy and his collaborators thus defined the chemical signatures of these key proteins well before cDNA cloning and sequencing became routine procedures. It was a monumental task. Although Src tyrosine kinase had been cloned 2 years earlier, until the PKA sequence was elucidated no one knew what a protein kinase looked like. It was Eddy's sequence of the PKA C-subunit that unambiguously showed that cancer biology and glycogen metabolism were part of the same lineage (21). A decade later, in 1991, we published the first structure of a protein kinase (22). Eddy was always searching for clues about function, like the phosphorylation sites and the inhibitory function that was embedded in the sequence of the PKA inhibitor, PKI (23, 24).

In the 1970s and 1980s, the annual Federation Meeting, which included the American Society of Biological Chemists (later in 1987 to become the American Society of Biochemistry and Molecular Biology), was the place where biochemists gathered each year to share their data. In the 1970s and 1980s, I also came to know the people in the world of protein phosphorylation, including the international players, through the Cyclic Nucleotide Gordon Research Conferences (GRCs) and through many meetings in Europe. This is where I first encountered Eddy's world. I first met Philip Cohen and Shmuel Shaltiel, for example, at GRCs. Through Shmuel, who was also passionate about unraveling the secrets of the PKA C-subunit, and in this regard was my scientific soul mate, I was indirectly linked to Eddy. Eddy first met Shmuel in 1963 when Eddy not only spent time in Paris but also traveled to the relatively new Weizmann Institute in Israel, where Shmuel, a graduate student, met him at the airport (25). Eddy actually began that sabbatical year of 1963 with a CIBA Foundation meeting in London on "Control of Glycogen Metabolism" organized by his good friend, Bill Whelan. While his children were in boarding school in Switzerland, Bev and Eddy traveled to both France and Israel, so this year set the stage for many future international meetings. At these early conferences, the protein kinases, protein phosphatases, and cAMP, along with the G proteins that were just being discovered, were intertwined; they were all part of the same story. Ludwig Heilmeyer, who overlapped with Philip in Eddy's laboratory in Seattle, moved in 1970 to Germany, and he organized many NATO Summer Schools on protein phosphorylation in Europe, and Eddy attended many of these European meetings. Friederich Herberg, Ludwig's graduate student, came to University of California, San Diego as my postdoctoral fellow in 1990. He is my single direct link to Eddy's academic tree.

So, from the very beginning, our community was truly international and spawned many close personal friendships. The Salk/Fred Hutchinson Cancer Research Center meetings also quickly became a regular feature of our community. These many meetings indelibly established from the very beginning in the 1960s an international protein phosphorylation network. American Society for Biochemistry and Molecular Biology, Federation of American Societies for Experimental Biology, International Union of Biochemistry and Molecular Biology, Keystone Symposia, and the Biochemical Society as well as others, such as the 1993 Lorne Conference in Australia, would continue and solidify this tradition by sponsoring many symposia on protein phosphorylation, which continue to this day.

## Our Everlasting Debt of Gratitude

Eddy was a deep scholar whose love of science dominated the field. Interdisciplinary thinking was woven into all our minds from the beginning. Sharing of ideas and information was also an essential part of this community. Listening to students and fellows was always a deeply shared commitment. We all grew up with this philosophy and with Eddy as our role model. A joy of science and a joy of life in general always seemed to radiate from Eddy (Fig. 3), and we all acknowledged him as our unequivocal leader for over half a century. Evidence of this recognition and of our devotion for this remarkable man were the many birthday celebrations: the 65th in Pitlochry, Scotland, for Eddy and on Orchas Island for Ed; the Miami Winter Symposium in 1989 organized by his lifelong friend, Bill Whelan (26); many 80th birthday celebrations; and most special of all, the 100th birthday symposium in 2020, which unfortunately had to be virtual, where Eddy participated actively with his typical enthusiasm for all the talks and warm personal attributes. His tree of students and fellows exemplifies the breadth and diversity of his thinking, but he was mentor to so many more, and we will all miss him.

**Fig. 3. Dancing at the 100th American Society for Biochemistry and Molecular Biology Anniversary celebration in 2006. Eddy Fischer and Susan S. Taylor. Image credit: American Society of Biochemistry and Molecular Biology.**


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