Jeremy Knowles

From research contributions in understanding the molecular details of enzyme catalysis to involvement in education and university administration, Jeremy Knowles offers a broad perspective on chemistry and chemical biology.

"In intellectual terms, scientists tend not to grow old as gracefully as humanists," notes Jeremy Knowles. In his case, it is obvious that nothing could be further from the truth. Although at 70 he is no longer running an active research laboratory, he insightfully and eloquently discusses current trends in chemical research and education.

Starting with his graduate work in physical organic chemistry, Knowles was fascinated by chemical reactivity, trying to understand "why some reactions went ten times as fast as others." During his postdoctoral research at Caltech he was exposed to biological catalysis at a seminar on α-chymotrypsin, an enzyme that accelerates the reaction it catalyzes by six orders of magnitude or more. He was immediately taken with the important and interesting problems of biology, and he remembers thinking, "Here I am, struggling—and failing—to understand a factor of 10. Would it not perhaps be more important to fail to understand something big than to fail to understand something small?"

From this epiphany, he began a research career as an enzymologist, first at Oxford University and then in the chemistry department at Harvard, which resulted in pioneering contributions to the current understanding of enzyme catalysis. Among the many important advances from his laboratory were the first full free energy profile of an enzyme-catalyzed reaction, the concept of 'perfection' in enzyme catalysis and an investigation of the stereochemistry of phosphoryl transfer. From these foundations, Knowles went on to tinker with nature through the 'directed evolution' of enzymes.

Research at the interface of chemistry and biology was not yet widespread in the 1970s and 80s, and Jeremy Knowles was certainly one of the leaders in mixing these disciplines. Despite this nontraditional blend, the chemistry department at Harvard was entirely welcoming to him. Indeed, Robert Burns Woodward, a colleague at Harvard, said to him, "Jeremy, if it's interesting, it's chemistry." Building on this openness, the Harvard chemistry department was one of the first to rename itself to include chemical biology. According to Knowles, faculty colleagues from across the traditional chemistry disciplines recognized that in many cases "what was going on experimentally was chemistry, but the problems were very often biological ones."

In 1991, after three decades as an enzymologist, he decided to pursue a different career and accepted the deanship of the Faculty of Arts and Sciences at Harvard. He wound down his research efforts "to avoid doing two things, both of them badly," and spent 11 years focusing on the challenges of running an organization with over 600 faculty members, 10,000 students and an annual budget of $500 million.

This hiatus from science gave him the unusual chance to rediscover biological chemistry with fresh eyes. He was surprised to find that some fields had barely progressed in a decade. In those fields, "people were still tilting with inadequate lances at the same old windmills." However, in other areas he expresses surprise that "things that in 1991 seemed impossible, in 2002 were done," including the vastly improved understanding of biological machines, the atomic-level description of the ribosome and single-molecule biochemistry.

He notes that science often alternates between periods of "cartography," or mapping what is there, and periods of analyzing these data to generate new concepts and understanding. Knowles describes the two types of scientists involved by reference to the well-known metaphor from the Greek poet Archilochus. The fox "runs over the intellectual landscape and covers an enormous amount of ground, basically on the surface," whereas the hedgehog "is much slower, burrows away, is probably more prickly, and is concerned with a deeper understanding of a smaller area of the landscape." As a self-described hedgehog, Knowles feels lucky to have worked during a time when advances in protein structure determination were allowing a much richer understanding at the molecular level of the reasons enzymes are so formidably effective. With the popularity of systems approaches, many parts of biology seem now to be in the cartographic phase. Showing his hedgehog quills, Knowles hopes that this will soon be followed by a period in which the "biological acronymic soup is reduced, and we can begin to distill out some of the principles of biological organization."

In addition to his contributions in research, Knowles has a long-standing interest in chemical education and is now teaching a class on antibiotics. What he did not expect was the difficulty of discussing even simple chemical molecules, such as penicillin, with first-semester freshmen. Although the field of chemistry continues to evolve, Knowles is "quite depressed by how little high school chemistry syllabi have changed in 30 years." At the college level, the challenge of chemistry education becomes even more difficult. In Knowles's view, "we add on the top everything that is exciting and new, and we don't think nearly hard enough about what we should be cutting out from the bottom." Arriving at the best chemistry curriculum requires, in his opinion, a careful and regular assessment both of what should and should not be taught.

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As dean, Knowles noticed some disturbing trends in graduate education and in the early career stages of scientists. The average length of time to obtain a science PhD in the United States is now more than 6 years, and the degree is often followed by lengthy postdoctoral work, particularly for students in the life sciences. He feels strongly that "scientists should be liberated much sooner to go out into the world, be independent in their research, be fueled by their own creativity, and make their own mistakes." He also feels there is a danger to a training system that fails to free students soon enough. Similarly, he says that the increase in the average age of RO1 grantees is "shameful, absolutely shocking." Our granting system, he believes, should be more supportive and generous at the very beginning; it should "fund the truly creative young minds."

Although he spends time on teaching and on continued involvement in university planning, Knowles chose not to restart an active research group after his time as dean. He had become "interested in too many things," and now he has the time to pursue a variety of topics. For instance, in shaping a new course on his long-standing interest in chirality, he has become fascinated with the evolutionary and biological questions of human handedness. Perhaps the hedgehog is now turning into a fox?

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