BIOGRAPHICAL MEMOIRS

Daniel E. Koshland Jr.

March 30, 1920–July 23, 2007
Elected to the NAS, 1966

A Biographical Memoir by David A. Sanders

Figure 1 Daniel Edward Koshland Jr.

Daniel Edward Koshland Jr. was a highly influential American-born biochemist known both for his scientific acumen and his acerbic wit, as well as for his service to his profession. His contributions to the study of protein structure, enzyme catalysis, and allostery can be found in all textbooks of biochemistry. He then turned his attention to bacterial chemotaxis as a paradigm for understanding the molecular mechanisms of sensory responses. He was the editor of *Science*, the leading multidisciplinary journal of science in the United States, from 1985 to 1995. Notably, the reorganization of the biological sciences that he spearheaded at the University of California, Berkeley (UC Berkeley) became a model for other research institutions. Koshland received the National Medal of Science (1990) and the Welch Award in Chemistry (2006). In 1998, he received a Special Achievement Award from the Albert and Mary Lasker Foundation; after his death, it was renamed the Lasker-Koshland Special Achievement Award in Medical Science in his honor. Dan Koshland was elected to the National Academy of Sciences in 1966, and Marian Koshland was elected in 1981.

I never saw Dan Koshland in an unconfident mood. Dan was certain that science could cure all of humanity's ills. He was positive that the United States of America was a force for good in the world and that the University of California, Berkeley (UC Berkeley), was and should remain the greatest university for the life sciences on Earth. Fundamentally, Dan Koshland believed with good justification in the immense capability of Dan Koshland. It was not for no reason that, with a modicum of self-mockery, Dan referred to his alter ego in his editorials for *Science* as Dr. Noitall and that he responded to profusely extravagant praise of his expertise with the trademark phrase, "A vast understatement of my true worth."

The late Stanford University professor of applied physics Theodore "Ted" H. Geballe (who once joked that Dan was responsible for Ted's marriage to Dan's sister Frances, known as "Sissy," because Dan had paid him five dollars to take her out on a date) told me an illustrative story about Dan's self-possession. One night, when they all lived in New York, the Koshland and Geballe families were traveling together to a Broadway musical. They were late, Dan was driving, and they seemed to be lost. Dan turned his car onto a jammed

Figure 2 Marion Elliott Koshland. *Courtesy of American Association of Immunologists.*

Manhattan street and not seeing any theater declared, "Just as I thought, it's not on this block."

In many other ways, however, Koshland was remarkably unassuming. I was a graduate student in his laboratory at UC Berkeley from 1983 to 1989. At my first meeting with him, he insisted on my calling him "Dan," not Professor Koshland. Despite his being one of the heirs to the Levi Strauss fortune, Dan dressed very modestly. His father, Daniel E. Koshland Sr., had married his own cousin, Eleanor Haas, and joined his brother-in-law Walter A. Haas at the Levi Strauss & Co., becoming its CEO in the late 1950s. On occasion, Dan would take calls from his broker in his office, but in general people were largely unaware of his wealth. He always flew economy class. At times, he seemed somewhat embarrassed by his family fortune. Dan wouldn't let his father pick him up right in front of the public school that he attended, because he thought the Buick driven by Dan Sr. was too ostentatious a vehicle. I only learned about his affluence because my father, Gabe Sanders, who was exactly thirteen days younger than Dan, sent me clippings of magazine articles about the Koshlands that showed their rank among the wealthiest Americans. Dan and his wife, revered immunologist Marian Elliott Koshland—"Bunny" to all their friends—did own an estate-like home and property in Lafayette, California, where a striking, original abstract painting by Helen Frankenthaler hung on the wall in their dining room.[1]

One day when I was in the lab, Dan called me and another of my fellow graduate students, Gideon E. Bollag, into his office. After asserting that Gideon and I were "the most trustworthy people he knew," he asked us, to our great surprise, to be witnesses to his will! He reassured us that our role would be limited by sharing with us some strategies he had deployed to discourage challenges to the distribution of his assets. We were stunned by his request that we assume this responsibility. Nevertheless, we both agreed. Fortunately, Dan lived for many more years after we left the laboratory, and he must have drawn up other wills subsequent to my time in his research group, because I was never called to testify when his estate was settled.

EARLY LIFE, EDUCATION, AND TRAINING

Dan was born March 30, 1920, in New York City. His parents, the aforementioned Daniel E. Koshland Sr. and Eleanor Haas Koshland, were heirs, respectively, to wool and denim jeans fortunes. When Daniel E. Koshland Sr. joined Levi Strauss & Co. in 1922, he moved the family to the San Francisco Bay area, where his family had become pillars of the Jewish community. Dan Sr.'s parents lived in a San Francisco mansion called "Le Petit Trianon" (it was a replica of the chateau at Versailles of the same name), but Dan Sr. himself chose to reside his family in Hillsborough near San Mateo, California. Dan Jr. recalled that, as a child, it seemed to him that one or another person in his extended family was having a birthday celebration nearly every week. For each such occasion, Dan would always write a celebratory poem, an endeavor that would help hone the outstanding writing skills he manifested later in life.

