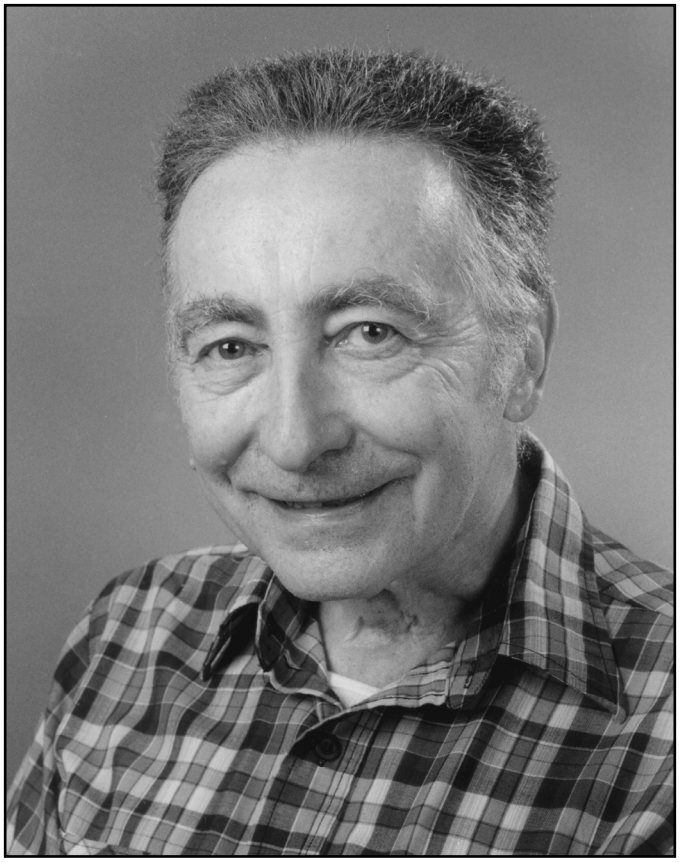
ROBERT HEINZ ABELES



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ROBERT ABELES has been described as a founder of modern enzymology and one of the most influential biochemists/chemical biologists of the second half of the twentieth century. Born in Vienna in 1926, Abeles escaped with his family to Chicago in 1939, at the age of thirteen. His undergraduate education was in Chicago, and his doctoral studies at the University of Colorado, but the transformational influence in his early career was postdoctoral study from 1955 to 1957 with Frank Westheimer in the chemistry department at Harvard. There he began to hone the mechanistic framework for appreciation of the chemical reactions of life that distinguished his subsequent forty-year academic and research career.

After initial faculty sojourns at Ohio State and Michigan, Abeles moved to the then-new department of biochemistry at Brandeis in 1964 and remained there for thirty-six years till his death in June 2000. He and his colleague William Jencks defined the heyday of Brandeis as a national center for chemically oriented biochemistry for thirty years.

Abeles, more than any other individual I have met in the past four decades, combined deep chemical intuition about biological transformations with an inimitable ability to prospect for novel reactions. He specialized in a particular form of biochemical pattern recognition. When a reaction occurred in nature for which respected scholars could not formulate a reasonable mechanistic pathway, Abeles and his research group would march in, isolate the responsible enzyme(s), and begin the unveiling and demystification. Out would come definitive and elegant findings, supported by methodologies and experiments that would lead to rational mechanisms that would become the mechanistic paradigms for whole classes of chemical reactions in living organisms. Out also would come new insights into enzymology, which always tied back to fundamental principles of organic, inorganic, and physical chemistry. Through their corpus of work, Abeles, his colleague Jencks, and his mentor, Westheimer, changed the rules for chemists and biochemists in their thought processes about the chemistry of life. Every biochemical transformation could ultimately be explained by the rules of chemistry, and nature was shown repeatedly to be a superbly inventive chemist.

Abeles excelled in two areas of enzymology. In addition to the unmasking of novel chemical reactions in biology, he was also markedly inventive in design, testing, and analysis of enzyme inhibitors with the aim of enacting principles for new therapeutics. Abeles's reach extended from transition-state analogs to mechanism-based inactivators. He did not feel he was trying to create new drugs in his own laboratory; rather, his aim was to teach the professional medicinal chemists and pharmacologists what principles and approaches to use to maximize their chances of therapeutic success.

Abeles was justly recognized and celebrated during his career with elections to learned societies and the bestowal of deserved awards and recognitions such as induction into the American Chemical Society's Medicinal Chemistry Hall of Fame and the Welch Award in Chemistry. But he was innately indifferent to such external recognitions. He only wanted to know what was new and what was next in deciphering the chemistry of life.

