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EFRAIM RACKER

*1913—1991*

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*A Biographical Memoir by*  
GOTTFRIED SCHATZ

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*Biographical Memoir*

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*June 28, 1913–September 9, 1991*

BY GOTTFRIED SCHATZ

WHEN HE ENTERED OUR Vienna laboratory on a hot summer day in 1961 I was struck by his youthful stride that belied his white hair, his foreign-looking bow tie, and a curious tension in his face. My friends told me later that I had just seen Efraim Racker, one of the foremost biochemists of our time, and that this was his first visit to Vienna since he had fled this city more than twenty-three years ago.

In 1961 Racker's work on biological ATP production had made him one of the stars of bioenergetics, the branch of biochemistry dealing with energy conversion by living cells. I had already made up my mind that I wanted to do my postdoctoral work with him and asked him the next day whether he would accept me. He drew me aside to quiz me about my work, but interrupted me after my first few sentences by asking, "How come you speak English so well?" Flattered, I explained in my German-accented English that I had spent my last year of high school as an exchange student in the United States. His immediate riposte, "How come you speak English so badly?" made us both laugh and started a lifelong bond between us that was severed only when he died thirty years later.

Racker was born on June 28, 1913, in the town of Neusandez in Poland to Jewish parents who moved to Vienna

before his second birthday. His family was not wealthy, and settled in the second district of Vienna called Leopoldstadt, then largely an enclave of recent immigrants from the eastern reaches of the Austro-Hungarian Empire and beyond. Most of these immigrants were poor Jews who had hoped for a better life, but then faced anti-semitism, the deprivations of the First World War, the social unrest that followed the collapse of the empire in 1918, and the rise of fascism that culminated in the Nazi takeover of Austria in 1938. During these stormy years Racker attended elementary school and high school whose formal atmosphere did not appeal to him at all. He much preferred playing soccer or chess in the Augarten, the local park. Even as an old man he loved competitive sports such as soccer, Ping-Pong or tennis and was an excellent chess player, but had only vague notions about the usual staple of classical schooling such as the names of Greek goddesses or the Habsburg family tree; however, to the end of his life he retained an intimate knowledge of the literature, the music, and the art of the Vienna he had known. Young Efraim was fascinated by the public lectures of the writer and critic Karl Kraus, knew many of the local musicians, and was profoundly influenced by the paintings of Egon Schiele. For his twelfth birthday one of his aunts gave him a painting set which soon accompanied him on his regular forays into Augarten and started his lifelong passion for painting. Encouraged by the painter and art educator Victor Löwenfeld, who had become his artistic mentor, Racker initially decided to become a painter. After finishing high school he passed the highly competitive admission examination to the Vienna Academy of Art, but was once again turned off by the rigid and formal style of training he encountered. He soon left the academy to study medicine at the University of Vienna.

In the early thirties the fame of Vienna's Medical School had largely faded, and quite a few of the professors and students belonged to right-wing student organizations called *Burschenschaften*. Many of these *Burschenschaftler* later joined the Nazi movement. I got to know many of them during my own student days in postwar Austria. They were then aging but unrepenting, and I shudder when picturing Racker among them, for it was easy to see that he was Jewish. How many hidden scars did these years leave? Perhaps they explain why Racker always had such a strong gut reaction against power, arrogance, and pompousness. This trait made him a great chairman and scientific adviser, but sometimes a difficult adversary of deans, provosts, and other members of official hierarchies.

Although disappointed by medical school, Racker was captivated by the discoveries of Sigmund Freud whose home and office in Berggasse 16 he passed on his daily walk to the university. Had Racker remained in Vienna, he would probably have become a psychiatrist. Indeed, his older brother Heinrich, who later fled to South America, was a psychoanalyst. The two brothers were very close and Racker often told me of their many late-night discussions on Freud, Adler, and their often high-strung disciples. Racker would have made an excellent psychiatrist; many of his postdoctoral fellows (including myself) had good reason to beware of his uncanny ability to read other people's minds; however, fate decided that his interest in the workings of the human mind should lead him to study brain metabolism and, later on, biological ATP production.

