IN MEMORIAM

Remembering Daniel E. Koshland Jr. (1920–2007)

Daniel E. Koshland Jr. was remembered by his many students, postdoctoral fellows, colleagues, friends, and family in a memorial and symposium held on the University of California Berkeley campus on September 16, 2007, following his sudden death July 23. Dan was a remarkable presence in all these lives. He displayed that rare combination of intelligence, passion, skill, charm, and wit that made everyone admire him. Many former members remembered their time in the Koshland laboratory as the most dynamic and exciting of their careers.

Dan was born in New York City in 1920, and grew up in San Francisco following his father's move to become an executive with the Levi Strauss Company. He received his BS degree in chemistry from the University of California in 1941 and retained a love of the University for the rest of his life. After a stint working on the Manhattan Project, he completed his Ph.D. at the University of Chicago working with a young Frank Westheimer and, after a short postdoctoral stay at Harvard, began his independent career at the Brookhaven National Laboratory in 1951.

Dan used his chemical training and thinking to analyze how enzymes catalyze chemical reactions. During this early period he made a number of seminal contributions to our understanding. One of his most important ideas was the induced-fit hypothesis: the notion that enzymes change shape upon interaction with their substrates. Before induced fit, the prevailing model was the “lock

and key,” which Emil Fischer had proposed in the late nineteenth century. The induced-fit hypothesis was amply confirmed by thousands of atomic-resolution structures of proteins and protein–substrate complexes that became available only years after Dan made the proposal. More recently, modern nuclear magnetic resonance techniques have shown that structural fluctuations can occur even in the absence of interactions with substrates.

His notions of induced fit led to a model for cooperative binding of ligands to multi-subunit proteins that he proposed with George Nemethy and David Filmer. The KNF or sequential model proposed that the binding of substrates or other ligands to one subunit of an oligomeric protein causes a structural change that propagates to the contact surface between subunits. It is the interaction of substrate-bound subunit surfaces with substrate-free subunit surfaces that generates either positive or negative cooperativity depending on the relative energetics of those interactions. This model provided a way to understand negative cooperativity in ligand binding and half-of-the-sites reactivity that was not possible using the other important model for cooperativity, namely the concerted conformational change model proposed by Monod, Wyman, and Changeux.

Dan returned to his beloved University of California in 1965. It was an exciting time in Berkeley when I joined the Koshland lab as a postdoc in 1969. Allostery, cooperativity, catalytic, and regulatory mechanisms were in

the air. So were antiwar protest chants, helicopters, and tear gas. Dan had attracted a wonderful group of undergraduates (Bob Tjian), graduate students (Dan Storm, Jim Haber, Steve Mockrin, Bill Stallcup, Bob Bell), and postdocs (Alex Levitzki and Stan Parsons). Much of the lab was working on enzyme mechanisms and regulation, but Dan had started thinking about the biochemistry of sensory transduction. Together with Peter Lovely, we began working on bacterial chemotaxis and somewhat later, we were joined by Bob Macnab. In a wonderful set of experiments, Macnab and Koshland showed that bacteria sense temporal changes in the concentration of chemicals and have a memory of their chemical environment that is updated on a seconds or minutes timescale. We now understand that this memory and its updating are the result of reversible methylation of transmembrane chemotaxis receptors.

The Koshland lab went on to make many more contributions to our understanding of bacterial chemotaxis with a particular emphasis on the chemotaxis receptors. Many of the leaders in the field are former Koshland lab members; they include Jeff Stock, John Spudich, Bob Weis, Joe Falke, Barry Taylor, and Ann Stock.

Dan loved to discuss ideas—the bigger the better. These discussions were often intense but never became rancorous. Dan always knew when to lighten the atmosphere with a particularly appropriate quote, joke or one of his favorite one-liners. For example, if the argument reached a stalemate Dan would sometimes admit that he had been wrong—once in the second grade.

The Koshland lab also worked on a range of other problems, including protein kinase C, learning, time-resolved crystallography, and from time to time some of the classical problems in enzymology. Dan published over 600 manuscripts during his long career. He was just beginning a project on alternative energy sources at the time of his death.

From 1985–1995, Dan was the editor of *Science* magazine. He instituted a number of structural changes that modernized the journal and increased its importance and impact, particularly in the biomedical area. He would sometimes overrule the staff to accept controversial papers that he felt had new and important ideas to contribute. In part this was a reaction to the difficulties he had in publishing his ideas concerning induced fit in

the 1950s. In editorials he disguised as interviews with the infamous Dr. Noitall, he used humor and satire to illustrate his positions. Dr. Noitall was a self-proclaimed expert in all fields. The interviews always began with Dan citing a long list of Noitall's imagined accomplishments and Noitall's first response always the same:

"A vast understatement of my true worth."

In the 1980s Dan became concerned that the biological sciences at Berkeley were not keeping up with rapid advances in cloning and eukaryotic molecular biology. Worse, archrival Stanford seemed to be well ahead. Working with the administration and kindred faculty, Dan was the driving force behind a complete reorganization of the biological sciences at Berkeley. A dozen distinct departments were condensed into three. Many new faculty members were hired, and the biological community at Berkeley is now among the world's elite. All academics have to marvel at the skill and tenacity required to carry out institutional reorganization on this scale.

The Koshland family has a long history of active philanthropy and Dan continued this tradition. He was a significant benefactor to Haverford College, the Weizmann Institute, as well as the University of California. He helped to fund and design the Marian Koshland Science Museum of the National Academy of Sciences in Washington, DC.

Dan Koshland was recognized by a long list of awards. These include the National Medal of Science in 1990, the Albert Lasker Award in 1998, the Welch Award in Chemistry in 2006, and several honorary degrees. He was also a member of the National Academy of Sciences and the American Academy of Arts and Sciences.

Dan's partner through most of his scientific career was his wife, Marian, the distinguished immunologist who died in 1997. Dan is survived by their children, Douglas, Gail, Ellen, Phlyp, and James, and his second wife, Yvonne.

Daniel E. Koshland Jr. is remembered as a great family man, scientist, visionary, philanthropist, and friend. And to paraphrase the words of Dr. Noitall—a vast understatement of his true worth.

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