Dan Jr. attended the public schools in Hillsborough until tenth grade. Then, persuaded by a charming cousin and spurred by a compulsion to counter the dismissive attitude of certain East Coast private preparatory schools that a West Coast public education was inferior, Dan accepted the challenge of attending Phillips Exeter Academy in New Hampshire. Dan did not have to work very hard to excel during his education in the public schools and, despite the increased workload at Phillips Exeter, was more than able to continue his academic success. He made a deal with himself, however, that he would come back to California for college and attend UC Berkeley. Dan's view, which he espoused throughout his life, was that it was important to obtain the perspectives gained from training and experience at a variety of locations, but equally important, ultimately, to return home to one's roots. In his case, though, he felt a twinge of temptation to remain on the East Coast for college. But his mother's declining health—she had multiple sclerosis—provided the

Figure 3 Yvonne Cyr Koshland. *Courtesy of Oral History Project, Bancroft Library, UC Berkeley.*

impetus for Dan to live up to his initial resolve to return home to California and attend UC Berkeley.

Dan enjoyed playing sports, but he was near-sighted and spent much of his youth reading. He claimed that it was two books associated with Paul de Kruif, *The Microbe Hunters* and *Arrowsmith* (the latter authored by Sinclair Lewis, but with substantial assistance from de Kruif), that sparked his interest in science. It is noteworthy that in *Arrowsmith* the German-Jewish professor Max Gottleib, who combined literature and philosophy with microbiology in his lectures, urges the hero, Martin Arrowsmith, to study physical chemistry before taking his bacteriology class. Dan Koshland, a descendant of a Bavarian Jewish family, was drawn to biology, and in particular biochemistry, but was persuaded that he first needed to study physics and chemistry, so he majored in chemistry at UC Berkeley, graduating with a bachelor of science degree in 1941.

In a bacteriology class in his junior year, Dan sat next to freshman Yvonne Cyr, who was in turn, sitting next to Ted Geballe, Dan's future brother-in-law. Dan briefly dated Yvonne, a victor in a college beauty contest, but he was somewhat reticent about his intentions. She thus chose to marry student-body president James P. "Jim" Keene; they would become the parents of Christopher Keene, a conductor of the New York City Opera. Much later in life, however, Dan would encounter Yvonne again.

As detailed in a story he liked to tell, Dan learned an important lesson while he was an undergraduate. He and another student enrolled in a summer course in advanced inorganic chemistry taught by Wendell M. Latimer, chair of the Department of Chemistry at UC Berkeley. Dan, always a very good student, achieved top grades in each of three examinations during the term. After he turned in his final and was walking out of the room, Latimer picked up the paper and asked "Would an 'A' be sufficient?" Dan responded, "Yes," but then was horrified when Latimer began to tear up the exam, signaling that Dan had so excelled in the course that Latimer didn't need to waste his time scoring the test. Shocked and in defiance, Dan blurted out, "I just spent three hours working on that exam; you owe it to me to correct it!" Latimer laughed and graded the exam. Dan's classmates ridiculed him mercilessly about that incident. The last laugh was had by Dan, however. As a senior, he was the recipient of the James Monroe McDonald Scholarship, which was awarded "only to male students, capable of using correct English and possessing good character and courteous manners" and was bestowed "primarily for meritorious work of students giving promise of special ability in their chosen field." In Dan's words, he ascertained "that acting obnoxiously was not always bad."

The Manhattan Project and "Bunny"

After graduation, Dan secured a position at Shell Chemical Company, where he was assigned to do unfulfilling work on aviation fuels. During his stint there, the attack on Pearl Harbor occurred on December 7, 1941. Dan tried to enlist in the U.S. Navy, but his poor eyesight disqualified him from service. Characteristically, when Dan recalled this episode later in his life, he contrasted the eagerness with which men wanted to serve their country in World War II with their reluctance to participate in the Vietnam War.

Soon after his rejection by the Navy, an opportunity to employ his talents for the nation's war effort presented itself. Wendell Latimer, remembering his highly talented but occasionally annoyingly self-possessed student, reached out to Dan and asked him to quit his post at Shell and move to the University of Chicago to join chemist Glenn T. Seaborg there to work on "the most important job in the world." The "job" was, in fact, the Manhattan Project. Remarkably, Dan, with just his undergraduate degree in chemistry, was put in charge of a group of fourteen working on the solution chemistry of plutonium, despite his never having had any previous experience working with radioactive substances. Although the dangers of radioactive materials were explained to Dan and his coworkers, they appeared to adopt a rather cavalier attitude toward the hazards; Dan maintained that mindset for decades afterwards. Supposedly, at some point, he was reputed to have kept a sample of plutonium in his desk (purportedly, a common phenomenon among people who had worked on the Manhattan Project). In 1951, Seaborg received the Nobel Prize in Chemistry for his continued work on the transuranium elements.