Racker's graduation from medical school almost coincided with Hitler's march into Austria. Racker wisely decided to leave while this was still possible and fled via Denmark to Great Britain where the biochemist J. Hirsh Quastel offered him a job at Cardiff City Mental Hospital in Wales. In this

rather remote place the two of them tried to detect biochemical defects that could explain the mental abnormalities of their patients. Racker apparently decided to tackle this problem from the bottom up, for his first publication was humbly entitled "Histidine detection and estimation in urine";<sup>1</sup> however, there was nothing humble about the opening sentence: "During the last 10 years, many attempts have been made to detect changes in the liver metabolism of patients suffering from mental disorders." The inexperienced M.D. from Vienna clearly had set his aims high! He also studied the effect of oxygen deprivation on the metabolism of tissue slices, but quickly realized that his hopes of finding biochemical causes for mental diseases were doomed since too little was known on the metabolism of normal cells.

But once again Racker's scientific career was buffeted by the political gales that started to blow across Europe. When Great Britain entered the war Racker suddenly found himself an enemy alien whose experiments with human urine near the strategically sensitive coast posed a security risk. He lost his job at Cardiff and, together with many other refugees from Nazi Germany, was interned on the Isle of Man, where he practiced medicine for the first time in his life. Although he enjoyed being a "real doctor," he soon decided to try his luck as a researcher in the United States, not knowing that he was embarking on a twenty-five-year odyssey. He started out doing a brief stint as a research associate in the Physiology Department of the University of Minnesota at Minneapolis (1941-42), but then once again worked as a physician in New York City's Harlem Hospital (1942-44). His career as a biochemist started in earnest only in 1944 with his appointment as staff member in the Microbiology Department of New York University Medical School. He often spoke with great fondness of this department and

the great scientific debt he owed to several of its members, particularly to Severo Ochoa and Colin MacLeod, the department chairman. It was during the eight years in this department that he finally became a professional biochemist. Still, when he was offered the position of associate professor at Yale Medical School in 1952, he accepted and moved to New Haven. In 1954 his odyssey seemed to end when he accepted the position of chief of the Nutrition and Physiology Department at the Public Health Research Institute of the City of New York. Little did our modern Odysseus know that Manhattan would be but another way station in his wanderings and that he would reach his Ithaca only twelve years later.

It was at the Public Health Research Institute that I joined him as a postdoctoral fellow in the summer of 1964, and I will never forget my shock when I first saw this Mecca of bioenergetics. The institute was a decrepit and grimy building wedged between a run-down police garage and a coal-fired power plant whose dusty emissions darkened the window panes and settled into every crevice of the laboratory. The address "Foot of East 16th Street" should have warned me; it certainly warned cab drivers who often refused to go there. The laboratories had most of the required equipment, but many of the instruments were old and not well maintained. Cockroaches, many of ghastly dimensions, were everywhere, as floating corpses in buffer solutions, uninvited guests in lunch boxes, or electrocuted culprits in short-circuited electric equipment.

Yet I had one of the most exciting and productive years of my life in that building. It was brimming with talented, motivated people from all over the world, and "our" fourth floor appeared to have the best of them. There were Racker's trusted colleagues Maynard Pullman, Ray Wu, and Harvey Penefsky, all of them already well known in their own right.

Many of the postdoctoral fellows at that time, such as Ron Butow, Yasuo Kagawa, Howard Zalkin, and Richard McCarty later went on to distinguished careers. Two irreverent graduate students, Peter Hinkle and Gladys Monroy, loved to disagree with Racker and injected spice into our lunch discussion. Lunches were taken together in what was grandly called a lunch room and usually consisted of a homemade sandwich and, for Racker, a small can of Hawaiian fruit punch, a mysterious concoction fortunately restricted to North America. There were visiting professors such as Michael Schramm. And there was Racker himself, "Ef" to his senior colleagues. At that time he did not yet invite postdocs to address him by that nickname, but I did so anyway and he did not seem to mind. Having just turned fifty-one, Ef was a splendid leader, full of vigor, wit, enthusiasm, and self-confidence. Aided by one or two technicians, he managed to work at the bench nearly every day, yet keep all of us under close surveillance. Here in his lab he was not tense at all; he was outgoing, relaxed, and clearly aware of the fact that he was at the height of his scientific powers. And there certainly was no trace of a bow tie. In fact, the best that could be said of his dress was that it matched the building. Coming to work on Saturdays was *de rigueur*; offenders were received on Monday morning with a frosty "How was your weekend?" and usually sinned no more. In order to avoid rush hour traffic, work started at about 10:00 a.m. and went on until 7:00 p.m. or longer. We were a proud and happy crowd, but we also understood why Ef had his detractors. He either liked you or he did not. If he did not, his quick mind and sharp tongue could leave long-lasting wounds. We learned that doing science was not only joyful exploration, but also a game of intellectual domination and that Ef played that game well. Maynard Pullman was a welcome support when Ef's presence or impatience became



too overpowering. Maynard was universally respected for his discoveries in the field of oxidative phosphorylation and well liked for his warmth and balanced judgement. He could stand up to Ef for us, and often did. Harvey Penefsky kept more to himself, but was much in demand for precise scientific information and critical discussion.

