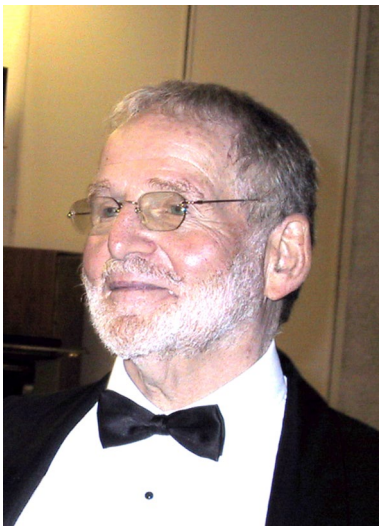
H. Ronald Kaback 1936–2019

Almost exactly a year ago, I wrote an article about my peerless mentor Ron Kaback, highlighting not only his extraordinary scientific contributions but also his enormous and inspiring impact as a mentor[1]. Although Ron had by then been facing health challenges for quite some time, it is still surreal and painful that this obituary is being written so soon thereafter. H. Ronald Kaback, distinguished professor in the Department of Physiology at UCLA, died on 20 December 2019. Ron was without a doubt one of the most original, creative and influential American biochemists of the last few decades. His research focused on transport across biological membranes, a field he truly pioneered. He was passionate about science to a degree that almost defies description. Ron's name is virtually synonymous with the most extensively investigated membrane transport protein in the world: the lac permease of *Escherichia coli*.

Ron was born in Philadelphia in 1936. After graduating from high school in his hometown, he attended Haverford College, where he was a biology major interested in sports (particularly football). Ron benefited greatly from a special program that brought world-renowned scientists, including Nobel laureates, to Haverford to lecture and interact with just seven biology majors. As Ron himself said, one of the main driving forces for his interest in science was his desire to prove to his skeptical professors that he could be a football player and go on to medical school "without being intellectually compromised." Ron published his first paper at Haverford, from which he graduated in 1958. He then enrolled at the Albert Einstein College of Medicine in New York, where, as a medical student, he developed his own strand of research in the laboratory of Adele Kostellow. Ron generated the first osmotically sealed membrane vesicles from bacteria. These vesicles, which came to be known as kabackosomes, are capable of transporting solutes just as well as intact cells do — but they make for a much better controlled experimental system because they lack cytoplasm and so do not metabolize any substrates they accumulate. Astonishingly, Ron faced a great deal of resistance to the publication of his seminal kabackosomes paper, which only saw the light of day much later thanks to his determination and persistence[2]. This brilliant idea, which revolutionized transport research, is emblematic of what Ron's mind was capable of. Kabackosomes were Ron's most important scientific contribution during the early part of his career.



Credit: Antonio De la Vieja

After graduating from Einstein, Ron worked, starting in 1964, in Earl Stadman's enzymology laboratory at the National Institutes of Health (NIH) as a way to meet his Selective Service requirement without having to be drafted and sent to Vietnam. In Stadman's laboratory, he continued pushing the transport field forward using his membrane vesicles. Ron was later offered a position of his own at the NIH, and in 1970, he moved to the newly founded Roche Institute of Molecular Biology in Nutley, New Jersey, where he was able to pursue his research without having to apply for grant funds. His final move came in 1989, when Ron became an Investigator at the Howard Hughes Medical Institute and Professor of Physiology at UCLA, where he spent the rest of his career.

In the 1960's, one issue of great contention in bioenergetics was Peter Mitchell's chemiosmotic hypothesis, which states that the transmembrane electrochemical gradient of protons ($\Delta\tilde{\mu}_{H^+}$) is the driving force for oxidative phosphorylation, active transport, the functioning of the flagellar motor, and other cellular processes. Most transport scientists, Ron very much included, were steadfast opponents of Mitchell's hypothesis, and Ron set out to prove Mitchell wrong experimentally using his vesicles. Ironically, Ron's experiments actually demonstrated that $\Delta\tilde{\mu}_{H^+}$ is indeed the driving force for the accumulation of many substrates[3], and Mitchell himself regarded Ron's results as the first piece of conclusive evidence in favor of his chemiosmotic hypothesis, which became widely accepted as a result of these findings. Ron had shown that Mitchell was right.