Dan told a few stories about how he first met Marian Elliott, who had received her bachelor of science degree in bacteriology at Vassar College in 1942 and came to the University of Chicago initially to study medicine. These different accounts can be reconciled, but the main goal of Dan Koshland, the raconteur, was producing the pleasure that the storytelling gave to his listeners and to himself. In an episode reminiscent of the scene in the movie *Gigi* in which Maurice Chevalier sings, "I Remember It Well," Dan recalled at his fiftieth wedding anniversary that he first saw her in green slacks, but Marian insisted that she never owned green slacks. It was in a Chicago bookstore the day after he saw the woman wearing the green slacks that Dan first spoke with Marian. Soon thereafter they were both at a dinner party where Marian was being outrageous and referred to Dan as a "typical Harvard type." They immediately sensed a connection with one another; their relationship persisted even after Dan was transferred in 1943 to the Clinton Laboratories in Tennessee (now the Oak Ridge National Laboratory), where he worked under the supervision of nuclear chemist Isadore Perlman, another alumnus of UC Berkeley. After Marian switched from medicine to basic research, she was awarded a master of science degree from the University of Chicago in 1943. She and Dan married in 1945. According to Dan, it was the best decision of his life and, eventually (and perhaps apocryphally), the basis of one of his many memorable and humorous catchphrases about male-female relationships: "Behind every successful man is a surprised woman."

What followed in their life was the first instance of the Koshlands having to negotiate what is now referred to as the "two-body problem." Marian, now a Koshland, sought a job at Oak Ridge, but she wanted to obtain it on her own merits. So she applied under her maiden name, Marian Elliott, rather than Marian Elliott Koshland, which she would subsequently use in publications throughout the rest of her professional life,. Ironically, but satisfyingly enough, she was hired and assigned to work on the biological uptake of plutonium under the supervision of one Daniel E. Koshland Jr.

The contrast between their investigative styles, which continued throughout their later careers, became evident during this era, the only time of their extensive scientific collaboration. "Never repeat an experiment" was Dan's dictum. By this, he meant that one should always build on an initial result to do the next experiment. It could be that the subsequent experiment was a slight variation on the earlier experiment, but it should never be exactly the same. Marian was more cautious and believed that any given experiment should be repeated to ensure that the result obtained could be replicated and, thus, one could be certain of the outcome. Apparently, there were heated debates between the two of them about the proper way to conduct science. Later in their careers, they only collaborated on a single study, published in 1959.[2]

Graduate School and Job Hunting

In 1946, Dan and Marian left Tennessee and returned together to the University of Chicago to attend graduate school. Dan pursued a degree in organic chemistry under the guidance of Frank H. Westheimer, and Marian chose the field of immunology under William Burrows, which is how, according to the stories, she acquired the cognomen "Bunny," by which she was known to close friends and colleagues to the end of her life. Characteristically, with his love of mathematics, Dan, who always wanted others to share his enthusiasms, urged Bunny to take a course on differential equations. During this period, Bunny gave birth to two—Ellen (1947) and Phyllis (1949)—of what would eventually be the couple's five children.

At that time, Westheimer was an associate professor of chemistry at the University of Chicago (physical organic

Figure 4 The Koshland children — Ellen (13, at the bottom), Phyllis (10), the twins James and Gail (8), and Douglas (6). Bellport, New York, 1959. *Photographer: Daniel E. Koshland Jr. Image courtesy of Douglas E. Koshland.*

chemistry was his specialty). He shared with Dan a German-Jewish background, a love for science stemming from reading Paul de Kruif's *Microbe Hunters*, and an ability to quote from Gilbert and Sullivan's *The Mikado*. Westheimer attributed his obtaining an offer of a faculty position in the Department of Chemistry at the University of Chicago—and nowhere else—to the fact that, unlike many other departments, it was not antisemitic. Dan would come to have a similar employment experience. On Westheimer's first date with his future wife, Jeanne, in 1946, he spoke to her about the Nobel Prize in Chemistry divided amongst James B. Sumner (half), John H. Northrop (one quarter), and Wendell M. Stanley (one quarter). Stanley would feature in the future story of Dan and Bunny Koshland.

When Dan joined Westheimer's laboratory, biochemistry was largely focused on tracing metabolic pathways. Westheimer and Dan instead were interested in pursuing the chemistry of the enzyme-catalyzed reactions that achieved those metabolic transformations, that is, enzyme mechanisms, despite the generally dismissive attitude most organic chemists had towards biochemistry. Nonetheless, for Dan's doctoral dissertation research, and taking advantage of the expertise with radioactivity he had gained during wartime, he devised a route to synthesize D-glucose labeled in the C1 position with ^{14}C and found that, when fermented anaerobically by yeast, all the radioactivity appeared in the methyl group of the ethanol produced (and not in CO_2), confirming in convincing fashion the route for yeast glycolysis proposed by Embden and Meyerhof a decade before.

To give a sense of the attitude towards chemistry then abroad at the University of Chicago (never mind its, at the time, ugly step-sister biochemistry), Westheimer recounted a welcoming dinner in 1936 for new faculty, for which they had to pay themselves, and at which Pres. Robert Maynard Hutchins declared that "there is no better reason for a great university to have a Department of Chemistry than to have a school for barbers." After World War II, however, as Westheimer recollected, Hutchins reluctantly changed his opinion and averred that if the University of Chicago was going to have scientists, then they had to be the very best. Westheimer pronounced that Dan Koshland was the best graduate student he ever trained, although, much later at Harvard University, Westheimer took over as doctoral advisor for now renowned chemist Steven A. Benner when Benner's original thesis preceptor, legendary synthetic organic chemist R. B. Woodward, passed away.

