
JEREMY RANDALL KNOWLES



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28 APRIL 1935 · 3 APRIL 2008

Jeremy Knowles had two fascinating and challenging careers. As a chemist for 30 years, he made major contributions to understanding the catalytic action of enzymes, huge protein molecules that govern myriad biological processes. As Dean of the Faculty of Arts and Sciences at Harvard University for a dozen intense years, he catalyzed actions of a host of people that enhanced many institutional processes. To both his careers, Jeremy brought extraordinary ability and zestful devotion.

Born in Rugby, England in 1935, Jeremy received his secondary education at Magdalen College School, Oxford (1946–1953). He then served his two years of National Service as a pilot officer in the Royal Air Force (1953–1955). He commented that the stint taught him “to always have in mind a target.” At Balliol College, University of Oxford, he pursued chemistry and graduated with first class honors in 1959. Jeremy also had abiding interests in music and art. He served as an organist at several Oxford venues, and sang madrigals and in choirs. Romance, fostered by choir singing, led to his marriage in 1960 to Jane Sheldon Davis. In their adventurous life to come, they became a marvelous duet. His Balliol tutors, especially R. P. Bell, excited his lasting interest in a challenging target: chemical kinetics, which strives to elucidate the molecular pathways that govern the speed of reactions. Jeremy continued at Oxford, working with Richard Norman to study electronic effects on rates of aromatic substitution reactions, and completing a D.Phil. in physical organic chemistry in 1961.

HIS ENZYME ERA

A postdoctoral fellowship brought Jeremy to the California Institute of Technology from 1961 to 1962. There he became intrigued with the extraordinary specificity and rates of enzyme-catalyzed reactions that went a million times faster than unaided reactions. Later, he recalled, “I had been trying, and failing, to understand a factor of 10 variation in reaction rates of small molecules.” He asked, “Would it not be perhaps more important to fail to understand something big than to fail to understand something small?” That spurred him to focus his research, over the coming three decades, on the remarkable properties of enzymes.

Jeremy returned to Oxford as a tutorial fellow of Wadham College (1962–1974), a permanent post he felt “exceedingly lucky” to have obtained. It enabled him to do independent research, even though he had not yet had any publications on his newfound passion, enzyme catalysis. His appointment owed much to his other ardent

interests—music and the arts. As a Balliol student, Jeremy had joined several clubs not connected with science and had served as an organist at several Oxford venues. The fellowship was funded by a gift, specifically to support organic chemistry, but made to Wadham College, not to the university. Hence the college could select the tutorial fellow without approval of the university. Indeed, Sir Ewart Jones, the professor of organic chemistry, objected. However, Jeremy was chosen by Sir Maurice Bowra, the warden of Wadham College, “not a great admirer of chemists but surprised and charmed by Knowles’ other interests.”

Soon his superlative performance in research and teaching gained unstinting admiration, and Jones saw to it that Jeremy was made a university lecturer (1967–1974). Jeremy also undertook collaborations with Robert Williams, Rodney Porter, John Albery, and others that led to forming the Oxford Enzyme Group. It was a propitious time to pursue unraveling the amazing catalytic action of an enzyme. For that formidable task, knowledge of the molecular structure of the enzyme was an essential requisite. David Phillips had joined the Oxford faculty, having determined the first 3-D structure of an enzyme (lysozyme) by X-ray crystallographic analysis just a few years earlier. Acknowledging that knowing the structure is necessary but far from sufficient, Jeremy remarked, “Taking a photograph of a horse does not necessarily tell you how fast it can run.”

Among his research at Oxford, Jeremy launched a project that became epic, extending over three decades. It focused on the enzyme triosephosphate isomerase (TIM), an attractive target because the net reaction required the transfer of only two protons in order to interconvert two phosphosugars. Another attraction was that David Phillips had decided the structure of TIM would be his next major project. Moreover, TIM simply catalyzes the equilibrium between a single substrate (the reactant molecule) and a single product. As Jeremy first pointed out, in such a case, it was possible in principle to observe an enzyme-substrate complex directly by X-ray crystallography as long as the concentration of substrate in the crystals was sufficiently high. Eventually, his suggestion led to an important subfield that mapped structures of enzyme complexes with substrates and intermediates.

During leaves, Jeremy was a visiting professor at Yale University (in 1969 and 1971) and at Harvard University (1973). He resigned from Oxford to join Harvard as a full professor (1974), where he later was named Amory Houghton Professor of Chemistry and Biochemistry (1979). Although at Oxford he had been “very happily settled . . . the challenge of a new and exciting environment in the end became

dominant.” The new habitat proved congenial also for Jane and their three boys, Sebastian, Julian, and Tim. Jane became for many years the archivist for the Schlesinger Library, now at Radcliffe Institute, the major national resource for the History of Women in America.

