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### Induced Fit and Wit: Celebrating the Life of Daniel E. Koshland, Jr. (1920 - 2007)

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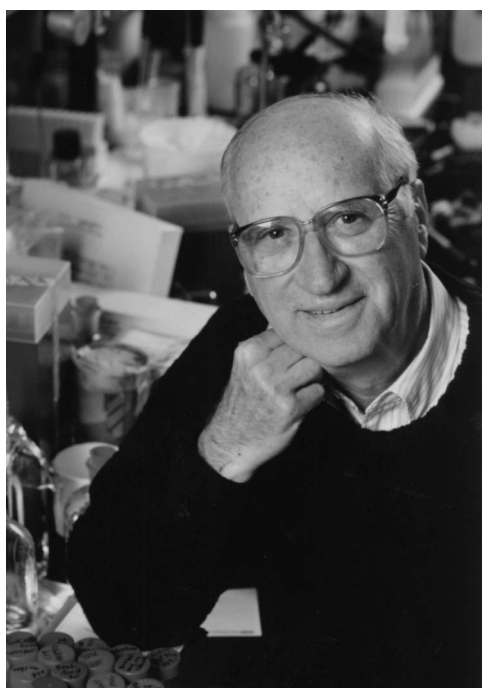
## Obituary

# Induced Fit and Wit: Celebrating the Life of Daniel E. Koshland, Jr. (1920–2007)

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The late Daniel E. Koshland, Jr. Dr. Koshland was a founding editor of *IUBMB Life* (The photograph was taken by permission from the University of California at Berkeley website: <http://www.berkeley.edu/news/media/download/>)

On a beautiful Sunday afternoon in September, scientists, friends, and family gathered in UC Berkeley's newly-opened Stanley Hall to celebrate the life of Daniel E. Koshland, Jr., Professor of Biochemistry at UC Berkeley, former editor of *Science*, and human being extraordinaire. There were hugs, laughter, and reunions of friends who had not seen each other

for decades. There was also sadness – for the loss of a friend and a giant. This seemingly disparate group of people had one common thread in the tapestry of their lives: they had all been touched by a visionary biochemist. An afternoon of science – a symposium called ‘Induced Fit: The Science and Wit of Daniel E. Koshland, Jr.’ – preceded a memorial. At the symposium, students whose careers had been launched by Koshland, colleagues who had been mentored and inspired by Koshland, and the two of his children who chose careers in science (Doug Koshland, Carnegie Institution and Gail Koshland, University of Arizona) presented research talks in which the enormous influence of Dan Koshland and his incomparable humor permeated the outstanding scientific presentations.

Koshland received a BSc in Chemistry from UC Berkeley in 1941. In 1949, the same year his wife, Marian (Bunny) Koshland earned her PhD in Immunology, he was awarded a PhD in inorganic chemistry, working with Wendell Latimer, from the University of Chicago. He joined the Manhattan Project, working with Glenn Seaborg in Chicago, and could have earned his reputation as an inorganic chemist. Instead, with the type of bold action that he repeated numerous times throughout his scientific career, he immersed himself in biochemistry. After two years of postdoctoral work at Harvard working in Fritz Lipmann's laboratory, he and his wife moved to Brookhaven, where they raised their five children. He was recruited back to UC Berkeley in 1958. As he liked to explain, he told Marian that if they moved to Berkeley he would be nice to her forever, but if they stayed in Brookhaven, she would need to be nice to him forever. They moved.

In 1958, in a symposium on amino acid activation, Koshland proposed a revolutionary theory that he coined ‘induced fit’ (see ‘Application of a theory of enzyme specificity to protein synthesis’ (*1*)). The title of the paper revealed nothing about the theory or its importance. Koshland suggested that ‘the substrate may cause an appreciable change in the three-dimensional relationship of the amino acids at the

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active site'. In contrast to the dogma at that time suggesting a precise fit, like a key to a lock, between an enzyme and its substrate, Koshland suggested that a fit 'occurs only after the changes [in the enzyme were] induced by the substrate itself'. This now textbook concept has been visualized by crystallography and proven correct over and over again for molecular recognition events from substrate/enzyme interactions, ligand/receptor interactions, and an abundance of other protein-protein and small molecule-protein interactions.

The stories on how Koshland began his interest in bacterial chemotaxis in the 1970s, an interest that he maintained for the rest of his life, are not in total agreement. In a detailed review in *Physiological Reviews*, entitled 'A Model Regulatory System: Bacterial Chemotaxis' (2) Koshland provided a number of reasons to study this model system, but perhaps the most compelling was his new interest in solving memory. He theorized that bacteria have a basic memory that allows them to compare past and present, and he was determined to unlock the mystery of how it worked. His work on bacterial receptors has served as a paradigm for mammalian signaling; it demonstrated, among many other things, how chemical modification can provide a means for a cell to 'remember' the experience of its environment – a gradient of nutrients, for example.

