BIOGRAPHICAL MEMOIRS

Robert Heinz Abeles

January 14, 1926–June 18, 2000
Elected to the NAS, 1976

A Biographical Memoir by Dagmar Ringe and Lizbeth Hedstrom

Robert Heinz Abeles, Bob, has been described as a founder of modern enzymology and one of the most influential biochemists and chemical biologists of the second half of the twentieth century. He developed many of the techniques and discovered most of the general principles that drive this field today.

Bob Abeles was born on January 14, 1926, in Vienna, Austria. He emigrated with his family when he was thirteen years old, arriving at New York's Ellis Island and moving on to Chicago in 1939. His education was interrupted during World War II, when he served in the Allied Occupation Forces in Europe from 1944–1946. He was a member of the Ritchie Boys, the elite unit responsible for gathering more than half the actionable intelligence on the battlefield. Because he was a German speaker, he was engaged in debriefing German POWs. Among other actions, he was involved in the capture of Axis Sally, an American who had broadcast Nazi propaganda from Berlin. After the war, he returned to Chicago, where he attended Roosevelt College and then received undergraduate and master's degrees from the University of Chicago. He earned his Ph.D. from the University of Colorado School of Medicine under Cosmo Mackenzie in 1955 and then took a postdoctoral position in the Department of Chemistry at Harvard University. His postdoctoral advisor Frank Westheimer was probably his most influential mentor. Bob began to develop the mechanistic framework that distinguished his work in defining the chemistry of living systems at this time. In 1956, he joined the faculty at Ohio State University as an assistant professor of chemistry and

Robert H. Abeles, 1975. Courtesy of the Robert D. Farber University Archives & Special Collections Department, Brandeis University.

four years later moved to the University of Michigan as an assistant professor of biological chemistry. Bob was recruited to the Brandeis University faculty in 1964, by Nathan Kaplan, as an associate professor of biochemistry, rising to professor in 1967. Kaplan was just starting the new Graduate Department of Biochemistry, in which Bob became a major star alongside William "Bill" Jencks. Bob became chair of the department in 1973 and remained in the position until 1988. In addition to his work in academia, Bob consulted with many of the major pharmaceutical companies, including Sandoz and Merck.

The bibliography of Bob Abeles reads like a what's what of mechanistic enzymology. He was convinced that enzymatic reactions could be described by the principles of organic chemistry, a novel concept because enzymes seemed to do chemistry often not possible in aqueous systems. His innate curiosity and unerring instinct for important questions drove him to investigate the mechanisms of numerous enzymes, including examples of almost every reaction class. This was at a time, before the advent of recombinant protein expression, when protein purification was a tedious chore and the characterization of a single enzyme could easily constitute an entire scientific career. Not only did Bob's work reveal principles of enzyme catalysis, but his chemical intuition also led to groundbreaking designs of enzyme inhibitors and mechanism-based inactivators, laying the foundation of rational drug design.

The elucidation of the reactions of coenzyme vitamin B12, adenosylcobalamine (AdoCbl), was perhaps his greatest achievement.[1] Some B12 reactions involve carbon migration, a transformation declared impossible by leading organic chemists at the time. Abeles found that B12 reactions involved homolytic cleavage of the carbon-cobalt bond in a series of elegant experiments showing that hydrogens from the substrate are incorporated into the cofactor.[2] His work demonstrated that B12 reactions are radical rearrangements and placed the coenzyme AdoCbl into the role of radical initiator, the first example of radical chemistry in a biological setting.[3] Not only is radical initiation the common step in all B12-requiring enzymes, but it is the mechanistic paradigm for the much larger class of radical S-adenosyl methionine (SAM) enzymes now recognized to occur throughout all the kingdoms of life.

His unique insights into how to trick an enzyme to self-inactivate ("commit suicide") are legendary, leading to the coining of the terms "suicide substrate," or "mechanism-based inhibitor"—namely, a compound that, as a consequence of the basic chemistry of the reaction catalyzed, covalently couples to an active site residue and thereby permanently inactivates the enzyme.[4] The results led to surprises and new chemistry, as illustrated by his revolutionary use of fluorine in designing inhibitors. In particular, the use of fluoromethylketones as transition-state analog inhibitors for serine proteases had far-reaching influence.[5,6] One of us (DR) realized how important that work was when attending a meeting in the then Deutsche Demokratische Republik (DDR); now that the usefulness of fluorine-containing inhibitors had been demonstrated, everyone wanted to make them.

