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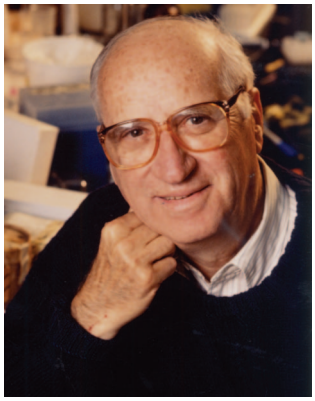
In FOCUS

Daniel E. Koshland, Jr. (1920–2007)

Robert Tjian*

Howard Hughes Investigator and Professor of Biochemistry & Molecular Biology, University of California, Berkeley, California



Daniel E. Koshland, Jr. circa 1991. Image courtesy of Robert Holmgren.

***Corresponding author, jmlim@berkeley.edu.**

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Dan Koshland and the University of California had a mutual love affair. As an undergraduate in the late 1930s, Dan developed a keen interest in chemistry, which he took with him during the war years to Chicago and the Manhattan Project. In 1965, after further training in organic and biochemistry at the University of Chicago and Harvard and an independent research position at Brookhaven, Dan was lured back to Berkeley by the great biochemist/microbiologist Horace (Nook) Barker. According to legend, Dan polled his wife Marion (Bunny) and the five children about a move from New York, and despite firm opposition, he reportedly claimed unanimous support. Bunny relented, knowing that Dan would forever be beholden to her for agreeing.

Dan's work on enzyme catalysis and his initial formulation of the induced fit mechanism came from his first independent research at Brookhaven. This insight morphed into broad disciplines of biology and biochemistry in the succeeding decades of his work and in the efforts of his disciples. We now know that the concept of "induced fit" explains more than just substrate specificity during enzyme catalysis. The notion that proteins are flexible and conform like a "glove around a hand" to ligand–protein interactions applies more widely than Dan could have imagined. For example, it is now clear that receptor-mediated signal transduction cascades require multiple protein conformational changes induced by both small-molecule or -peptide ligands as well as protein–protein interactions. In transcriptional regulation and chromatin function, dramatic induction of protein conformational alterations in large multisubunit complexes *via* activator–DNA interactions as well as activator–coactivator transactions represents the norm rather than the exception. In enzyme catalysis, Dan recognized negative cooperativity and half-of-the-site reactivity as a prominent theme that was not widely appreciated until much later. In formulating these molecular mechanisms, Dan relied on a rigorous training in mathematics that fed a passion for quantitative reasoning and informed his subsequent work in bacterial behavior. He took great pleasure in the application of computation to his work, knowing full well the path was strewn with casualties.

In 60-plus years as a scientist in New York and at U.C. Berkeley, Dan published over 350 papers of which more than 80 were in the *Journal of Biological Chemistry*. Three of his most important papers dealt with three distinct research areas that included mechanisms of enzyme catalysis and allostery, bacterial chemotaxis, and receptor signal amplification. More so than most even highly accomplished scientists, Dan was fearless in pursuing his nose into new areas of biology. He challenged all around him to look for the new, and he did so with a sense of delight in discovery.

And he never lost his sense of mischievousness, particularly when it came to relations between Cal and Stanford University. As our cross-town rival, Stanford was the root of all evil. No opportunity was missed to disparage anything about Stanford and Stanford graduates. On one memorable occasion, Dan fell ill at an *Annual Reviews* re-

ception near the Stanford campus and was rushed to the hospital ER, where he was admitted for observation. Fortunately, after the danger passed, Sam Gubins, the Editor of *Annual Reviews*, returned from the hospital to report that Dan was in fine form but complained that those bastards at Stanford took a sample of his blood!

Given Dan's background in chemistry as a student of Latimer, Seaborg, and Westheimer, it was natural that he served to bridge the life science and chemistry departments at Berkeley and in so doing influenced a generation of leaders such as Pete Schultz, Alex Pines, Carolyn Bertozzi, and many others. Dan used chemistry and quantitative analysis to great advantage in his work on receptor/ligand signal amplification and bacterial chemotaxis. In an era of increasing emphasis on nucleic acids, Dan emphasized understanding molecular mechanisms through functional and structural analyses of proteins. However, like any progressive biochemist of the 21st century, Dan was not reluctant to apply the tools of molecular genetics and genomics as they developed.

His work in bacterial chemotaxis blended the best of Dan's skills. He and his students developed techniques to track bacteria swimming in gradients of attractants and repellents and discovered that bacteria sense a change in concentration over time, not in space. Julius Adler, who pioneered the genetic analysis of bacterial chemotaxis and discovered the role of protein methylation in modulating response, stimulated Dan to apply his chemical knowledge to examine the role of protein covalent modification in biological regulation. In 1981, Goldbeter and Koshland published a pioneering study on amplified sensitivity of biochemical responses controlled by protein phosphorylation and dephosphorylation. This idea and subsequent work on zero-order ultrasensitivity by LaPorte and Koshland have informed our understanding of complex pathways from cell cycle control to development.