My own encounter with Frank Westheimer centered on the impact that his influential 1987 article, "Why nature chose phosphate,"[3] had on my own graduate training under Dan. In this same regard, after the Koshlands received their Ph.D. degrees in 1949, Dan embarked upon a completely independent project, supported by an Atomic Energy Commission fellowship, in the laboratory of organic chemist Paul D. Bartlett at Harvard. There, Dan conducted studies on the hydrolysis of acetyl-phosphate, a topic that would ultimately become highly relevant to the research carried out much later by me in Dan's lab at UC Berkeley on the phosphorylation of the response regulators of bacterial two-component regulatory systems and on acetate kinase in my own lab and that of my wife, Miriam Hasson, at Purdue with our collaborator, Greg Ferry, at Virginia Tech. During their time at Harvard, Bunny gave birth to the twins, James and Gail (1951).

Pervasive antisemitism, as well as racism and sexism, in academic appointments was a deplorable fact at the time that Dan began looking for more permanent academic employment. He interviewed for a position in the Department of Chemistry and Biochemistry at the University of California, Los Angeles (UCLA). And in his conversation with UCLA's Max S. Dunn, a biochemist, it appeared to Dan that he had been given what seemed a firm commitment of a job offer. But then Dunn asked Dan the origin of his last name. "German," Dan replied, and after a pause, "and Jewish." According to Dan, the response that followed from Dunn was classic: "Some of my best friends are Jews." Thereafter, Dan heard no further word from UCLA. At that time, he did not share his exchange with Dunn with anyone else.

The very next year, Dunn returned to Harvard to seek potential faculty members for his department at UCLA. Bartlett suggested that Dan go for another interview. Dan demurred and, to explain why, he then shared his prior experience with Dunn, not knowing how Bartlett himself felt about antisemitism. To his credit, Bartlett, it turned out, was furious about Dunn's behavior and telephoned physical organic chemist William G. Young, a colleague who was dean of physical sciences at UCLA and the first member from that institution elected to the National Academy of Sciences. Unbeknownst to Dan, a Jewish student of Young's, Saul Winstein, had been a National Research Fellow with Bartlett before returning to UCLA.

Soon afterwards, Dan received an offer for a one-year appointment at UCLA. He declined, knowing that Dunn was the only other biochemist in the department. Dan learned later that his incident with Dunn was not an isolated one and that Dunn was thereafter removed from any further faculty recruitment efforts by UCLA.

Brookhaven National Laboratory

The only solid offer of employment Dan received was in the Biology Department at Brookhaven National Laboratory on Long Island in New York in 1951. Although disappointed not to have secured a position at an academic institution, he thought that he would be able to move to one in a year or two, but his time on Long Island would be significantly more protracted. Dan's research at Brookhaven was focused initially on using radiochemicals for studying enzyme mechanisms, which was consistent with the mission of the laboratory.

Bunny applied to the Medical Department at Brookhaven, but they did not hire women researchers. The chair of the Biology Department, Howard J. Curtis, made an arrangement whereby Marian would edit an annual symposium volume and would consequently be provided with a laboratory. Having recently given birth to the twins and, not long after, to their fifth child, Douglas (1953), Bunny considered leaving scientific research, but Dan convinced her that she could succeed despite working in the laboratory just part-time.

Dan and Bunny settled into a home and the community of Bellport, New York. They won the prize for funniest costume at the South Bay Art Association annual Bal Masque in 1960, dressing as a horse. Dan parlayed the fame of this triumph into being elected to the Board of Education of Central School District 4, where he rose to be president. Beforehand, he had been president of the Bellport Citizens' Council for Public Schools.

On March 8, 1963, Bellport High School burned to the ground. A friend of Dan's daughter Phyllis recalled that they escaped from the gymnasium, and Phyllis carried a basketball outside, wondering what she should do with it, as she watched the fire. Dan led the successful effort to build a new high school and renovate the junior high school.

Dan also participated in a lobbying effort in support of a New York legislative bill that called for increased state aid for local school districts. He provided a statement that was included in the *Congressional Record* in 1963 with regard to the necessity for continued federal funding for his school district among others, because it served the children of a national facility. Incidentally, his daughter Gail won an award for an "exceptional project" titled, "Blood Types and Blood Cells," in the science fair at Kreamer Street Elementary School in 1964. Even in those days, it was recognized that it was important to be as supportive of children as possible and, hence, with respect to the science fair entries that were not considered exceptional, it was reported that "Since all projects were worthy of recognition, each participant was presented with an honorable mention award." Another tidbit reflecting the mores of that era, the report of the 1961 teachers' dinner mentioned the presence of "Dr. and Mrs. Koshland," although, to be fair, sometimes the couple was referred to as "Mr. and Mrs. Daniel Koshland" in *The Patchogue Advance,* a now-defunct newspaper for residents of the south fork of Long Island.

Emerging during this period were important experiences and skills that would stand Dan in good stead later in his career. First, he considered it his civic duty to participate in politics as an elected official. Second, he thereby learned how to ask legislative bodies for money to support education. Third, he knew how to get academic buildings constructed.