The list of enzymes that Bob studied in his laboratory and the methods he used are too long to catalog in detail. Suffice it to say that he studied the mechanisms of every reaction class, including enzymes that use all matter of cofactors (NAD, flavin, deazaflavin, methoxatin, pyridoxal, pyruvoyl, Fe/S clusters, and metals in addition to B12) and intermediates (carbanion, carbocation, radical, and covalent enzyme). His last great project was the discovery of the metabolic pathway for the degradation of 5-methylthioadenosine to regenerate methionine and produce carbon monoxide. An unusual enzyme in that pathway can use either iron or cobalt (or nickel) to produce different products.[7] The mechanisms for these transformations from the same protein differing only in metal cofactor are still not understood.

The first time one of us (DR) met Bob was when he approached Greg Petsko and me to collaborate on a structural problem. He had developed two chloropyrones, one of which reacted just as expected with chymotrypsin and the other of which reacted quite differently with the enzyme and allowed reactivation with time. Bob wanted to know the difference and hoped that structures of the complexes would tell him. I took on the project. During our discussions, it became clear that he didn't believe in crystallography: he saw enzymes as soft and flexible, not crystalline objects that could not move. Nevertheless, the structure revealed the secret—the pyrone ring opened in one case, but not the other—and Bob was converted to a believer in the power of structure to provide insight into mechanism.[8,9] In fact, he recognized the power of the method and demonstrated how it should be used to understand the role of protein flexibility on mechanism. His insight was all the more remarkable because watching structures on the screen, which has a flicker not usually detected by the observer, made him nauseous. But the results were more important, so we made static pictures that he could study.

Bob's office was a tiny space equipped with a desk and a blackboard, directly adjacent to the laboratory, giving him immediate access to the work being done and the coworkers doing it. I had many occasions to sit on the radiator in that office while discussing projects and results, no extra chair being there, only his big black desk chair. Each time he told a favorite story first, having nothing to do with science: his horse, woodworking (his favorite hobby), political jokes at the expense of the liberal establishment, or his latest pet peeve. Conversations about science were always stimulating, far-reaching, and full of insights. One of his favorite stories was about an occasion when he was picked up at the airport by Bill Jencks to drive to a meeting. They became so engrossed in the science that they missed the turnoff and had to retrace their trip for over an hour.

Bob preferred to interact with graduate students and postdocs in the laboratory. He would make the rounds every day starting at 11 a.m., sandwich in hand (you could do that then), and ask each person what they had accomplished the day before. He would then throw out half a dozen or more

questions, which might or (more often) might not be the same questions as the previous day. Students quickly learned to save some data for the times when experiments went awry, so that they would never be caught empty-handed. Woe to the student who was invited into Bob's office, especially if they were asked to sit in the big black chair—Bob's WWII-honed interrogation skills were soon to be directed at them!

The Abeles laboratory, and Brandeis in general, was remarkable for its number of women trainees. Although he enjoyed an off-color joke, Abeles judged people on a single metric, unclouded by personality or gender—either a person was smart, or they weren't. He recognized talent rather than pedigree and had an uncanny ability to see character as well as potential.

Bob thought intuitively, springing from one idea to the next. He would then reconstruct the argument in a linear fashion with a simplicity and clarity that belied the intellectual leaps required to make the connection. For example, he recognized that S-adenosylhomocysteine was a potent inhibitor of SAM-dependent methylases, and therefore cells must have a way of removing this metabolite. This insight led to the delineation of the methionine salvage pathway. Bob's ability to distill complex concepts into simple logical steps made him an exceptional teacher. His course in enzyme mechanisms, taught with Bill Jencks, was a transformative experience for generations of students.