In the 1980s a very small part of his lab turned its attention to protein kinase C, 'the memory protein'. Daria Mochly-Rosen (postdoctoral fellow, 1983–1985) came to his lab to work on bacterial chemotaxis. After a few weeks of working with bacteria, she told Koshland that she would prefer to work on mammalian signaling. 'He did not miss a beat, turned to his bookcase and gave me an inch-thick file of copied papers', recounts Mochly-Rosen. 'He told me, "Why don't you crystallize this new enzyme? It's bound to be a key enzyme in regulation of memory".' The enzyme was protein kinase C, the year was 1983, and the reason Koshland was convinced that protein kinase C was involved in memory exemplifies the way Koshland thought: he had read that the enzyme is activated by the tumor promoting phorbol esters, a discovery that was then only a few months old. When painted on the skin, phorbol esters cause cancer but only after several repetitions of the treatment. Koshland was convinced that something in the skin must 'remember' the exposures to cause the transformation and because phorbol esters bind protein kinase C, protein kinase C was the *memory* enzyme. Koshland thought if it had memory to cause cancer, it could mediate cognitive memory too – reasoning typical of his daring leaps. 'I failed in the crystallography project (still unsolved 25 years later) but I learned from a great scientist how to dare', says Mochly-Rosen. 'He pushed us to think outside the box, to follow on wild guesses and hunches and not worry about sticking our neck out with a speculation – as long as we labeled it as a speculation. This advice guided me well throughout my career'. The second postdoctoral fellow charged with solving memory with protein kinase C was Alexandra Newton (1986–

1988). 'He stopped me in the hall after I had been in his lab for about a week and asked, "Have you solved memory yet?" My reply of "Yes, but I forgot the answer" triggered a reaction so typical of Koshland – a warm smile and a sparkle in his eyes driven by his delight at seeing humor in science and in life'.

Koshland was a giant in biochemistry, and while he is best known in textbooks for his paradigm-shifting concept of induced fit, there are countless other examples of how his work inspired scientific thinking decades later. For example, his finding on ultra sensitivity (3) was rediscovered as the basis for a key event in development more than 15 years later (4). Some of his discoveries have become such a staple of current biomedical research that most do not remember who made the original discovery. Notably, the now common practice of substituting a phosphorylated amino acid with an acidic amino acid was first published by Koshland (5). Similarly, the now common practice of creating chimeric receptors for structure function studies originated in the Koshland lab (6).

Koshland was selfless in his support of science and education. He was a founding editor of the flagship journal of the International Union of Biochemistry and Molecular Biology, *IUBMB Life*. He was also the Editor in Chief of *PNAS* (1980–1984) and the Editor in Chief of *Science* (1985–1995). At UC Berkeley, he was a mover and shaker – literally. Among many of his activities there, one of the most difficult was the administrative change he triggered in the departmental structure. He inspired, cajoled, convinced and persuaded the 16 biological sciences departments to unite into a large integrated department (with three sub disciplines). This was not a small feat. It was his conviction, political skills, and what he used to call his 'Pollyanna trait' (in addition to his ability to escape the turmoil by flying out to Washington to carry out his duty as the editor of *Science*) that enabled him to accomplish this monumental restructuring. The idea that both research effort and student education can be better in such an organization was proven to be correct and has been since modeled in many other universities.

As a mentor, Koshland was brilliant. He was generous with his time, he provided a challenging environment, and he was extraordinarily supportive. He launched the careers of hundreds of undergraduates, graduate students, and postdoctoral fellows. Saturday afternoon pizza provided by Koshland was one of many ways he connected personally with his lab, providing a venue for debate about everything from a strange result to football, from science policy to world politics – no topic was inappropriate. Both his family and people in the lab remember how Koshland would randomly pick a side and argue it until the other agreed just to turn around and argue in favor of the other side. During his 10-year tenure as editor of *Science*, he invariably tried out his editorials by the fictitious 'Dr. Noital' at Saturday pizza, regaling his students with his wit and insight. He also delighted in presenting everyone who left his lab with a limerick that captured both the essence of the student's project and the

essence of their personality in rhyme. His sense of humor, sharp mind and strong opinions came across in his editorials and in daily conversations with him.

Koshland said that, like his own father, he hoped to die while working – and he did. He died young at heart, fulfilling his wish that he would ‘die young as long as possible’. All who were fortunate to have their lives touched by him had their lives indelibly changed for the better. He loved life and was passionate about everything and everyone who was part of it. And he was the best practitioner of the saying he used to repeat ‘Eat dessert first, life is uncertain’.

#### ACKNOWLEDGEMENTS

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