Jeremy Randall Knowles CBE. 28 April 1935 — 3 April 2008

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"Data Supplement"

http://rsbm.royalsocietypublishing.org/content/suppl/2010/05/03/rsbm.2009.0022.DC1

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JEREMY RANDALL KNOWLES CBE
28 April 1935 — 3 April 2008
Jeremy Randall Knowles was remarkable both as a celebrated organic biochemist and as a wise administrator, and throughout his career he retained a lasting love of music and the arts.

He was for several years a tutorial Fellow of Wadham College and a lecturer in chemistry at the University of Oxford, 1962–74. In 1974 he left Oxford permanently for Harvard University to become Professor of Chemistry; in 1979 he was named the Amory Houghton Professor of Chemistry and Biochemistry. To the surprise of many, he later gave up this chair to become the Dean of Harvard University’s Faculty of Arts and Sciences, a post he held with great distinction from 1991 to 2002. He returned to Harvard’s University Hall again as Interim Dean from 2006 to 2007.

Jeremy Knowles was born in Rugby in 1935. His father, Kenneth Knowles, was an academic economist who moved to Oxford in 1945. Knowles’s early education from 1946 to 1953 was at Magdalen College School in Oxford. Before going up to the University of Oxford on a Balliol College Exhibition, he spent his two years of National Service, 1953–55, in the Royal Air Force as a Flying Officer. He commented that he learnt from this experience to ‘always have in mind a target’. At Balliol College he read chemistry and was taught by R. P. Bell FRS for physical chemistry, W. A. Waters FRS for organic chemistry, and R. J. P. Williams (FRS 1972), to whom he was sent out for inorganic chemistry. All recognized his considerable ability. His Balliol tutors, especially Bell, gave him a lasting interest in chemical kinetics. He
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took a first-class honours chemistry degree in 1959. His fourth-year research project—Part II of the chemistry course—and his subsequent DPhil, completed in 1961, were supervised by Professor R. O. C. (later Sir Richard) Norman (FRS 1977), and concerned the mechanism of aromatic substitution. These efforts gave rise to the first four of his 270 papers (1–4)*, the first of which was published jointly with his supervisor and G. K. Radzio, subsequently Director of the Medical Research Council. The work was completed while Knowles was a Senior Harmsworth Scholar of Merton College and a Lecturer at Christ Church, Oxford.

In 1961–62 he took leave from these positions for a postdoctoral Fellowship at the California Institute of Technology. He initially embarked on calculations of energy states of metal chelates with Professor George Hammond but soon found a much deeper interest in the work of Dr Bryan Jones on the specificity and kinetics of the enzyme α-chymotrypsin. Knowles was inspired, and the remarkable properties of enzymes became the focus of his research efforts for the remainder of his scientific career.

THE OXFORD YEARS

Knowles always admitted that he was exceedingly lucky to have obtained, late in his 1961–62 stay in the USA, an independent permanent post in Oxford to do research—especially because he had no publications on his newfound passion, enzyme catalysis. His good fortune came about in fair part through his other genuine interest, music and the arts. Already as a student at Balliol College he had joined several clubs with no connection to the sciences and had served as an organist at several Oxford venues. These activities helped considerably in gaining the support of Sir Maurice Bowra, the then Warden of Wadham College. When Knowles applied for a tutorial Fellowship in chemistry there, Bowra, who was not a great admirer of chemists, was surprised and charmed by Knowles’s interests. The funding of the Fellowship had come from a benefaction to Wadham—and not to the university—from the Tate & Lyle Company, for organic chemistry. It was thus possible for the college to select a tutorial Fellow without input from the university and despite the university’s wishes, as expressed by Sir Ewart Jones FRS, who was then Professor of Organic Chemistry. Bowra’s intuition proved to be inspired. Not only did Knowles become a very successful tutorial Fellow and lecturer in organic chemistry, but through his abilities he also overcame any objection to his selection and became a valued colleague of Professor Jones, who made him a University Lecturer in 1967.

Knowles’s first publications as an independent investigator were on the mechanism of α-chymotrypsin (5, 6), the serine protease he had been introduced to by Bryan Jones. During these early years he also turned his attention to the aspartyl protease pepsin (8), the mechanistic understanding of which was, at the time, muddled. His efforts with this enzyme were perhaps not as successful as he might have wished—in fact even with the aid of crystallographic structures, not available then, a final mechanistic picture only came into focus years later. Without doubt, though, Knowles’s experimental analysis and thoughtful writings on these two proteases helped him enter the highly competitive community of mechanistic enzymologists. His standing was soon firmly secured through his work on several new systems, two initiated in Oxford.

