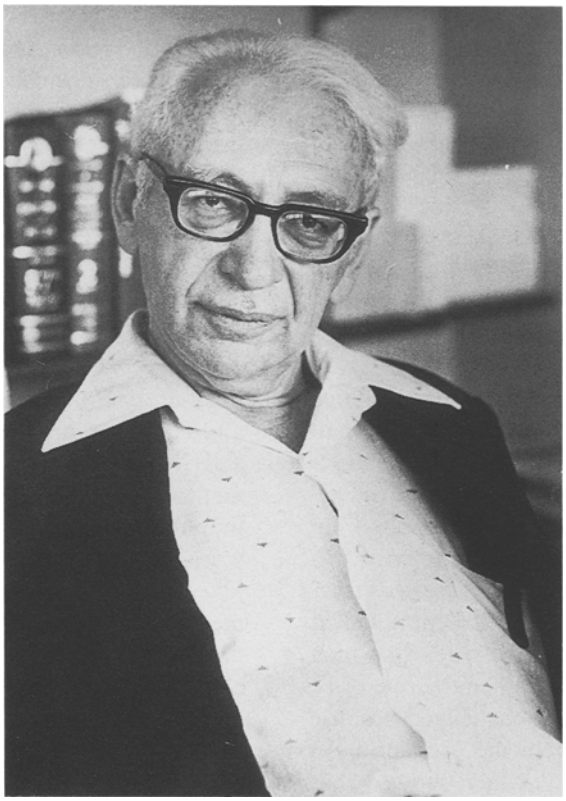

Efraim Racker, 1913–1991

Efraim Racker died from a stroke, September 9, 1991 at the age of 78. He was a brilliant experimentalist and stimulating teacher whose work in biochemistry had a remarkable breadth and an individual style that few have equaled. He was as active as ever when he died, with a research group of twelve, including visiting professors, postdoctoral associates, technicians, and students.

After escaping in 1938 from Vienna, where he had graduated from Medical School, Racker began research with J. H. Quastel in Cardiff, Wales, on the effect of amines on brain metabolism. His frustration at attempting applied research on the biochemistry of schizophrenia when there was so little knowledge of basic metabolism led to strong views about the necessity for basic research. Much later he returned briefly to the study of amine metabolism in brain and discovered a brain-specific monoamine oxidase.

After moving to the United States, Racker joined the faculty in the Department of Microbiology at New York University Medical School in 1944 where he taught a virology laboratory course and continued work on metabolic pathways.

Racker was primarily an enzymologist whose research philosophy was to purify enzymes to "resolve and reconstitute" complex systems. He believed in doing experiments first and building theory later. This philosophy, often expressed as "don't waste clean thinking on dirty enzymes," was upgraded in 1985 with some tongue-in-cheek to "don't think, don't purify: clone." A perfect illustration of this philosophy is given by his first major achievement: the mechanism of energy coupling in glycolysis. In the beginning he was funded by the March of Dimes and so studied the effect of polio virus on rates of glycolysis. He found that iron in the virus inhibited glyceraldehyde-3-phosphate dehydrogenase and that glutathione prevented the inhibition. This led to the study of glyoxylase, which uses glutathione as a cofactor, where he isolated and identified the first biological thioester: lactylglutathione. Following that experimental trail placed him in a position to discover the

thioester mechanism of glyceraldehyde-3-phosphate dehydrogenase in 1952. This mechanism became the model for the chemical hypothesis of oxidative phosphorylation which was the prevailing paradigm for about 20 years.