Induced Fit

It was at Brookhaven that Dan Koshland promulgated his "induced fit" hypothesis of enzyme-substrate interaction. In 1894, Emil Fischer proposed that enzymes, subsequently shown to be proteins capable of catalyzing chemical reactions, bound their substrates through a "Schloss-und-Schlüssel" (lock-and-key) mechanism.[4] This hypothesis provided an explanation for why any given enzyme was so specific for accelerating only the chemical transformation of a particular molecule—namely, that the enzyme and its substrate had to fit each other spatially. Dan's experiments and his analysis of the literature indicated to him that the concept that a substrate merely had to engage with the enzyme in the same manner as does an incoming piece in a jigsaw puzzle was too simplistic and thus our understanding of enzyme mechanism had been incomplete.

Instead, ever the chemist, Dan recognized that, to catalyze a reaction, the chemical groups on an enzyme had to be brought into a precise alignment with respect to those of the substrate and, further, that binding of the substrate could provide the energy to elicit changes in the structure of the protein that allowed the groups on both the enzyme and the substrate to reorient into the configuration optimal for catalysis. Dan considered the metaphor of the mutual shape changes that occur when a hand is placed in an empty glove. But to describe his idea, Dan instead coined the term "induced fit." A chemically similar but unreactive species would not promote the necessary conformational alterations, thus providing a mechanism for the ability of an enzyme to discriminate a substrate from other molecules. Importantly, Dan's hypothesis relied on the concept that all proteins, enzymes included, were not rigid, but flexible entities, able to undergo dynamic changes. Although the experimental techniques available at the time had been inadequate to demonstrate such malleability in protein structure, subsequent studies of protein denaturation and atomic-scale views of a growing number of proteins and enzymes by X-ray crystallography and later by nuclear magnetic resonance spectroscopy supported Dan's hypothesis. He found such evidence gratifying. Cumulatively, such findings helped to overcome much of the initial wariness about his ideas and promoted growing acceptance of induced fit as a general principle in enzyme-substrate and protein-ligand interactions.

At the time, though, Dan's initial attempts at publishing his innovative proposal were frustrated by the skepticism of certain referees. But Dan managed to first introduce the concept of induced fit in an article he wrote in 1958 entitled, "Application of a Theory of Enzyme Specificity to Protein Synthesis."[5] Therein, Dan not only explains and illustrates induced fit for enzymes, but also describes and depicts a model for protein synthesis dependent upon induced fit. Unfortunately, tRNAs and the role of the ribosome in protein synthesis were being discovered at this time, and Dan's protein-synthesis model was quickly rendered obsolete. Fortunately, Dan was able to explicate the rationale for the necessity of the "induced fit" hypothesis for enzymes at greater length in a chapter in the first volume of *The Enzymes,* entitled "Mechanisms of Transfer Enzymes."[6]

A comparison of the attitudes of Emil Fischer and Dan Koshland illuminates the differences between them, and no doubt is also reflective of the eras in which they lived. Both shared an interest in demonstrating that investigation of isolated cellular components could illuminate how cells and organisms operate. But Fischer, by temperament, was opposed to theoretical speculation, whereas Dan's very being pulsated with it. Also, Fischer was not overly fond of his Schloss-und-Schlüssel hypothesis, referring to it in only three of his subsequent 400 papers and therein only briefly, insisting that it was just a means for conveying his idea. Dan, on the other hand, believed very strongly that it was good practice to come up with catchy names for discoveries or novel concepts and to promulgate them as much as possible.

In 1958, Dan received an offer of a joint appointment at the Rockefeller Institute (later Rockefeller University) with the proviso that he commute into Manhattan one day a week to conduct a seminar in theoretical organic chemistry. That same year, Dan published an article with Norman S. Simmons at UCLA and James D. Watson, then at Harvard, entitled "Absence of Phosphotriester Linkages in Tobacco Mosaic Virus."[7] This work on the virus connected Dan back to the phosphate chemistry he learned at the University of Chicago and, as we'll see, forward to UC Berkeley. Around that time, William J. "Bill" Ray Jr. joined Koshland as a postdoctoral fellow after obtaining his Ph.D. in organic chemistry from Purdue University; and, several years later, Henry "Hank" Weiner would join Dan at Brookhaven after also obtaining his Ph.D. in organic chemistry from Purdue.

In the next year, Dan published one of his favorite research articles, entitled "Purified Muscle Proteins and the Walking Rate of Ants," by Harvey M. Levy, Nathan Sharon, and himself.[8] How do I know that this study was one of his favorite articles? It was one of only two papers of his that he ever gave me copies to read, the other being "The Bacterium as a Model Neuron," which was published in 1983, the year when I was considering joining his lab as a graduate student.[9] The "ants" paper exemplified two of Dan's enduring passions: displaying the power of the application of mathematics to science, and demonstrating the relevance of test-tube biochemistry to biology.

"Reporter group" was a term Koshland, with his penchant for coining neologisms, introduced in 1964 to describe a chemical moiety introduced into a protein that could convey information on changes to its environment under different conditions. For example, a group attached near an active site could interact directly with a substrate. Alternatively, a group placed at a site distant from the active site could register conformational changes that are propagated upon substrate or inhibitor binding. Such probes provided additional supporting evidence for induced fit in enzyme function. Interestingly, a compound Dan developed for this sort of purpose, namely 2-hydroxy-5-nitrobenzyl bromide (commonly referred to as "Koshland's reagent"), which at low pH covalently attaches an environmentally sensitive *p*-nitrophenol group specifically to tryptophan residues in a protein, was originally designed, according to Dan, to modify tyrosine residues.