* Numbers in this form refer to the bibliography at the end of the text.
The use of photoaffinity labelling by Knowles in 1969 was the result of a collaboration with Professor Rodney Porter FRs, who in 1972 shared the Nobel Prize in Physiology or Medicine for studies on immunoglobulins, and George Fleet. Lysine derivatized with the photoactive reagent 2-nitro-4-azidophenyl (NAP) was used to elicit the production of polyclonal antibodies. Radiolabelled NAP-lysine was then bound to the purified antibodies and photolysed. After cleavage of the antibodies into smaller fragments, it was found that most of the labelling was in a region of the heavy chain close to the hypervariable region (7, 10). This result helped to confirm that one of the hypervariable regions was responsible for antibody specificity. Knowles went on to develop photoaffinity reagents for enzymes and for membrane proteins (9, 11, 22), in the process doing much to establish his reputation.

Although essentially all of Knowles’s efforts were already devoted towards the understanding of enzyme mechanisms, his research programme was greatly helped in the early 1970s by the funds from and collaboration within the Oxford Enzyme Group, which he was instrumental in initiating. The group was formed through a policy change in the funding of chemical research by the Research Councils. Sir Ewart Jones and Sir Ronald Nyholm FRs had pleaded with the Research Councils for exceptional additional funding for chemistry, which they maintained had inadequate support. Their wishes had been granted but on condition that there was a problem of sufficient magnitude to be solved, a problem moreover that needed, as it was necessary to claim, a well-funded large group of research workers. Jones consulted with Knowles, who then discussed the possibility of a large joint effort with R. J. P. Williams, his colleague in Wadham College, who also had a deep interest in enzymes. They succeeded in bringing together a large company of like-minded chemists and biochemists to form the Enzyme Group, which was successful in many detailed protein studies for some 20 years (and in obtaining many large grants).

It was within the group that Knowles’s distinguished work on several enzymes began. Two problems in particular occupied his interest: the mechanism of the glycolytic enzyme triosephosphate isomerase (affectionately known by the Knowles group as TIM) (scheme 1) and the general manner of enzyme-catalysed phospho group transfer.

His first publication on triosephosphate isomerase described the use of bromohydroxyacetone phosphate, a substrate mimic designed to react with the active-site base (9). After incubation of the enzyme with radiolabelled reagent, an active-site peptide was obtained, labelled on a tyrosine residue. Further work suggested that the neighbouring glutamate was the active-site base in the enzyme, with transfer to tyrosine occurring in a second step (12). Subsequent X-ray crystallographic studies by Professor D. C. (later Lord) Phillips FRs fully confirmed this conclusion while providing additional structural insights (Phillips et al. 1977). Knowles continued the study of triosephosphate isomerase for many years after he left Oxford. As described below, of particular note was his work in collaboration with John Albery

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Scheme 1. Triosephosphate isomerase effects catalysis by means of a cis-enediol intermediate. A single base in the enzyme mediates the proton transfer and the pro-R-hydrogen of the starting material is removed. (Reprinted, with permission, from Hansen (1995). Copyright © 1995 Elsevier.)
(FRS 1985), another pupil of R. P. Bell’s, to analyse the free-energy profile of all the steps of the reaction catalysed by this enzyme.

The second problem that had intrigued Knowles before he left Oxford was that of enzyme-catalysed phospho group transfer. The questions posed were twofold: first, does each transfer step involve retention or inversion of stereochemical configuration at phosphorus; and second, does phospho group transfer proceed directly between substrates or involve a covalent phospho-enzyme intermediate? Before he could pursue these topics in depth, Knowles had left Oxford, and we interrupt this description of his research with an account of this relocation.