Abeles had a pragmatic "no b-s" approach to life as well as science. At one point, he was enrolled in a clinical trial—he handed a pill to a postdoc with the instructions to take a nuclear magnetic resonance spectrum. He was indeed in the treatment group but nonetheless dropped out of the study when he failed to observe any improvements after a few weeks. He was devoted to his wife Barbara, daughter Lisa, and son Steven, but largely kept his family life separate from his laboratory. His dogs were the exception to this rule—he favored Irish setters but switched to calmer golden retrievers in his later years. The dogs came to the lab every day, even when Bob was traveling elsewhere.

Bob was famously incapable of remembering the names of people, with the notable exception of those fortunate to have the same name as his wife, Barbara. Once while introducing a new postdoc, he stopped perplexed in front of Rob Kuchta, who helpfully provided a much needed clue: "Think of your own name…." Another of Abeles's favorite stories was the time that he saw a familiar man in a restaurant and asked "do I know you?" The man replied that he was Kevin White, the mayor of Boston.

Bob was justly recognized for his work with numerous awards and by elections to learned societies, including the Edward Swissman-Bristol Myers Award in Medicinal Chemistry in 1987, the Repligen Award (now named the Abeles and Jencks Award) in the Chemistry of Biological Processes of the Division of Biological Chemistry of the American Chemical Society (ACS) in 1988, the ACS Alfred E. Bader Award in 1990, the Rose Award of the American Society for Biochemistry and Molecular Biology and Germany's Alexander von Humboldt Senior Scientist Award in 1994, and the Welch Award in Chemistry in 1995. He was elected to the American Academy of Arts and Sciences in 1973, the National Academy of Sciences in 1976, and the American Philosophical Society in 1999. He received an honorary doctoral degree from the University of Chicago, his alma mater. The Humboldt Award gave him the opportunity to visit laboratories in Europe. The story he brought back was his pride in giving a complete lecture in German. His frustration was that he did not know the German word for extension cord, a concept that antedated his abilities in the language.

Bob was a master scientist, a master woodworker, and a master teacher. He left a far-reaching legacy of scientists whom he trained in how to unravel enzyme mechanisms and how to apply these insights to design therapeutic compounds. He inspired an even larger group of scientists who followed his work, leaving an indelible mark on academia and industry.

References

1 Abeles, R. H., and D. Dolphin. 1976. The vitamin B12 coenzyme. *Acc. Chem. Res.* 9(3):114–120.

2 Frey, P. A., M. K. Essenberg, and R. H. Abeles. 1967. Studies on the mechanism of hydrogen transfer in the cobamide coenzyme-dependent dioldehydrase reaction. *J. Biol. Chem.* 242(22):5369–5377.

3 Finlay, T. H., J. Valinsky, A. S. Mildvan, and R. H. Abeles. 1973. Electron spin resonance studies with dioldehydrase. Evidence for radical intermediates in reactions catalyzed by coenzyme B12. *J. Biol. Chem.* 248(4):1285–1290.

4 Abeles, R. H., and A. L. Maycock. 1976. Suicide enzyme inactivators. *Acc. Chem. Res.* 9(9):313–319.

5 Gelb, M. H., J. P. Svaren, and R. H. Abeles. 1985. Fluoro ketone inhibitors of hydrolytic enzymes. *Biochemistry* 24(8):1813–1817.

6 Imperiali, B., and R. H. Abeles. 1986. Inhibition of serine proteases by peptidyl fluoromethyl ketones. *Biochemistry* 25(13):3760–3767.

7 Dai, Y., T. C. Pochapsky, and R. H. Abeles. 2001. Mechanistic studies of two dioxygenases in the methionine salvage pathway of Klebsiella pneumoniae. *Biochemistry* 40(21):6379–6387.

8 Ringe, D., J. M. Mottonen, M. H. Gelb, and R. H. Abeles. 1986. X-ray diffraction analysis of the inactivation of chymotrypsin by 3-benzyl-6-chloro-2-pyrone. *Biochemistry* 25(19):5633–5638.