Despite his gruelling schedule Ef always seemed to have time. He never closed the door to his office; he never secluded himself in the library to read the latest journals; and he never used his hours at the institute for working on a manuscript or the book he was then writing.<sup>1</sup> Yet he answered every letter and rarely missed deadlines. But, as if that were not enough, he also spent much of his time at home painting, producing brilliant acrylics, which he then gave to his scientific friends and collaborators. In later years he also sold his paintings for the benefit of the Edsall Fund, which he had set up to aid needy students. Although few of his friends knew this, he was also a voracious reader who over the years amassed an extensive and varied personal library. He knew how to organize his time. He never wasted a minute. *Gemütlichkeit* was not for him.

I spent my first postdoctoral weeks in 1964 reading most of Ef's previous publications. Upon moving to Minnesota in 1941 he had continued his search for a biochemical basis of brain diseases by studying the effect of a polio virus infection on glycolysis in mouse brain. Right away, an exciting result: the virus inhibited glycolysis. After his first move to New York City in 1942 more excitement: one could also inhibit glycolysis by adding a purified preparation of another neurotropic virus directly to the brain homogenate. And then disappointment: the inhibition was caused by iron which contaminated the virus preparations.<sup>3</sup> At this point most others would have given up. Indeed, the discovery of this artifact called into question Ef's previous papers on

this topic and might well have stopped his scientific career before it had ever taken off. But Ef's ingenuity converted this defeat into his first scientific triumph. Undeterred, he went on to show that the inhibition could be overcome by glutathione, a ubiquitous cysteine-containing tripeptide whose role in metabolism was still poorly understood; however, there was good evidence that glutathione was an essential cofactor of the enzyme glyoxylase which converts glyoxal to glycolic acid. When Ef showed that this reaction proceeded through a carboxyl-S-glutathione intermediate he had identified the first "energy-rich" thioester of biological relevance. Glyoxylase was a rather esoteric enzyme, but this could not be said of the glycolytic enzyme triose-phosphate dehydrogenase which resembled glyoxylase in its sensitivity to compounds reacting with sulfhydryl groups. Could it be that triose-phosphate dehydrogenase worked through a similar thioester intermediate? The enzyme catalyzes the energy-yielding oxidation of an aldehyde (glyceraldehyde-3-phosphate) to a carboxylic acid and couples it to the energy-requiring formation of 1,3-diphosphoglyceric acid with inorganic phosphate as phosphoryl donor. Warburg had already proposed that this reaction proceeded by direct addition of inorganic phosphate to the aldehyde group and subsequent oxidation of the adduct to 1,3-diphosphoglyceric acid. Undeterred by Warburg's authority, Ef and his technician Isidore Krimsky showed convincingly that the aldehyde group reacted first with an enzyme-bound sulfhydryl group, that the resulting thio-hemiacetal was then oxidized to an energy-rich thioester, and that this thioester was "phosphorylyzed" by inorganic phosphate to 1,3-diphosphoglyceric acid. Warburg first scoffed at what he called "Racker's Umweg" (Racker's detour), but later had to concede that nature took the Umweg rather than the direct route. Although the reactive sulfhydryl group was later shown to

belong to the enzyme itself rather than to tightly bound glutathione, the elucidation of the mechanism by which a biological oxidation is coupled to ATP formation still ranks as one of the most important biochemical discoveries of all time. The simplicity of this reaction was so persuasive that for the next twenty years most biochemists were convinced that oxidative phosphorylation in mitochondria and bacteria had to obey the same principle. How wrong they were!

After moving to Yale in 1952 Ef continued his work on carbohydrate metabolism. He discovered and purified transketolase, a key enzyme of the pentose phosphate pathway. This finding, together with work by others such as Bernhard L. Horecker, eventually led to a detailed description of the entire pathway.