The first time I met Robert Abeles was in 1969, when I served as his host for a graduate student–run seminar at The Rockefeller University. That was my fourth year as a life sciences graduate student at Rockefeller in the laboratory of Professor Fritz Lipmann, and I was pondering possible postdoctoral opportunities. I invited as speakers biochemists whose work sparked contemporary interest, and who were on my own hot list. Abeles gave a scintillating talk on the role of coenzyme B12 in radical-based transformations in biological systems (perhaps his most notable achievement in a remarkable four-decade career of scientific discoveries). At dinner he was approachable and straightforward, brimming with a seemingly endless set of mechanistic puzzles and conundra on which he had insights and approaches to test. I was dazzled and ultimately delighted when I was accepted into Abeles's group as a postdoctoral fellow. That was the transformational experience in my scientific trajectory.

About a week after I arrived in the Abeles laboratory at Brandeis in July 1970, I got up my nerve to ask if I could work on some problem other than the role of coenzyme B12 in enabling radical-based enzyme chemistry, the subject for which he was already internationally famous. I wanted to do something new and take with him the risk that the new direction might not be fruitful. He was open to suggestion. After two weeks of furious library work on my part as I got up to speed on several topics that Bob thought might be intriguing and about which I had known nothing, we agreed to start on the study of enzymes that use vitamin B2 (riboflavin) coenzymes to carry out oxidation-reduction chemistry. That project worked better than we could have expected, and I learned the profound excitement of illuminating some previously murky corner of nature. My academic career was jump-started both by the process of collaborative success and by gaining the skills to prospect for interesting chemical phenomena in biological landscapes.

The two years I spent at Brandeis were, in retrospect, magical. I came in very early every day, to set up experiments and use the various instruments and analytical equipment before demand from coworkers outstripped supply. Bob would wander in shortly thereafter and we would spend on average thirty to forty-five minutes talking about results and experiments he was mulling over on several projects under

way in the lab or ones that might be started. I would ask him about papers I had been reading and enzymes whose mechanism might be decipherable. It was a two-year seminar on how to think about the chemical logic of biological processes, and it set me off on my own career-long prospecting for the hidden logic of nature's chemical machinery.

I learned never to argue or engage in political discussions with Abeles because that would have eaten up all the available one-on-one time. This was during the Nixon years of the Vietnam War. Abeles and I had different views about the context and operation of that conflict. He had grown up in Vienna and had been fortunate to emigrate with his family to Chicago. He served as an eighteen-year-old in World War II in Europe and because of his fluency in German sat in on interrogations of captured German officers to help with interpretation and intonation. I was always aware that Abeles had a fantastic ability to listen to someone, be attuned to inconsistencies, and sort out the truth, a great virtue for an interrogator and a discovery scientist.

The other giant in biochemistry in the same department at Brandeis in that era was William Jencks. Abeles and Jencks taught a mechanistic enzymology course together that was eye-opening to me as a postdoctoral fellow. They also held occasional joint research group meetings where the intellectual atmosphere seemed electric. Abeles and Jencks were almost perfect complements in their approach and style of inquiry and remarkably synergistic with each other. They clearly taught each other, and their coworkers were equal beneficiaries. They join other famous biochemical duos, such as Stein and Moore and Brown and Goldstein, who dominated their eras. The rigorous physical organic chemical thinking applied to biological catalysis provided the foundations for the fields of bioorganic chemistry and molecular enzymology, and for today's chemical biology. The Abeles and Jencks groups for almost three decades became the training ground for dozens of students and fellows, effectively the Abeles and Jencks school, who became leading proponents of those intellectual arenas into the twenty-first century.

On one level Abeles could be direct and intimidating (shades of his wartime interrogation experience), but he was, at another level, informal, an amusing raconteur, and a lively participant in discussions. He was a longtime devotee of the annual Enzymes Gordon Research Conference and attended every talk, sitting in the front row and enjoying the cutting-edge science unveiled in those meetings. If Abeles liked a scientific story from a young presenter, that was a very good predictor of future leadership in the field.

Bob Abeles understood excellence and truth and without fanfare used them as yardsticks in all of his professional and scientific life. Part of his inspiration to the scientific community he trained and educated

was the example he set unconsciously and matter-of-factly for how to lead a scholarly scientific life. Abeles had more than his share of health burdens, from Hodgkin's disease in the 1970s to increasingly severe Parkinson's disease at the end of his life in June 2000. But he always maintained a fine sense of wonder and appreciative awe when he learned about some new elegance in the logic and machinery of the chemical transformations in our bodies that keep us all going.

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