**GOING TO HARVARD**

In 1969 and 1971 Knowles came to America to be a visiting professor at Yale in the Departments of Molecular Biophysics and Chemistry (during his 1969 sabbatical he spent ‘eight blissful months’ working in the laboratory). On his next sabbatical in 1973, as the Sloan Visiting Professor at Harvard, he taught a graduate course that was warmly received, and in the following year he resigned his position at Oxford for a permanent post at Harvard. His first position was as a professor of chemistry but later, in 1979, he was appointed Amory Houghton Professor of Chemistry and Biochemistry. Why did Knowles leave Oxford, where he and his family were well settled and where he had built a very fine reputation as an outstanding tutorial teacher and lecturer (figure 1)? He was also well on his way towards becoming an international figure in enzymology. There was the challenge and excitement of a new environment to be sure, but staying in Oxford also had disadvantages resulting from constraints.
on academic positions. For example, it was very difficult for Oxford to promote a tutorial Fellow/University Lecturer to an independent professorship except as Head of a department. The opportunities for dedicated research were therefore somewhat limited by duties within colleges and departments. After Knowles left for Harvard, the University of Oxford made several attempts to attract him to posts either as an independent professor or as a Head of a college, but by that time Knowles and his family had established themselves firmly at Harvard and in America.

At Harvard Knowles turned out to be everything they expected of him. He was an excellent teacher and his two-semester course on the nuances of enzymology educated many students. More generally, as when he was at Oxford, he was sometimes described as the perfect lecturer for his meticulous preparation, his communication skills and his sense of theatre (Cornish-Bowden 2008). He treated research by his graduates and postdoctoral students in fair part as a continuation of their intellectual training and not just as an enquiry in depth on a specific topic. As a result several of them have taken up academic posts in many parts of the world. He was as proud of his pupils and their successes as he was of his own research.

**TRIOSEPHOSPHATE ISOMERASE**

At Harvard, Knowles’s research programme also blossomed. He began a long and detailed study with John Albery of the free-energy profiles of enzymes. Albery was stronger on kinetic theory and mathematical derivations, whereas Knowles was now expert in and had considerable practical experience with enzyme function. Knowles was also quick to see both the implications of their work and ways in which to test the veracity of their conclusions experimentally. They were an ideal complementary pair. Much of their work concerned the free-energy profile for triosephosphate isomerase. In essence what they showed was that the energetics of the enzyme ground state and transition state complexes is such that the overall rate of the catalysed reaction is maximized (figure 2).

The experimental details underlying this result were published in eight successive papers in *Biochemistry* in 1976 (14–21). The enzyme proved ideal for such an analysis, as the substrate
and product were close enough in free energy to allow both the forward and backward reactions to be thoroughly studied. Four kinds of experiment were performed (23): (i) specifically tritiated or deuterated substrate was used, and the amounts of label retained in the product and lost to solvent water were determined; (ii) unlabelled substrate was allowed to react in tritiated solvent, and the label present in reisolated substrate and in product was measured; (iii) the initial steady-state kinetic isotope effects with deuterated substrate were studied; and (iv) most simply, the steady-state rates for unlabelled substrates in unlabelled solvent were examined.

To quantify the effectiveness of a particular enzyme in a metabolic pathway, Albery and Knowles defined an ‘efficiency function’ ($E_f$). For an enzyme fully optimized by evolution, the efficiency function has a value of 1.0. Triosephosphate isomerase was found to have an efficiency of 0.6, indicating that it is close to a perfect enzyme. To quote Albery and Knowles (21):

> For triosephosphate isomerase, we have shown that the catalyzed reaction has a value of $E_f$ near to unity; that is, this enzyme is as efficient as it can be for a system free in solution. Qualitatively, it is evident that, since all the intermediates are of higher free energy than that of the state for [enzyme + predominant substrate], and since the highest free energy barrier is that representing the binding of the less stable substrate to the enzyme, there is no catalytic advantage to be gained by further adjustment of the free-energy levels of the intermediates, or of those transition states that do not relate to diffusion processes.

In contrast, acetate ion, a simple general base, catalyses the same reaction with an efficiency of only $2.5 \times 10^{-11}$ (21).

Albery and Knowles listed three factors that contribute additively to the efficiency of enzyme-catalysed reactions: (i) the enzyme binds the ground and transition states equally well, a feature termed ‘uniform binding’; (ii) the enzyme discriminates between intermediates, binding each with a distinct affinity so that all can be transformed at an equal rate (‘differential binding’); and (iii) the energies of the transition states are lowered relative to those of the flanking intermediates (‘catalysis of an elementary step’). Enzymes that function in vivo far from equilibrium between reactants and products were subsequently shown not to be adequately described by the original efficiency function, a limitation that Albery and Knowles fully addressed in 1989 (41). Nonetheless, it is safe to conclude that their conceptual insights into the thermodynamic underpinnings of enzyme efficiency will stand the test of time.