When Ef returned from Yale to New York City in 1954 in order to join the Public Health Research Institute, he first continued to work on the mechanism of glycolysis and the pentose phosphate pathway. By then most of the steps of glycolysis were known, but there was disagreement on how the process was regulated. Why was glycolysis of intact cells inhibited by respiration ("Pasteur effect")? Why did glycolysis inhibit respiration ("Crabtree effect")? And why did most tumor cells, unlike normal cells, convert glucose to lactate even under aerobic conditions ("aerobic glycolysis")? The answers could only come from work with reconstituted *in vitro* systems. Together with Ray Wu and Shimon Gatt, Ef investigated the effect of respiring mitochondria, nucleotides and specific inhibitors on glycolysis catalyzed by a cytosolic extract from Ehrlich ascites tumor cells and showed that glycolysis was dependent on the continuous regeneration of ADP and inorganic phosphate by an ATPase. The family of glycolytic enzymes thus included an ATPase, but these *in vitro* systems could not tell which of the many cellular ATPases was responsible for the regulation in intact cells.

This important finding did not receive the attention it deserved, probably because biochemists were then mesmerized by allostery and preferred to place the burden of glycolytic control solely on the shoulders of phosphofructokinase. Even today we do not fully understand how glycolysis is controlled in living cells and why most tumor cells exhibit aerobic glycolysis. Ef and Ray stopped working on this problem in the mid-sixties, but Ef returned to it during his final years.

I was always captivated by Ray Wu's quiet charm and professionalism. Watching him set up his complex enzyme systems with intense concentration taught me much about how to do a successful experiment. Wu rarely spoke up or contributed jokes during our lively lab discussions, but was a great help for us postdocs and a close and trusted friend to Ef.

Ef's return to New York City from Yale in 1954 had also not dimmed his interest in the pentose phosphate pathway. Together with Dan Couri he reconstituted the pathway from purified components and showed that the reconstituted system catalyzed the complete oxidation of glucose-6-phosphate. Together with June Fessenden and others Ef also continued to investigate the detailed mechanism of several enzymes of this pathway.

Soon after Ef had moved to the Public Health Research Institute Maynard Pullman joined his department. Pullman had set his sights high: he wanted to go after the Holy Grail of bioenergetics, the mechanism of ATP synthesis in mitochondria and chloroplasts. For a start, he decided to isolate the mitochondrial enzymes which coupled the oxidation of nutrients to the synthesis of ATP from ADP and inorganic phosphate. Pullman was aware that this was a formidable undertaking and must have been very pleased when the gifted Harvey Penefsky joined him as a graduate student.

Following a procedure pioneered by David Green, they obtained fresh bovine hearts from a nearby slaughterhouse, disrupted them in a mechanical blender, and isolated from the resulting homogenate several grams of mitochondrial membrane fragments which still catalyzed oxidative phosphorylation. They wanted to use these “submitochondrial particles” as their starting material for resolving, and ultimately reconstituting the individual enzymes of respiration-driven ATP synthesis. Both knew that David Green at the University of Wisconsin, Paul Boyer at the University of Minnesota, and Albert Lehninger at Johns Hopkins University were hot on their trail, and the race was on.

It was a long and frustrating race for several reasons. First, the structure of biological membranes was at that time unknown. Second, nobody knew how to assess the purity of a hydrophobic protein since SDS-polyacrylamide gels did not appear on the scene until 1967. Third, most biochemists assumed that ATP synthesis was coupled to respiration through a “high-energy” intermediate of the type that functions in glycolytic ATP production. This intermediate (fondly called x-squiggle-y) was avidly sought, but never found. By the mid-sixties the many futile attempts had led to frustration and heated controversies; however, most outsiders have later painted an exaggerated picture of the situation, perhaps because the mercurial temperament and acid humor of some of the leading mitochondriacs did not appeal to everyone. By today’s standards relationships between the competing laboratories remained civilized; experimental discrepancies were usually resolved by joint experiments and I cannot recall any instance where a laboratory withheld requested reagents or information from a competitor.