Not long after his move to Harvard, Jeremy created much excitement by publishing unprecedented results in an unprecedented way. Eight back-to-back papers appeared in the December 1976 issue of *Biochemistry*. All listed Jeremy as the corresponding author and John Albery, his Oxford collaborator, as a coauthor. The first paper “established the theoretical and experimental foundation for using the effects of isotopic substitutions on reaction rates to dissect the free energies of each step in an enzyme-catalyzed reaction.” The following papers mapped out for TIM the first complete energy profile of the enzyme interacting with the substrate. The energy barriers for the chemical steps of catalysis turned out to be lower than that for the purely physical step for the diffusion-controlled binding of the enzyme to the substrate. Thus, diffusion was found to be the slowest step, which determines the overall reaction rate. The chemical steps, rearranging bonds, were all faster.

John and Jeremy concluded that TIM, as well as some other enzymes, had evolved to come close to “catalytic perfection.” After evolution had optimized the chemical steps to match or exceed diffusion, “there is no catalytic advantage to be gained by further adjustment of the free energy levels . . .” They also identified factors that produced the efficiency of enzyme-catalyzed reactions. More experiments with TIM elucidated many other aspects. Particularly, mutagenesis experiments revealed that some mutations markedly inhibited the activity of an almost-perfect enzyme, others had no effect or could partially compensate damaging mutations at different sites. Such studies demonstrated the means to introduce directed evolution, which became a flourishing field.

Beyond TIM, Jeremy and his coworkers elucidated the precise mechanisms and energetics of several other enzymes, often discovering new phenomena. Both the discoveries and his virtuoso leadership were greatly esteemed. As commended by a distinguished colleague, E. J. Corey, Jeremy had, “A powerful and deep intellect, a relentlessly logical and thorough style of research, and great care in selecting and executing projects.” Corey added, “His achievements are fundamental, important, and enduring . . . reminiscent of his icon, J. S. Bach.”

Jeremy was also outstanding as a teacher and mentor at both undergraduate and graduate levels. His lectures were “rigorous, but clear, engaging, and witty.” His research students found his lab

“wondrous and welcoming,” delighted with him and the chance to do frontier science. Between Oxford and Harvard, he mentored more than 50 doctoral recipients. Many went on to become professors or researchers in biotechnology.

In outside advisory roles, Jeremy served on the boards of the Howard Hughes Medical Institute; Biogen, Inc.; Celgene Corporation; Vertex Pharmaceuticals; and Corning, Inc. Jeremy was elected a Fellow of the Royal Society, the American Academy of Arts and Sciences, the American Philosophical Society, the American Association for the Advancement of Science, and a Foreign Associate of the National Academy of Sciences. His scientific awards include the Charmian Medal, the Bader Award, the Repligen Award for Chemistry of Biological Processes, the Prelog Medal, the Robert Welch Award, the Nakanishi Prize, and the Davy Medal. He received honorary degrees from the University of Edinburgh and the Eidgenössische Technische Hochschule in Zurich, and was appointed a Commander of the Order of the British Empire in the Queen’s Birthday Honours List of 1993. The Royal Society of Chemistry established the Jeremy Knowles Award in 2008 “to recognize and promote the importance of inter- and multi-disciplinary research between chemistry and the life sciences.”

HIS DEANSHIP ERA

At Harvard, chemistry professors are expected to serve a three-year turn as chair of the department. During his turn (1981–1983), Jeremy performed so well that President Derek Bok tried to recruit him to be Dean of the Faculty of Arts and Sciences (FAS). Jeremy initially declined the invitation; then 48, he did not want to give up his research. Eight years later, however, a new president, Neil Rudenstien, renewed the request and Jeremy accepted. In retrospect, he took the opportunity to take on “an exciting, invigorating, and energizing new set of challenges to look at—and that proved correct.”

Jeremy was welcomed by the *Harvard Crimson*, the undergraduate newspaper, as “exuberant, witty, and at ease in the corner office of University Hall.” Veteran administrators were “startled by his intensity . . . his work habits, editing mania, impossibly high standards, charm, frugality, and sheer persistence.” But for his first few years, Jeremy felt he had to be a “wet-weather dean.” Faced with an unsustainable budget deficit, he firmly restrained departmental and administrative budgets, and reluctantly had to “say no” to most new proposals. His “comparative frugality” policy did allow faculty recruitment to go on; faculty salaries were never frozen, and undergraduate financial aid was

“protected.” As means became available, he began investing in improving physical infrastructure that had suffered from deferred maintenance, starting with dorms occupied by freshman students. Also, he scaled up the information systems staff as faculty offices and student rooms were rewired.