After the *lacY* gene, which encodes lac permease, was cloned and sequenced[4], Ron's group purified lac permease to homogeneity, reconstituted it into proteoliposomes and showed it to be fully functional[5]. From there, Ron's group began to determine the roles of specific amino acid residues in lac permease, replacing them by site-directed mutagenesis and eventually demonstrating that only nine residues are essential to the activity of the protein. In quick succession, Ron pioneered studies of helix packing using thiol crosslinking between two cysteine residues engineered onto a functional transporter lacking native cysteines. Using a battery of site-directed techniques — including second-site suppressor analysis coupled with chemical modification, thiol crosslinking, excimer fluorescence, the engineering of Mn(II) binding sites onto the protein, electron paramagnetic resonance, and chemical cleavage and identification of monoclonal antibody epitopes — he generated a helix-packing model[6] with a resolution of ~4 Å. Ultimately, in 2003, Ron and his collaborators determined[7] the crystal structure of a conformationally restricted lac permease mutant in the inward-facing conformation at a resolution of ~3.5 Å. He went on to investigate the alternating access mechanism and to determine the protein's structure in the outward-facing conformation using nanobodies[8]. Ron recently reported on an engineered occluded apo intermediate of the protein. His quest to answer key questions about the structure and mechanism of the lac permease was relentless.

Unsurprisingly, Ron received numerous honors over the course of his career. He was elected to the American Academy of Arts and Sciences in 1986 and to the National Academy of Sciences in 1987. He received the Lewis S. Rosenstiel Award (1973), the 3M Life Sciences Award (shared with Peter C. Nowell, in 1993), the Anatrace Membrane Protein Award (2007), the Distinguished Alumni Award from the Albert Einstein College of Medicine (2009) and the Peter Mitchell Memorial Medal (2012), to name but a few. Ron published over 440 papers in many of the leading international journals.

Major symposia were organized in his honor to celebrate his 60th and 80th birthdays, in Villefranche-sur-Mer, France, and Bethesda, Maryland, USA, respectively; both were moving events attended by large numbers of former trainees and colleagues who came from far and wide.

Ron Kaback gave countless lectures and seminars around the world, and he always cut a unique figure wherever he went. He was known not only for his brilliance, intelligence, talent and creativity but also for his wit, his sense of humor and, in his younger years, for his Afro and cigar smoking. Ron was unconventional in many ways, and he never went unnoticed. He was loyal to and supportive of his trainees, colleagues and friends to a fault, and for life. He seemed like an unceasing idea-generating machine — and although not all his ideas were good, reasonable or feasible, his ceaselessness ultimately yielded plenty of ideas that were actually great and bore valuable fruit. Over the last six decades, Ron pushed the field of membrane transporters from the phenomenological to the biochemical and even to the atomic level. By combining detailed biochemical and biophysical studies, he gained an unparalleled mechanistic understanding of all the types of reactions that lactose permease mediates: active transport, facilitated diffusion, efflux, exchange and counterflow. The approaches developed in Ron's laboratory have been applied directly to many important human transporters to elucidate their physiological and pathophysiological roles.

Ron's lifelong companion was his wife, Molly (known as Teenchy) Schreibman, whom he first met in high school and who supported him and his career in myriad ways, all while pursuing her own careers as a medical technician and later as a teacher. They had three children: Elizabeth, George and Josh. Ron's numerous trainees continue to do research at many different institutions around the world and are a vital part of Ron's legacy. Ron's death is an incalculable loss for the scientific community at large, but his powerful legacy will endure. He will not be forgotten. ❐

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