We postdocs loved to gossip about the relationships between the key players. Ef seemed to be closest to Britton Chance whose brilliance, boyish temperament, and experi-

mental skill matched his own. He genuinely liked Paul Boyer, Henry Lardy, Albert Lehninger, Bill Slater, and Lars Ernster and respected their scientific rigor and masterful grasp of biochemistry, but in the mid-sixties none of them worked directly on the resolution of oxidative phosphorylation and scientific interactions were less frequent. Our gossip usually focused on David Green and his group. Green was imaginative, self-assured, flamboyant, and quick with tongue. He usually disagreed with Ef, easily matched him as a debater, and was Ef's perennial foil. When Peter Mitchell emerged as a major figure in the field several years later, he and Ef developed a friendly rapport, yet it seemed to me that they were never quite at ease with each other.

But I am getting ahead of my story. At first, progress in Ef's department was amazingly fast. In order to solubilize the enzymes coupling respiration to ATP synthesis, the sub-mitochondrial particles were vigorously shaken with tiny glass beads in a shaker originally described by the Australian biochemist Peter M. Nossal. Mike Kandrach, our gifted and eccentric mechanic, soon built a monstrous U.S. version which he himself considered so dangerous that he screwed it to the floor of a separate room, operated it by remote control, and allowed nobody else to touch it. This contraption emitted a lugubrious rumble that shook the building and would have sent any contemporary Californian diving for the nearest earthquake shelter. When these tortured mitochondrial fragments were sedimented in an ultracentrifuge they still respired, but no longer synthesized ATP. Adding back the supernatant from the centrifugation sometimes restored ATP synthesis, as Pullman and Penefsky had hoped, but this effect was quite irreproducible, particularly after the first few attempted purification steps. The project seemed to be stuck; but, being the master biochemist that he was, Pullman systematically varied his experimental pro-

ocols until he found that the partially purified soluble fractions restored ATP synthesis nearly every time if they were stored at room temperature. In order to protect the garden of oxidative phosphorylation from unworthy intruders God had guarded the entrance by a cold-labile enzyme! But the assay was still very tedious until Pullman began to suspect that the cleavage of ATP which was catalyzed by the soluble fraction might be just another activity of the mysterious factor that restored oxidative phosphorylation. He started to monitor purification by assaying ATPase activity which was much faster and easier than assaying restoration of oxidative phosphorylation and from then on progress was fast: when he and Penefsky purified the ATPase from the supernatant it was indeed identical with the "coupling factor" of oxidative phosphorylation. The splitting of ATP in a test tube was clearly a reversal of the reaction which the enzyme catalyzed in living cells. Since the ATPase was the first defined factor that coupled respiration to ATP synthesis it was named Factor 1, or  $F_1$ . The first enzyme of oxidative phosphorylation had been identified and purified!

This fundamental discovery was published in 1960. It was greeted with universal admiration, and hopes were high that the enzymology of oxidative phosphorylation would soon be understood. In a letter he wrote me to Vienna early in 1963 Ef suggested various topics for my upcoming postdoctoral stay with him. He discouraged me from planning to work on oxidative phosphorylation with the words "Progress on this front is now quite fast and by next year our interests may have shifted to other topics." In the following years of slow progress I could always enliven my seminars by showing a slide with this sentence in Ef's own handwriting.

But for a while Ef's prophesy seemed to be correct. Together with Vida Vambutas he purified a closely similar cou-

pling factor from spinach chloroplasts. The purified chloroplast  $F_1$  (termed  $CF_1$ ) restored light-driven ATP synthesis to EDTA-treated chloroplast fragments, but did not cleave ATP unless it was gently treated with trypsin. This result confirmed the general expectation that photophosphorylation and oxidative phosphorylation functioned by a similar mechanism. In experiments that he first did himself and later together with Yasuo Kagawa, a gifted and hard-working postdoctoral fellow from Japan, Ef subfractionated sub-mitochondrial particles with cholate and salt and identified a membrane factor that anchored  $F_1$  to the membrane and rendered it cold-stable and sensitive to the toxic antibiotic oligomycin. As oligomycin was then considered the most specific inhibitor of oxidative phosphorylation its lack of effect on the ATPase activity of  $F_1$  had been the most serious argument against a role of  $F_1$  in oxidative phosphorylation. The identification of a factor conferring oligomycin sensitivity on soluble  $F_1$  not only silenced this criticism, but also paved the way towards resolving the membrane-embedded components of the oxidative phosphorylation machinery. Kagawa and Ef named their insoluble  $F_1$ -binding factor  $F_o$  (in contrast to what is generally thought the subscript does not signify zero, but the letter o for oligomycin).