Midway and onward during his deanship, Jeremy was able to anticipate better fiscal weather. Alumni, “passionate in their willingness and commitment,” were strongly supporting a fund drive and endowment investment returns were high. He authorized major linked renovations that drew together 17 departments and other units of the humanities, which had long been haphazardly dispersed, into the Barker Center and Boylston Hall. Memorial Hall was restored and reshaped to provide freshmen students a large, elegant dining hall and quarters for many other activities, located right next to their dorms in Harvard Yard and the Science Center. The massive renovation of Widener Library began. In 1999, Jeremy launched several ambitious initiatives in the sciences, including the Bauer Center for Genomics Research, the Center for Imaging and Mesoscale Structures (now the Center for Nanoscale Systems), and the Center for Brain Science. Jeremy was also involved in planning the complex of new science buildings that now occupy the “North Precinct” of the campus. For the social sciences, he led the planning for the Center for Government and International Studies, which opened in 2006.

Throughout his deanship, Jeremy fostered collaborations. He charged committees of faculty to examine FAS operations and recommend improved practices. These addressed such problems as attracting women to the science faculty, making more effective faculty recruitment, assessing investment in new interdisciplinary fields, and innovative teaching. Scrutiny by the committees helped him win support for action on junior-faculty compensation, graduate-student financial aid, leave policy, and acceptance by the FAS of a lead role in underwriting the early planning to develop the new campus in Allston.

By the end of his term as dean (1991–2002), Jeremy had doubled the funds for undergraduate aid and also liberalized and made more secure graduate student aid packages. He also began an effort to strengthen scholarship in emerging fields by increasing the size of the FAS faculty, which had long been nearly static. During his term, the number of tenured faculty reached 442, an increase of about 10 percent. The number of tenured women faculty more than doubled, to 78, increasing to 19 percent.

Jeremy delivered countless talks, always sparkling. Often he lightened a serious message with a memorable quip. A much-quoted one,

given to a convocation of incoming freshmen, was his vivid description of what he saw as the most important goal of higher education: “to enable graduates to recognize when someone is talking rot.” He also inaugurated a series of lunchtime concerts and took part as narrator for a performance of *Peter and the Wolf* by the student orchestra. At his “graduation as an inestimable dean” (2002), he was awarded the Harvard Medal and named a Harvard University Distinguished Service Professor.

Four years later, Jeremy returned as interim dean, serving along with Derek Bok as interim president, in a pivotal year during which the faculty completed major reforms of the general education curriculum in Harvard College. Jeremy had been diagnosed with prostate cancer years before. It seemed to have been contained but suddenly spread. By April 2007 he was close to death, but there followed a “remarkable gift year.” It let Jeremy share many loving conversations with a host of friends and family.

Here are benedictions by three Harvard presidents:

Jeremy Knowles was a dear friend, a widely admired scientist, and a leader of exceptional ability and exceptional devotion to Harvard. Along with unflinching wit and charm, he possessed enormous energy and the highest intellectual and ethical standards. His final service as a dean must surely rank as one of the most selfless actual acts of loyalty in Harvard’s history. Under very trying circumstances, he succeeded in restoring a badly needed sense of momentum and progress at a critical time.

—Derek Bok

Deans and leaders like Jeremy come only rarely. He had a penetrating mind. He had wit and charm and taste. Above all, he understood the nature of a university and what it meant to search for knowledge, or discover even a single truth. The standard could never be too high. . . . Once he had decided to leave his lab and serve the University more than chemistry, nothing less than all his energy and stamina would do.

—Neil Rudenstine

Jeremy fixed things. . . . The work of a dean, he once told me, capitalizing each word, is Making Things Right. And Jeremy devoted himself to that purpose. . . . What was ever so much fun as working with Jeremy? Remember his appearance in drag to celebrate the Radcliffe merger? . . . We will all miss it terribly—the

wit, the mischievousness, the joy he took in what he did. What a prodigiously talented person he was, not just dean of deans but brilliant scientist, magical wordsmith and orator, accomplished musician, unlicensed architect, creative and consummate doodler.

—Drew Faust

Elected 1988

DUDLEY HERSCHBACH
Baird Professor of Science, Emeritus
Harvard University

Author's Note

This memoir, particularly the comments in quotes, draws from conversations with Jeremy and colleagues as well as from some published sources:

- Corey, E. J., and N. L. Rudenstine. "Jeremy R. Knowles." *Angewandte Chemie International Edition* 47, no. 46 (2008): 8772–3.
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- "A Dean for All Weathers." *Harvard Magazine*, May–June 2002, 48.
- "A Dominant Dean." *Harvard Magazine*, May–June 2008, 69.
- "Jeremy Knowles, Your Dean" (FAS 09-011, Alumni Communications, Harvard College). Booklet for Memorial Service on May 30, 2008.