After the appearance of the landmark Biochemistry papers, the Knowles group turned to a series of mutagenesis experiments that helped to further characterize the catalytic workings of triosephosphate isomerase. These studies revealed, not surprisingly, that it is rather easy to decrease the activity of an almost perfect enzyme and exceedingly difficult to increase it (44).

An interesting separate point is that triosephosphate isomerase is an eight-stranded β-barrel. This barrel structure is quite rigid, and mutations that leave its hydrogen-bonding network intact have no influence on the rate. By way of contrast, the loop from the barrel that contains the active-site residues is mobile and changes its structure on binding the substrate (45, 46). Although the rate of this transition is fast in triosephosphate isomerase, it is likely to be at least partly rate determining. The energetics of a relatively immobile protein bearing a mobile loop and bound substrate can impose unusual structural and electronic properties on individual amino acids in the active site, thereby influencing their reactivity in this and other enzymes. The thorough analysis of free-energy profiles performed by Albery and Knowles revealed features of enzyme catalysis that are not open to inspection by structure studies alone and suggest a need for further studies to elucidate the factors controlling the energetics of each step.
Jeremy Randall Knowles

While studying the mechanism of triosephosphate isomerase over some 25 years beginning with his Oxford days in 1970 and concluding with his group’s last publication on the enzyme in 1995, Knowles was stimulated to look in depth at the free-energy profile of another enzyme, proline racemase, in collaboration with Albery (34–40). This enzyme, which is far from perfect, employs a two-base mechanism using cysteine residues as proton-transfer centres (figure 3).

For this enzyme, the kinetics was studied under reversible conditions—the approach to equilibrium was monitored polarimetrically—rather than, as is typical, under irreversible conditions, and an intriguing feature was uncovered. Although saturation kinetics is typically interpreted as arising from the rate-determining conversion of enzyme–substrate complex to product (‘bound state saturated’), Albery and Knowles emphasized that such kinetics can also be limited by the rate-determining interconversion of the substrate-binding and product-binding forms of the free enzyme (‘free state saturated’). For proline racemase the former regime holds at low substrate concentration, whereas the latter pertains at high substrate concentration.

**PROLINE RACEMASE**

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**BETA-LACTAMASE**

Knowles also spent time during these years studying related enzymes to make comparisons with triosephosphate isomerase and proline racemase (29–31, 47–49), but two other research projects focused on quite different objectives. The first we note here is inhibitors of β-lactamase, which were examined to elucidate their modes of action (33). Although two different classes of inhibitor were known in 1976, for neither was the detailed mechanism of their interaction with β-lactamase understood. Knowles pointed out that one group, typified by clavulanic acid and penicillanic acid sulphone, contains a heteroatom at C5 of the bicyclic ring system of the parent penicillin, whereas the second class, as exemplified by the carbapenems, does not. Those in the first group were shown to function as ‘suicide inhibitors’ of the enzyme. After formation of the acyl-enzyme intermediate (a process exactly analogous to the first cata-
Figure 4. Interaction of penicillanic acid sulphone with \( \beta \)-lactamase. (Reprinted, with permission, from (33). Copyright © 1985 American Chemical Society.)

Figure 5. Interaction of carbapenem (MM13902) with \( \beta \)-lactamase. (Reprinted, with permission, from (33). Copyright © 1985 American Chemical Society.)
lytic step with penicillin itself), this intermediate can partition along three possible paths. The mechanistic details are shown in figure 4.

B is the initially formed acyl intermediate, and C, D and E are the three products that can then result, complex E being the permanently blocked enzyme. The discovery of this pathway was in large part due to the skilful use of hydrogen isotopes, which, as we have seen, was a notable feature of many of Knowles’s mechanistic studies.

The second class of inhibitors, the carbapenems, work in a different manner. The overall mechanism of inhibition, shown in figure 5, was published in 1982.