9 Ringe, D., B. A. Seaton, M. H. Gelb, and R. H. Abeles. 1985. Inactivation of chymotrypsin by 5-benzyl-6-chloro-2-pyrone: 13C NMR and X-ray diffraction analyses of the inactivator-enzyme complex. *Biochemistry* 24(1):64–68.

Selected Bibliography

1967 With P. A. Frey and M. K Essenberg. Studies on the mechanism of hydrogen transfer in the cobamide coenzyme-dependent dioldehydrase reaction. *J. Biol. Chem.* 242:5369–5377.

1969 With I. L. Givot and T. A. Smith. Studies on the mechanism of action and the structure of the electrophilic center of histidine ammonia lyase. *J. Biol. Chem.* 244:6341–6353.

With S.H. Mudd and H.L. Levy. A derangement in B 12 metabolism leading to homocystinemia, cystathioninemia and methylmalonic aciduria. *Biochem. Biophys. Res. Commun.* 35:121–126.

1970 With J. G. Voet. The mechanism of action of sucrose phosphorylase. Isolation and properties of a beta-linked covalent glucose-enzyme complex. *J. Biol. Chem*. 245:1020–1031.

1973 With T. H. Finlay, J. Valinsky, and A. S. Mildvan.Electron spin resonance studies with dioldehydrase. Evidence for radical intermediates in reactions catalyzed by coenzyme B 12. *J. Biol. Chem.* 248:1285–1290.

1975 With G. Rudnick. Reaction mechanism and structure of the active site of proline racemase. *Biochemistry* 14:4515–4522.

1976 With R. B. Silverman. Inactivation of pyridoxal phosphate dependent enzymes by mono- and polyhaloalanines. *Biochemistry* 15:4718–4723.

With A. L. Maycock. Suicide enzyme inactivators. *Acc. Chem. Res.* 9:313–319.

With D. Dolphin. The vitamin B12 coenzyme. *Acc. Chem. Res.* 9:114–120.

1979 With J. L. Palmer. The mechanism of action of S-adenosylhomocysteinase. *J. Biol. Chem*. 254:1217–1226.

With J. S. Wiseman. Mechanism of inhibition of aldehyde dehydrogenase by cyclopropranone hydrate and the mushroom toxin coprine. *Biochemistry.* 18:427–435.

1980 With J. Stubbe and S. Fish. Are carboxylations involving biotin concerted or nonconcerted? *J. Biol. Chem.* 255:236–242.

1984 With L. Hedstrom, A. R. Moorman, and J. Dobbs. Suicide inactivation of chymotrypsin by benzoxazinones. *Biochemistry* 23:1753–1759.

1985 With M. H. Gelb and J. P. Svaren. Fluoro ketone inhibitors of hydrolytic enzymes. *Biochemistry.* 24:1813–1817.

With C. E. Nakamura. Mode of interaction of beta-hydroxy-beta-methylglutaryl coenzyme A reductase with strong binding inhibitors: Compactin and related compounds. *Biochemistry.* 24:1364–1376.

1986 With B. Imperiali. Inhibition of serine proteases by peptidyl fluoromethyl ketones. *Biochemistry* 25:3760–3767.

1987 With T. C. Liang. Complex of alpha-chymotrypsin and N-acetyl-L-leucyl-L-phenylalanyl trifluoromethyl ketone: structural studies with NMR spectroscopy. *Biochemistry* 26:7603–7608.

1989 With R. A. Arkowitz. Identification of acetyl phosphate as the product of clostridial glycine reductase: Evidence for an acyl enzyme intermediate. *Biochemistry* 28:4639–4644.

1990 With K. Brady, A. Z. Wei, and D. Ringe. Structure of chymotrypsin-trifluoromethyl ketone inhibitor complexes: comparison of slowly and rapidly equilibrating inhibitors. *Biochemistry* 29:7600–7607.

1994 With S. Dhe-Paganon and J. Magrath. Mechanism of mevalonate pyrophosphate decarboxylase: evidence for a carbocationic transition state. *Biochemistry.* 33:13355–13362.

2001 With Y. Dai and T. C. Pochapsky. Mechanistic studies of two dioxygenases in the methionine salvage pathway of Klebsiella pneumoniae. *Biochemistry* 40:6379–6387.