In 1952 Racker moved to Yale and then in 1954 became Chief of the Division of Nutrition and Physiology at the Public Health Research Institute of the City of New York. At Yale, Racker discovered transketolase, the beginning of a series of contributions to the working out of the pentose phosphate pathway. By the late 1950's Racker began research on oxidative phosphorylation, together with Maynard Pullman and Harvey Penefsky, using the methods for large-scale preparation of beef heart mitochondria developed by David Green. His approach was to break up the mitochondria until phosphorylation activity was lost and then add back the supernatant protein fraction to restore activity. The first such fraction, called F_1, was found to be an ATPase, the study of which has become a major field in itself. When the role of F_1 in oxidative phosphorylation was challenged because it was not sensitive to oligomycin, he took pride in personally doing the experiments which showed that when attached to the membrane, F_1 was sensitive to oligomycin. The binding site for F_1 was named F_0. Racker's group characterized many properties of F_1, including its cold lability, that it is the "knobs" seen to be attached to the mitochondrial membrane by negative stain electron microscopy, and that it functioned to make ATP at all three coupling sites. They also discovered three other coupling factors, F_2, F_3 (now called OSCP), and F_6. In 1966 Racker moved to Cornell where he was Albert Einstein Professor in the section of Biochemistry, Molecular and Cell Biology. Throughout the first phase of resolution of oxidative phosphorylation, Racker used the chemical hypothesis of the mechanism, descended from his thioester mechanism, to interpret results, but the guiding principles were those of basic enzymology. It was clear by the early 1970's, however, that the chemiosmotic hypothesis of Peter Mitchell was basically correct and that, to further resolve the mitochondrial membrane into individual redox components capable of making ATP, methods to incorporate membrane proteins into liposomes were required. Thus, beginning with a simple procedure for putting cytochrome *c* inside submitochondrial particles in 1970, Racker developed membrane reconstitution methods and rapidly showed that all the respiration complexes could be suitably combined with F_0F_1 to catalyze oxidative phosphorylation. During this period a particularly dramatic experiment was done with Walter Stoeckenius in which bacteriorhodopsin was incorporated into liposomes together with F_0F_1, and light-driven ATP synthesis was created from bacteria and beef hearts. This experiment is usually cited as the best evidence for chemiosmotic coupling from reconstitution studies. However, the alternative to the chemiosmotic hypothesis was that proton transport was a side pathway of energy coupling, and the most important aspect of the reconstitution work was that it showed that all the complexes of the respiratory chain and F_0F_1 were proton translocating with the coupling activity predicted by Mitchell's hypothesis. The methods also allowed the mechanism of coupling by individual components of the system to be studied, work that is still in progress.

Racker then went on to use the reconstitution methods to study other membrane proteins. He was first to show transport activity by the isolated mitochondrial transporters for ATP, Pi and carnitine, the mitochondrial transhydrogenase and nonmitochondrial proteins including a sodium channel, acetylocholine receptor, calcium transport ATPase, and coated vesicle $H^+ - ATPase$. In his studies of other ATP-utilizing systems, he was the first to show synthesis of bound ATP on nonmembranous Ca^{++}-ATPase from ADP and P_i using a two-stage procedure of manipulating ion concentrations. This unexpected substitution of a change of concentration with time for a gradient in space has since been used by others to characterize the mechanisms of several ATP-driven pumps.

In the 1980's Racker returned to one of his earliest interests, the control of metabolism and the biochemistry of cancer. He had long emphasized that ATPase is necessary for glycolysis, since it generates the substrates ADP and P_i, and proposed that in many transformed cells the high glycolytic rate is caused by slippage in the coupling of the Na, K ATPase. He demonstrated such slippage in other purified ATPases but was frustrated by attempts to demonstrate it in cancer cells.

His work then shifted to characterization of protein kinases where he emphasized the problem of finding the relevant substrate. With typical reductionist philosophy he studied random peptide substrates, considering them as good as natural proteins which are not known to be the relevant substrate. He even showed that some random polymers had kinase activity themselves.

Racker wrote progress reports every ten years in the form of advanced bioenergetics textbooks which were very useful to students in the field. He also published a series of short essays on the importance of basic research subtitled "Letters to members of Congress." His ability as an artist and enthusiasm as a musician were well known. To his students and friends the stimulating and imaginative discussions about biochemistry will remain our fondest memories of Ef.

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