In this case the acyl intermediate G can either undergo simple hydrolysis leading to H, or tautomerize to the covalently bound complex J, which only very slowly deacylates to give the free enzyme. These inhibitors therefore do not cause the enzyme to commit ‘suicide’ (by forming an irreversibly blocked complex) but rather act as agents that are only slowly cleaved from the enzyme. An important point is that the above mechanisms were deduced solely from kinetic data and without knowledge of the structure of β-lactamase, which became available only in 1993 (Jelsch et al. 1993). Interestingly, the kinetic data obtained by the Knowles group did not always explain the dose levels of inhibitors needed in vivo—other factors, such as the ability of an inhibitor to cross the cell membrane, can also be important (32).

PHOSPHO GROUP TRANSFER

We now turn to the second major triumph in Knowles’s career, taking the first to be his success with Alb ery in illustrating the nearly perfect nature of catalysis by triosephosphate isomerase. This was the in-depth study of phospho group transfer. In the Oxford Enzyme Group, several different members used structural approaches to study enzymes employing phosphorylated substrates, whereas Knowles and Gordon Lowe (FRS 1984) were each separately examining the kinetics of phospho group transfer. In work published in 1975 (13) Knowles initially studied the enzyme phosphoglycerate kinase with the desire to discover whether the mechanism involved an intermediate phosphorylated enzyme or direct transfer between the substrates adenosine triphosphate (ATP) and phosphoglycerate. In a careful analysis Knowles came down against any presumption of a phosphorylated enzyme intermediate, but this early work did not reveal the exact path of transfer between the bound substrates.

Shortly thereafter, however, Knowles developed an elegant method to examine the mechanism of phospho group transfer directly: the use of isotopically labelled, chiral $^{[16}O,^{17}O,^{18}O$]phosphate monoesters. This method allows the stereochemical course of transfer to be determined unequivocally—that is, whether a reaction goes with inversion, retention or racemization at phosphorus. (Chiral phosphorothioates, in which $^{16}O$, $^{18}O$ and sulphur are used to create the chiral centre, had been employed previously by the group (24), but the replacement of one of the oxygen atoms in the phospho group by sulphur can lead to ambiguities.)

Knowles began by synthesizing 1-[(R)-$^{16}O,^{17}O,^{18}O]$phospho-(S)-propane-1,2-diol, which was shown to be enantiomerically pure by a demanding stereochemical analysis that involved metastable mass spectrometry (25). Next the stereochemical course of transphosphorylation from phenyl[(R)-$^{16}O,^{17}O,^{18}O$]phosphate to (S)-propane-1,2-diol as catalysed by alkaline phosphatase was analysed (26). The result was retention of configuration, consistent with the formation of a phospho-enzyme intermediate. Although the stereochemical course of each elementary step was not definitively established by this result, by 1980 Knowles was able to
argue convincingly that every enzyme-catalysed transfer of a phospho group proceeds by an in-line mechanism with concomitant inversion of configuration (figure 6) (27).

The subsequent use of $^{31}$P-nmr spectroscopy to determine the absolute configuration of chiral phosphate groups greatly simplified the stereochemical analysis (28) and facilitated the study of additional kinases, mutases and phosphatases. (Conceptually the $^{31}$P-nmr analysis, like the earlier metastable mass spectrometric method, relies on the conversion of a chiral phospho group into diastereomeric species that have different isotopic distributions depending on the initial configuration—($R$) or ($S$)—at phosphorus.) All in all, Knowles published some 30 papers on enzyme-catalysed phospho group transfer and showed that the in-line mechanism is general. We note that Lowe, his Oxford colleague, reached a similar conclusion at about the same time.

THE SHIKIMIC ACID PATHWAY

As a last example of Knowles’s work on enzymes, we turn to his studies of the shikimic acid pathway, through which the biosynthesis of the aromatic amino acids phenylalanine, tyrosine and tryptophan commences. This pathway is absent in animals; it is therefore an attractive target for antimicrobial and herbicidal agents—for example, the broad-based herbicide Roundup blocks the sixth step of the pathway. Knowles was particularly intrigued by two enzymes in the pathway: chorismate mutase and dehydroquinate synthase.

After much complex experimenting and analysis, the conclusion in the study of the mutase was that the enzyme probably functions by binding the substrate chorismate in a reactive conformation, such that it is poised to undergo a rapid Claisen rearrangement. Knowles thus referred to chorismate mutase as perhaps the simplest of all enzymes (43, 50). Dehydroquinate synthase proved to be a different type of puzzle. The mechanism seems to involve six steps, which in other systems require four separate classes of enzyme. Investigation by the Knowles group, however, showed that only two of the steps are actually catalysed by the enzyme, which in fact acts much like a ‘banal dehydrogenase’ (42). Knowles’s work on these two systems revealed an important principle: enzymes are economical in their function, catalysing only those chemical steps that require catalysis.