Modeling Cooperativity in Proteins

Thinking about protein dynamics through his contemplation of induced fit and observations about the behavior of reporter groups bound at locations distant from an active site led Koshland to ponder allostery, a form of regulation of protein activity in which the binding of a ligand at one site affects the conformation of a distal site on the same protein. The particular phenomenon in which Dan was initially interested was "cooperativity"—how the binding of ligand at one site in a multi-subunit protein affected the affinity of the protein for the same ligand at other sites. In 1965, Jacques Monod, Jeffries Wyman, and Jean-Pierre Changeux had published a highly influential mathematical model of allostery that accounted for both homotypic (cooperativity) and heterotypic (interactions between different ligands) effects.

In its consideration of cooperative effects, the Monod, Wyman, and Changeux (MWC) model postulated that an oligomeric protein composed of identical subunits exists in one or the other of two preexisting conformations in equilibrium with each other. One conformation has a high affinity for the ligand (the "R" state) and the other has a low affinity for the ligand (the "T" state). By this model, cooperativity is observed because binding of a ligand to one subunit promotes the likelihood that a molecule in the T state will convert to the R state, that is, ligand binding shifts the equilibrium toward more of the population of proteins occupying the R state. Thus, the MWC model proposed that the transition to the high-affinity conformation occurred simultaneously on all subunits. Therefore, in any given molecule, all of its subunits were either in the low-affinity conformation or the high-affinity conformation. In the original article, "R" and "T" were merely mathematical terms—association of "R" with a "relaxed" state and

"T" with a "tense" state has been attributed to protein chemist and crystallographer Max Perutz, renowned for his study of allostery in the behavior of the oxygen-binding protein hemoglobin. It is also only later that the MWC model is referred to as the "concerted" model of cooperativity.

In the next year (1966), Koshland challenged the MWC model by publishing, along with postdocs George Némethy and David L. Filmer, a different mathematical model for allostery in which a ligand-induced structural change in one subunit within an oligomeric protein was communicated to a neighboring subunit in the same protein via the concomitant changes exerted at the subunit-subunit interface, thereby forcing the neighboring subunit into a conformation more conducive to ligand binding.[10] The more sites bound, the greater the affinity of the remaining subunits in the oligomer for their ligand. Hence, the "KNF" proposal came to be known as the "sequential" model of allostery. The article was focused on determining which geometry of subunit-subunit associations would lead to model-predicted saturation curves for ligand binding that were most consistent with experimental data obtained by others for oxygen binding to hemoglobin. Dan always maintained that it took him quite some time to persuade a journal to publish this paper.

Negative cooperativity, the phenomenon whereby the binding of a ligand to one subunit reduces the binding of the same ligand to another subunit, is only predicted by the KNF model. No examples of negative cooperativity were known in 1966, but robust exemplars were discovered in subsequent years, including in Koshland's laboratory.

Fascinatingly, in the 1966 article, the MWC model is referred to as the "allosteric model," whereas a different model that they reject as inadequate is described as the "concerted" model, yet they also note overtly that the MWC model has a concerted aspect to it. In addition, although Dan's insight about induced fit underlay his interest in allostery and cooperativity, and despite later association of induced fit with the KNF mode, there is no use of the term in their paper. Indeed, the article declares the authors to be agnostic about whether a ligand promotes a conformational change or binds to a high-affinity form of the oligomeric protein, although they do assume the latter to be present initially at a low concentration. In fact, the term "sequential" is not used explicitly to describe the KNF model until a 1967 article by Koshland and Mary E. Kirtley, later at the University of Maryland School of Medicine in Baltimore, in which heterotypic ligand interactions are analyzed using the KNF model and wherein the MWC model is described as the "symmetry model."[11]

Dan would later aver that Monod, with whom he had a cordial rivalry, had a penchant for seeing symmetry everywhere in the natural world. Monod's own playful nature was displayed at a meeting in Paris when he gave Dan a carefully wrapped package as a gift for Bunny. Upon opening it, she discovered an ornate French cigarette lighter with the note, "Please help Dan throw some light on his theories." Dan had a somewhat less cordial rivalry with his eventual UC Berkeley colleague Howard K. Schachman. This friction was fueled, in part, by Howard's vocal adherence to the MWC model to explain the behavior of a classic allosteric enzyme, L-aspartate transcarbamoylase, which Schachman had spent much of his research career investigating.

Return to UC Berkeley

In 1964, Horace A. Barker, chair of the Department of Biochemistry at Dan's alma mater offered him a faculty position. Barker was known by his colleagues, friends, and students as "Nook." He came by this nickname because, when he was a tot, his family thought he resembled Baby Snookums, a character in the cartoon strip *The Newlyweds and their Baby* (Barker and that comic strip had both "appeared" in the same year). Given the success and prominence of the research and conceptual advances Dan had made at Brookhaven, he had received a number of offers of faculty positions elsewhere, but Bunny and he were content in New York, so he rejected them. But an offer from UC Berkeley (Cal to all of its alumnae and alumni) was different. Both ties to family in the Bay Area and his own undergraduate experience at UC Berkeley pulled him towards acceptance. He initially feigned that his interest was out of politeness, but Bunny was not fooled. A vote at the family dinner table about moving resulted in "nay" votes from his five children and Bunny, but Dan declared the "ayes" have it—citing the apocryphal story of Abraham Lincoln raising his hand in favor of the Emancipation Proclamation when all of his cabinet members had voted no.