Kagawa presented his results to a packed audience at the 1965 Annual Federation Meeting in Atlantic City. Although he had been intensively coached by some of the American postdoctoral fellows in the lab he struggled with the sounds and the grammar of the English language. He had particular difficulty pronouncing " $F_o$ ", making it sound like the exhortation "Ef, ho!" Still, all the experts in the audience realized that they were witnessing a landmark presentation. The response in Japan must have been similarly positive because Kagawa was soon offered an attractive full professorship at Jichi University where he still works today.



Ef's work with Kagawa also showed that the characteristic knobs which lined the inner face of the mitochondrial inner membrane in electron micrographs were, in fact,  $F_1$ : the knobs disappeared when  $F_1$  was stripped off, and reappeared when purified  $F_1$  was added back. At that time this was perhaps the clearest evidence for the molecular asymmetry of a biological membrane.

Buoyed by these advances, Ef's oxidative phosphorylation team now tried to isolate additional protein factors by mistreating phosphorylating submitochondrial particles in various ways. The particles obtained with our Nossal-type glass bead shaker were termed N-particles. Treatment with ammonia solution yielded A-particles, intensive sonication S-particles, and treatment with phospholipids P-particles. All these particles were defective in coupling respiration to ATP synthesis and could be partly reconstituted by adding back other mitochondrial protein fractions which were termed  $F_2$ ,  $F_3$ , and  $F_4$ . However, these fractions elicited only marginal effects and the effect were often irreproducible. Today we know that these fractions were impure and cross-contaminated with each other, that the factors under study had not always been completely stripped from the test particles, and that the non-linear response of the particles to added factors led many a hapless postdoc astray. Also, all efforts to reconstitute oxidative phosphorylation from completely solubilized submitochondrial particles proved unsuccessful.

By the beginning of 1966 the optimism in Ef's lab had faded somewhat and several of his postdoctoral fellows decided to chose other fields when they started their own laboratories elsewhere. As so often in a scientific career this lull coincided with a wave of official recognition. In the spring of 1966 Ef was elected into our National Academy of Sciences. A few months later Robert Holley (who was soon

to receive the Nobel Prize for his work on the structure of tRNA) and Robert Morison from Cornell University in Ithaca, New York, visited Ef and tried to persuade him to help create and lead the biochemistry department of a new biology unit at that campus. The innovative concept of this plan had received a generous grant from the Ford Foundation, and Ef's own position was to be endowed by one of the prestigious Einstein professorships through which the State of New York hoped to attract outstanding scholars to its new university system.

Ef had of course received offers before, but this one had the right ring. It also came at just the right time. Although Ef had grown up in Vienna he was never a "city type" and was beginning to loathe the inconvenience of working in New York City. In order to give his family the peace it needed he lived in faraway Mount Vernon and the daily commuting by car was proving to be a burden. The challenge of creating a new research unit may have also excited him, but I suspect that his decision was really swung by his wife Franziska. He had known Franzi (Frances to most Americans) in Vienna where she received her M.D. at about the same time as he. Born to an established Viennese family who lived in the rather fashionable ninth district, she, too, had emigrated via Great Britain to the United States. She had just obtained an advanced degree in public health at Harvard Medical School when Ef and she met again in the New World. They married in 1945. Intelligent, musical, practical, and charming, she was everybody's favorite and an adopted grandmother for many of the postdocs' children. She was then, and still is, an active and successful physician. As ambitious and strong-willed as Ef himself, she was a perfect companion for him by showing him unflinching devotion while guiding him with a firm and understanding hand. She loves nature and gardening (quite unlike Ef), and was attracted

by the prospect of living in the green hills of rural Ithaca and of being closer to her husband and her only child Ann, who was then sixteen years old. After only a brief deliberation Ef decided to take the plunge; in the fall of 1966 he moved his family and most of his laboratory to Ithaca.

The decision proved to be an excellent one. Cornell greeted Ef with open arms and gave him free rein in creating "his" department. His reputation helped him to recruit outstanding senior scientists such as Quentin Gibson from Great Britain, Leon Heppel from NIH, André Jagendorf from Johns Hopkins University, as well as his trusted colleagues Harvey Penefsky and Ray Wu. "Young Turks" were added by the arrival of Stuart Edelstein, Peter Hinkle, Richard McCarty, and David Wilson. While all of this was happening I was back in Vienna trying to get reaccustomed to Europe; however, in 1968 I decided to cross the Atlantic once again and join Ef's new department as a faculty member. All of us were housed in Wing Hall which had been refurbished and expanded. Research funds and jobs were still plentiful and our spirits high. We owned the world.