Dan also early on recognized the power of 3D structural analysis and embraced X-ray crystallography and other structural methodologies. Indeed, I was one of the early beneficiaries of his keen interest in structural biology when in 1971, just after I graduated from Cal, Dan and Bunny offered to sponsor me for a year of research at Oxford during their sabbatical in England. There, I worked with Sir David Phillips and was tutored by Louise Johnson on X-ray crystallography and structural analysis of lysozyme. During that wonderful year (1971–1972) in Oxford with Dan, I had the opportunity to work alongside Greg Petsko, Ian Wilson, and others, learning as much protein crystallography as possible. To this day, I have not figured out why I was so lucky to have been singled out by Dan among his many talented students to be so privileged, but I suspect that many of Dan's other former students and postdocs share this sense of family.

Later when I returned to California (1978) as a faculty member, my student/mentor relationship with Dan blossomed, and for the next 29 years until Dan's sudden death in July of 2007, we continued a most rewarding scientific father/son relationship. My frequent lunch discussions with Dan covered not only how to do science but everything from editorial management of journals, local and international politics, Cal sports, finance strategies, raising children, and an endless stream of hilarious jokes and anecdotes. Typical of his joie de vivre, he would say, "Tij, you should always have dessert first—life is uncertain." I also became close to several other members of the Koshland family, in particular Bunny, who shared with me an interest in gene regulation. It was a terrible blow to Dan when Bunny died in 1997. But as fate would have it, Dan reunited with Yvonne, a wonderful lady he had dated during his college years at Cal. Yvonne and Dan had 7 great years together, so I also got to know Yvonne. Through various points of contact and shared interests, I became friends with Dan's artist daughter Phlyp and molecular geneticist son Doug, two of Dan's five children.

Dan was more than a great scientist; he was a mensch who took responsibility selflessly and seemingly effortlessly. As Chair of Biochemistry (1973–1978) and later as Chair of the Chancellor's Advisory Counsel on Biology, he oversaw a series of key hires, including those of Randy Schekman and Gerry Rubin. Around 1980, Dan and Bunny realized that without a dramatic change in Berkeley's departmental structure, the university could not maintain excellence in research and teaching or stay competitive with our peer institutions. Thus Dan, together with a handful of faculty and endorsements from the Chancellor and Provost, spearheaded an unprecedented and sweeping reorganization of the biological sciences at Berkeley. This massive, some thought impossible, task culminated with the elimination of about 12 traditional departments and the formation of 3 new realigned departments (Molecular and Cell Biology, Integrative Biology, and Plant Molecular Biology). As Dan said to me last year, he considered the reorganization of Berkeley biological sciences one of the most rewarding accomplishments of his career.

The continued success of Cal in recruiting top students and faculty today stands as testimony to Dan's vision. As part of this legacy, Cal recently completed a 280,000 ft^2 modern research facility (The QB3 Stanley Building for Quantitative Biology), and a second 200,000 ft^2 facility (The Li KaShing Center for Biomedical and Health Sciences) is just beginning construction. Both of these state-of-the-art facilities, along with many other research projects and programs, have been possible not only because of Dan's scientific vision but also directly as a consequence of his personal philanthropy. As a member of the Koshland–Haas–Goldman–Friedman–Hellman families, heirs to the

Levi Strauss clothing empire, Dan and other members of his extended family have a legacy in the Bay Area and especially at the University of California.

Dan's sense of service extended to the nation. As the campus life science reorganization loomed, Dan assumed the position of the Editor in Chief of *The Proceedings of the National Academy of Sciences*, quickly infusing the academy journal with fresh energy, good judgment, and aggressive recruitment of high-quality papers. In 1985, he took on the even more ambitious role of Editor of *Science* and there transformed a somewhat staid and stale journal into a more vibrant and edgy science magazine that still enjoys top ranking today. As Editor, Dan often had to make bold and risky decisions based on his intuition and experience about science and scientists, which sometimes required overriding less insightful reviewers. This is, of course, what Editors with wisdom and independent scientific judgment should do but is seldom practiced these days. In typical Koshland fashion, he not only brought fresh ideas, new people, and an eye for details to *Science*, but also introduced a novel section, humorous and witty editorials in the form of Dr. Noitall.

Through it all, Dan had two most enduring traits: wit and calm self-assurance. He had an uncanny ability to rescue a tense situation with humor and charm. Though he came from a privileged background, his tastes ran to the simple. He drove a beat-up car and dressed accordingly. When asked if he would attend a campus performance by Luciano Pavarotti, he quipped, "Which team did he play for?" Unlike many men of his level of accomplishment, Dan did not crave attention. He often said, "It is very difficult to get things done if you worry about credit or popularity." Those of us who followed his example learned to treat colleagues and associates (students, laboratory technicians, administrative assistants, *etc.*) with dignity, generosity, and respect. Dan's passing leaves a gap that will only slowly be filled with the passing of time and the certain knowledge that he enriched the lives and educational experience of numerous students and colleagues at Berkeley and elsewhere.