According to Dan, at one point, Bunny woke up in the middle of the night and announced, "I made the decision." She continued to explain, to her startled husband, "Well, either we stay on the East Coast and I spend the rest of my life making it up to you, or we go West and you spend the rest of your life making it up to me. So, we move." One apparent manifestation of this deal was that, once in California, Bunny drove a silver Mercedes sports car, whereas Dan for years drove a dented old clunker.

Years before Dan's return to Berkeley, Wendell Stanley, fresh from having won his Nobel Prize, met with University of California President Robert G. Sproul at an airport in Wyoming and agreed to move from the Rockefeller Institute to UC Berkeley, which he did in 1948. Stanley set his sights on freeing biochemistry from its subservience to medicine and agriculture. He created a Department of Biochemistry and a Virus Laboratory jointly under his direction and supervision. Moreover, Stanley appealed successfully to the State of California for funding for a new building, completed in 1952, to house these new enterprises and had it constructed at a site in the same quadrant of the campus as the College of Chemistry (and not within any precinct close to the existing traditional biology-related departments), thereby displaying his predilections. After his death and in his honor, the Berkeley Virus Lab building was renamed Stanley Hall. In 2005, that building was demolished and replaced with a much larger research edifice, still named Stanley Hall.

But back then, all was not well. The biochemists under the leadership of Barker (who, as it happens, worked on methanogenesis, a field that, decades later, would also be explored in research conducted by both Dan Koshland and this author) were not content with Stanley's rule and bias towards virus research to the exclusion of other facets of biochemical research. Barker's personal papers from that era include a parody of a song from *HMS Pinafore* that includes, referring derisively to Stanley, the line, "For now I am director of the BVL." Stanley resigned as chair of biochemistry in 1953. Then, some of the more medically oriented biochemists moved to the medical school at UC San Francisco in 1958. The irony is that Wendell Stanley was brought to UC Berkeley to unify biochemistry but ultimately failed. It would be left to Dan Koshland to learn from Stanley's missteps.

Despite the tensions, it wasn't until 1964 that the remaining biochemistry faculty divorced themselves from those of the Virus Lab and decamped to a newly constructed eponymous building of their own in the biology quadrant of the campus. To honor Barker, the biochemistry building was renamed H. A. Barker Hall in 1988. After the physical split in 1964, the remaining virology faculty were re-established as the Department of Molecular Biology and continued to reside in the Virus Lab (by then, renamed Stanley Hall). It would not be until a reorganization of the biological sciences on the Berkeley campus, led by Dan Koshland, was completed in 1989 that biochemistry and molecular biology would be reunited. As part of that reorganization, a new building was constructed next to Barker Hall; it was originally designated the Genetics and Plant Biology Building but named Koshland Hall in Dan's honor after completion in 1990.

When the family relocated to Berkeley in 1965, Dan moved into the new Biochemistry Building, whereas Bunny joined Stanley in the Virus Lab, where she took a research position and rose from associate immunologist to immunologist. In 1970, in recognition of the quality of her work, Bunny was appointed to a full-time faculty position in the Department of Bacteriology and Immunology housed in the Life Sciences Building (now renamed the Valley Life Sciences Building, in honor of the family whose donation helped pay for its wholesale refurbishment). She would serve as chair of that department from 1982–89. During her tenure as chair, one of the new faculty she recruited was James P. Allison, who later received the 2018 Nobel Prize in Physiology or Medicine for discoveries he made at UC Berkeley that have made anti-cancer immunotherapy a medical reality.

It will likely not have escaped a reader's notice that the Koshlands moved to UC Berkeley during the height of the Vietnam conflict. Suffice it to say that Dan had disagreements with both undergraduate and graduate students about a number of political issues, including the value of anti-war protests. He dismissed such demonstrations as ineffectual.

Research at UC Berkeley

At UC Berkeley, Dan's laboratory initially focused its efforts on studies of the effects of chemical modifications of enzymes and characterization of covalent intermediates in enzymatic catalysis. G. Marc Loudon joined the lab as a postdoctoral researcher to work on one such project. In the same vein in 1966, postdoc Kenneth E. Neet and Koshland would publish a paper that included the term "chemical mutation" for the conversion by chemical means of the nucleophile at the active site of subtilisin from a serine hydroxyl to a cysteine sulfhydryl as a means to study the importance of the native residue at this position for catalysis.[12] This study thereby laid the conceptual groundwork for what would later be termed "site-directed mutagenesis," whereby recombinant DNA techniques are used to alter a specific residue in the sequence of a protein to assess its importance for its function.