Before moving to a description of Knowles’s service in a quite different capacity, we summarize our impression of him as an organic biochemist. His experimental approach was invariably well designed in both choice of method and enzyme target. His analysis of the results was intellectually scrupulous, and he drew conclusions in which he discussed possible difficulties. One publication then followed another to remove ambiguity. As a consequence he was able to
Jeremy Randall Knowles

analyse in great detail the mechanisms and the energetics of enzymes. An outstanding example of the former was the work on phospho group transfer. The latter was exemplified by his work with Albery on triosephosphate isomerase and proline racemase, which led to insights into perfection in enzyme catalysis and enzyme kinetics under reversible conditions, respectively.

DEAN OF THE FACULTY OF ARTS AND SCIENCES

A professor of chemistry at Harvard is expected to take his turn as Chair of the department, which is an administrative post demanding skill in the management of professors, usually of great distinction but of very independent determination. Knowles managed these duties (1980–83) so well that he impressed many colleagues outside the Chemistry Department and especially members of the university’s administration. To his admitted surprise, he was offered the post of Dean of the Faculty of Arts and Sciences by President Bok in 1983. He declared that at that time he was not ready to forgo his biochemical research. However, on being asked a second time—in 1991—he accepted this important administrative task, to the dismay of many of his science colleagues. Undoubtedly Knowles himself had many misgivings.

Before describing his very successful period in office from 1991 to 2002, it is worth noting that it was not just his clear ability as an administrator that was so noticeable at Harvard. He had a polished charm and a genuine admiration for a wide range of academic disciplines, teaching styles and research programmes. He helped to create a series of concerts at lunchtime, he supported the arts generally at Harvard and he even took to the stage himself once or twice. In many ways he was not typical of an American administrator.

There is a further side to the factors that influenced Knowles’s change of mind. We both talked with him occasionally between 1985 and 1991 and sensed that he felt he had done much of what he could do in enzyme chemistry. The remaining problems within his reach, uncovering the precise mechanisms and energetics of even more enzymes, he referred to as puzzle-solving. He knew that he was good, indeed very good, at solving such puzzles, but he also knew that true advances in the field would require the tools of a new generation of biochemists. The magnitude of the scientific challenge for him was less than it had been, and he loved a challenge.

The job of Dean of the Faculty of Arts and Sciences represented a genuinely big challenge, because all was not what it should have been in Harvard. Knowles threw himself into his new position and knowingly dropped his research entirely. He published very few papers after 1991.

The Dean of the Harvard Faculty has many tasks, but for Knowles two immediate areas stood out, and neither concerned chemistry or even science directly. They were that the humanities faculty was extremely dispersed and its departments were virtually isolated from one another, and that the finances of Arts and Sciences were in a poor state, running at an annual deficit of $12 million—a situation that clearly was unsustainable. The fact that Knowles saw the first problem so clearly is a reflection of that side of his interests, mentioned before, in music and the arts. He combined this with what all at Harvard recognized: a natural charm and a persuasive style. Anyone reading his Dean’s Yearly Reports cannot fail to see his wish to avoid confrontation while still making clear statements. He set out to see that the humanities faculty had central facilities that all could use. The renovations were quickly completed: the Barker Center, which drew 12 humanities departments together, and Boylston Hall, which housed Romance and other languages.
His other immediate concern was the heavy budget deficit. His approach was to engage different campus constituencies, including all the full professors, and while discussing the financial situation to urge on them the need to make savings. He deliberately avoided Finance Committee discussions and promised that, unlike in many another US university in the early 1990s, there need be no staff reductions. Within a few years Harvard’s deficit was reduced to $1 million per annum. At the same time a fund-raising campaign was launched, which by 2000 had raised $1.1 billion for the Faculty of Arts and Sciences.

Only after addressing the above issues did Knowles turn to the sciences. He met with groups of colleagues to plan investment in areas, often across disciplines, that held the greatest promise for discovery and application, such as genomics, imaging, mesoscale structures, computation, neuroscience and evolution. By 2000 many of these projected areas of cooperation had become a reality.