Ef proved to be a smooth administrator who coped effortlessly with the added burden of creating and running a big department. He had a talent for picking capable aides and letting them do things their own way. His teaching obligations were light. Because of his intuitive and idiosyncratic style of thinking he preferred to teach seminar courses, and the students loved him. For the first time in his life his appointment brought him in close contact with undergraduate students and it proved to be an immediate and reciprocal love affair. These intoxicating "hippie years" were hard on parents, but they were great for outgoing and unconventional academic teachers such as Ef. Even his sartorial negligence was a distinct advantage. In spite of his many new commitments Ef continued to work at the bench and

to supervise the postdoctoral fellows who now flocked to him in growing numbers. Some of the outstanding young people from this period include Günter Hauska, Richard Haganir, Baruch Kanner, Ladislav Kováč, Chris Miller, Maurice Montal, Nathan Nelson, Michael Newman, Jan Rydstrøm, Dennis Stone, Bernie Trumpower, and Charles Yocum. I became particularly close with Nathan Nelson who often reminded me of Ef himself. His amazing productivity was sustained by the help from his smart wife Hannah. Both of them became lifelong friends of Ef and his family.

With such a high-caliber cast the Cornell team soon scored its first successes. These successes were triggered by the team's growing conviction that oxidative phosphorylation was not mediated by a high-energy chemical intermediate, but by a transmembrane proton gradient as Peter Mitchell had proposed a decade ago. Ef's conversion to Mitchell's ideas was triggered by his many discussions with the brilliant Peter Hinkle, who had done postdoctoral work with Mitchell in Great Britain and who now saw it his mission to save Ef's soul by converting him to chemiosmosis.

Ef loved to argue with Hinkle, but in the end his conversion probably came from two experiments in which he participated himself. Prompted by studies done by Hinkle, Ef showed that the oxidation rate of cytochrome *c* by cytochrome oxidase reconstituted into liposomes was controlled by a transmembrane proton gradient. This "respiratory control" closely mimicked that seen with respiring intact mitochondria when ATP synthesis was prevented by lack of the phosphate acceptor, ADP. Second, he and Kagawa (who had returned to Ef's lab for an extended sabbatical) finally succeeded in reconstituting ATP-<sup>32</sup>Pi exchange, a partial reaction of oxidative phosphorylation, from pure F<sub>1</sub> and solubilized F<sub>0</sub>. This activity was only seen when the two components

were reconstituted into a sealed liposome and was lost when the liposomes were made leaky to protons.

Perhaps the most famous experiment from this period was done by Ef and Walther Stoeckenius, a German biologist working at the University of California at San Francisco. Stoeckenius had discovered bacteriorhodopsin, a purple chromoprotein from the archaebacterium *Halobacterium halobium* and, together with Dieter Oesterhelt, had found that this protein functioned as a light-driven proton pump in the bacterial plasma membrane. Why not incorporate this simple, pure proton pump into a liposome together with the  $F_1F_o$ -ATPase from bovine heart? If Mitchell was right and the two components oriented themselves properly in the liposome membrane (which was the big if), then the protons pumped out by the illuminated bacteriorhodopsin should flow back through the  $F_1F_o$ -ATPase and generate ATP from ADP and inorganic phosphate. Stoeckenius visited Ef at Cornell to do this experiment with him, even though neither of them gave it much of a chance. The gods must have been pleased to see two elderly scientists working together at the bench; the experiment worked and convinced even the most obdurate skeptics that Mitchell's hypothesis was correct. Almost two decades after elucidating a key reaction of ATP formation in glycolysis Ef had helped to nail down the mechanism of ATP formation in mitochondria, chloroplasts, and the bacterial plasma membrane.

In the years that followed, Ef and his collaborators reconstituted an astonishing array of different membrane enzymes into liposomes and established reconstitution as a powerful and generally applicable approach for unraveling the mechanism of pumps, transporters, and receptors. Numerous prestigious honors and prizes came his way, such as the Warren Triennial Prize in 1974, the National Medal of Science in 1976, and the Gairdner Award in 1980. But many biochem-

ists were disappointed when the 1980 Nobel Prize for Chemistry went to Mitchell alone. As usual, the Nobel committee did not divulge its reasoning, but many of the leading biochemists were surprised or even upset by the fact that Ef had not shared the prize. Only Ef himself seemed to be little concerned. He continued to work at the bench as usual, and painted more avidly than ever in his new enlarged studio which had been a birthday present from Franz. He also enjoyed his new role as grandfather; he was never more at ease than when playing with children.

There was also renewed excitement in the laboratory, for his long and distinguished career seemed to be headed for a triumphant finale. After having been a key figure in unraveling the enzymology of glycolysis, the pentose phosphate pathway, and oxidative phosphorylation, he had returned to the problem that had still defied him: the abnormal glycolysis in tumor cells. His previous studies had convinced him that glycolysis was controlled by cellular ATPases. Could one of these ATPases be hyperactive in tumor cells and thereby cause an abnormally high glycolytic rate?

It seemed like a stroke of luck that just at this time Mark Spector joined him as a graduate student. Intelligent, hard-working, and unusually skilled at the bench, Spector embodied many of the qualities Ef admired in others. A brilliant hypothesis was born and documented by a quick succession of experiments. A tumor gene encodes a protein kinase. This kinase phosphorylates and thereby activates another kinase. This second kinase activates a third, and so on until the last member of this "kinase cascade" phosphorylates a subunit of the ATP-driven sodium-potassium pump in the plasma membrane; phosphorylation of the pump renders it less efficient, increasing its rate of ATP consumption and thereby the rate of glycolysis. But in 1981 it became clear that Spector had fabricated his data,<sup>4</sup> and it

could not have happened at a worse time. The United States was just then going through one of its recurring crusades against human evil, and this time the evil was “scientific misconduct.” Ef found himself in the center of a storm and it was then that his true stature showed. He immediately published retractions of the questionable papers, withdrew those still in print, and offered to resign from his various committees until the issue had been resolved. He set an example of courage and honesty to us and future scientists. It was no coincidence that the American Society of Biological Chemistry chose this moment to award him their prestigious Sober Memorial Lectureship. To him it must have been a dark time, but to me and many of his friends it was perhaps his finest hour.

It was in one of the difficult years that followed that he spent the only sabbatical of his life in my Basel laboratory. Once again I admired his quick mind, his enthusiasm, his experimental skill, his undimmed scientific curiosity, and his truly astounding openness to new ideas. His books on bioenergetics and the social impact of science were much appreciated in Europe and he loved to discuss them with my students and postdocs. But a long day in the lab left him exhausted, and his private talks with me often touched upon the dark sides of life. His lectures still impressed and captivated his audience even though his deteriorating hearing made it difficult for him to handle the subsequent discussions.

Upon his return to Ithaca his letters became more frequent and unusually warm and personal, but his suddenly erratic handwriting made me worry about his health. On September 6, 1991, he came home from a hard Saturday in the laboratory and was felled by a severe stroke. He never regained consciousness and died in Syracuse three days later.

What kind of man was Efraim Racker? Someone as bril-

liant, artistic, and intuitive as he will always defy definition. Like many great scientists Ef had several personalities and therefore elicited different responses in different people. He was one of the last great figures of biochemistry's heroic age. He embodied the artistic, even romantic approach to a field of science that has become increasingly dominated by organized collective efforts. He could be egocentric, insensitive, even overbearing; but, those who knew him well will cherish the memory of his warmth, his immense intellectual range, his lack of prejudice, and his unshakable belief in the power of human reason and inventiveness. Once you were his friend, he was always for you and forgave you everything. Few knew that he was sometimes haunted by depressions which showed in the many leafless trees of his paintings and his never-ending fascination with the secrets of the human mind.

Perhaps one would only understand the many layers of Ef's character if one could retrace his formative years in the Vienna of his youth. But the world of his youth has been brutally shattered forever, and few are still with us to tell about it. Ef rarely talked about that time and maintained only infrequent contacts with relatives outside his immediate family. Upon his emigration he had even tried, with some success, to forget the German language and tended to stammer when being addressed in that language.

But every human life is mystery and best weighed by its influence on others. Efraim Racker showed me that scientific exploration and art are but two manifestations of the same powerful spirit that makes us human, brings us joy, and gives us wings.

MANY FRIENDS AND COLLEAGUES have helped me retrace Ef's private and scientific life and improve this brief account. My special thanks go to Franziska Racker, Judy Caveney,



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