Under his deanship there were improvements in support for undergraduates and encouragement to study foreign languages—in 2000, three-quarters of Harvard students took a foreign language course. As far as appointments were concerned, he refused to enter into ‘Star Wars’ bidding for top academics, but this view hardly affected recruitment adversely and almost no faculty members left the university.

**Recognition**

It remains for us to record that his ability was recognized by many awards. His quality as Dean of the Faculty of Arts and Sciences was recognized internally by his being awarded the Harvard Medal in 2002 and by his being named a Harvard Distinguished Service Professor in 2003. However, there is no greater tribute to his contributions as Dean from 1991 to 2002 than the request by the university for him to return as Interim Dean in 2006. Perhaps unknown at that time was that Knowles was suffering poor health, and by the spring of 2007 he had to step down.

In the Harvard Faculty of Arts and Sciences Memorial Minute in May 2008, Neil L. Rudenstein, under whom Knowles had served as Dean, wrote:

> 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. Many other things mattered of course. But if learning, teaching, and research were not the heart of the matter, why were we here? Once he had decided to leave his lab and serve the University in more than chemistry, nothing less than all his energy and stamina would do. He was no less a friend. If there was a need for more than mere intelligence or skill, he was there, with his strength and his commitment.

Knowles was honoured as a scientist on both sides of the Atlantic. He was a Fellow of the Royal Society, a Fellow of the American Academy of Arts and Sciences, a Fellow of the American Philosophical Society, and a Foreign Associate of the National Academy of Sciences. His awards for chemistry/biochemistry included the Charmian Medal, the Bader Award, the Repligen Award, the Prelog Medal, the Robert Welch Award, the Nakanishi Prize and the Royal Society’s Davy Medal. In 2008 the Royal Society of Chemistry established the Jeremy Knowles Award ‘to recognize and promote the importance of inter- and multi-disciplinary research between chemistry and the life sciences’. Knowles was an Honorary Fellow
of Wadham College and Balliol College, Oxford, and a recipient of honorary degrees from the University of Edinburgh and the Eidgenössische Technische Hochschule in Zurich. He was appointed Commander of the Order of the British Empire in the Honours List of 1993. Among outside advisory roles he was on the Boards of the Howard Hughes Medical Institute, as a trustee, of Biogen, Inc., Celgene Corporation, Vertex Pharmaceuticals and Corning Inc.

Throughout his adult life Jeremy was happily married to his wife, Jane. She was an archivist at Harvard for many years and friend to generations of Knowles group members. Jeremy was blessed with not only a wonderful wife but also with three sons, Sebastian, Julius and Timothy, and there are now seven grandchildren.

ACKNOWLEDGEMENTS

We wish to thank Jane Knowles for help with archival material from Harvard. Details of Knowles’s work as Dean are to be found in Harvard University Gazette from 1992 to 2008. We are also grateful to Joel G. Belasco and Ronald T. Raines for their many helpful comments on the manuscript. A full description of Knowles’s research accomplishments has been published by one of us (Hansen 1995). Appreciations of his life are to be found in the booklet of the proceedings of his memorial service entitled Your Dean, Faculty of Arts and Sciences 09-011 (Alumni Affairs and Development Communications, Harvard College, 2008).

The frontispiece photograph was taken in April 2004 by Professor M. L. H. Green FRS at Harvard University and is reproduced with permission. The online version is in colour.

REFERENCES TO OTHER AUTHORS


BIBLIOGRAPHY

The following publications are those referred to directly in the text. A full bibliography is available as electronic supplementary material at http://dx.doi.org/10.1098/rsbm.2009.0022 or via http://rsbm.royalsocietypublishing.org.

Biographical Memoirs


(20) 1986 (With B. G. Saver) Ribulose-1,5-bisphosphate carboxylase: enzyme-catalyzed appearance of solvent tritium at carbon 3 of ribulose 1,5-bisphosphate reisolated after partial reaction. Biochemistry 21, 5398–5403.

(21) 1987 (With J. M. Sue) Ribulose-1,5-bisphosphate carboxylase: fate of the tritium label in [3-3H]ribulose 1,5-bisphosphates during the enzyme-catalyzed reaction. Biochemistry 21, 5404–5410.


(44) 1991 To build an enzyme…. *Phil. Trans. R. Soc. Lond.* B **332**, 115–121.