A vignette from that exciting time illuminates the kind of relationships Dan established with the members of his lab. Dan was in Europe (a frequent destination, and on occasions when he was joined there by his children, they recall him reading the *International Herald Tribune* in the bathtub) to deliver the very next day an invited lecture on cytidine triphosphate synthetase (CTP synthetase). The evening before his talk he received an urgent telegram from postdoc Alexander Levitzki, who had found evidence for negative cooperativity[13] (1969) and "half-of-the-sites reactivity" (1971) in CTP synthetase.[14] Alex's telegram informed Dan that a mistake had been made, and that CTP synthetase was actually a trimer of identical subunits, not a tetramer (the existence of the tetramer was a critical part of the interpretation of Alex's data and thus of Koshland's upcoming presentation). Dan wisely regarded the message as a prank (as it was) and ignored it. This anecdote illustrates his skill at reading the personality of each member of his laboratory, his self-confident recognition of the nonsensical, and, contrariwise, his reluctance to acknowledge that there might be a flaw in any scientific result obtained in his own laboratory.

Figure 5 Dan Koshland celebrating the successful passage of the oral defense of the doctoral dissertation of his first UC Berkeley graduate student James E. Haber (right) in the Biochemistry Building (now H.A. Barker Hall), University of California, Berkeley, December, 1969. *Image courtesy of James E. Haber*.

Koshland's first graduate student at UC Berkeley, James E. Haber, published papers on the sequential model. Haber recalls,

> When I joined Dan's lab, in the Spring of the year he moved to Berkeley (1965), it was populated only by nearly a dozen postdocs. They taught me a lot. Very often Dan came in on Saturday morning (and therefore so did you!) and at noon he took us all to La Val's for pizza. I'm sure Dan didn't do any experiments, but he knew in detail what everyone was working on. I worked on allostery in hemoglobin (my own; Dan refused to donate), but the lab was in search of a sensory transduction system. Beef tongues, Hydra, and other candidates were investigated before Dan landed on Salmonella chemotaxis.

Despite his political disputes with Dan, especially about the Vietnam War, Jim Haber and Koshland contributed to the emerging field of bioinformatics and phylogenetics, in which protein-sequence analysis is used to establish evolutionary relationships, by considering in such cross-comparisons not only amino-acid residue identity, but also whether the residues at any given position share chemical similarity. Algorithms based upon their specific method ultimately did not improve sequence alignments and, unfortunately, their published article contributed to some of the persistent confusion about what "homology" means.[15] Nonetheless, it was among the first of its kind.

Contemporaneously, graduate student Daniel R. Storm and Koshland published an article[16] (1970) about the role of "orbital steering" (yet another Koshland neologism) in enzymatic catalysis that built on earlier publications from the Koshland lab. In a nutshell, Storm and Koshland emphasized that mere proximity of substrates within the active site of an enzyme is insufficient to explain the speed of enzyme-catalyzed reactions and proposed a model based on quantum mechanics to account for the reaction rate acceleration achieved by enzymes, arguing, in essence, that a major contribution to the catalytic power of enzymes is their ability to force the reactants into an orientation wherein the overlap of the orbitals required for bond breakage or bond formation is maximized. Other enzymologists, including William P. Jencks at Brandeis University and Thomas C. Bruice at the University of California, Santa Barbara, led a charge against orbital steering, declaring, perhaps paradoxically, that it was neither novel nor true. Yet, years later, in 1997, Dan and postdocs Andrew D. Mesecar and Barry L. Stoddard were still able to publish a combined X-ray crystallographic and kinetic study of isocitrate dehydrogenase that cited orbital steering in its title.[17]

Dan Storm related an episode from his time as a member of the Koshland lab. At his Ph.D. thesis defense, Storm declared that one of the great things about Dan Koshland was how accessible he was and then projected an image of himself slipping his thesis under the door of a bathroom stall. Did Storm mean that the only time that Koshland could be reached, in fact, was when he was in the men's room? Or, did Storm mean that, even in the bathroom, Dan was focused on science (...when he wasn't reading the *International Herald Tribune*, of course)? Storm left it to his audience to decide.

Bacterial Chemotaxis

Coeval with his enzyme research was Dan's developing interest in sensory systems. In 1966, Julius Adler at the University of Wisconsin, Madison, published an article in *Science* about the ability of the Gram-negative bacterium *Escherichia coli* to exhibit chemotaxis, that is, movement propelled by its bundle of peritrichous flagella up a chemical gradient of an attractant and, conversely, away from a repellant.[18] He credited investigations of the same phenomenon made in the 1880s–90s by Germans Theodor Wilhelm Engelmann and Wilhelm Friedrich Philipp Pfeffer and Dutchman Martinus Willem Beijerinck. Melvin I. ("Mel") Simon joined this field, initially focused on the structure of the flagellum from *Bacillus subtilis* as a model organelle.

With Dan's characteristic penchant for mathematics, he published his first article in this area of research in 1972 with postdocs Frederick W. "Rick" Dahlquist and Peter S. Lovely, entitled "Quantitative Analysis of Bacterial Migration in Chemotaxis."[19] For these studies, Koshland chose *Salmonella typhimurium* to distinguish his group's work from that of Adler and others. He also chose this bacterium because the tools for genetic analysis of *S. typhimurium* were very robust even at that time and because *S. typhimurium* was the forte of one of his colleagues in the Biochemistry Department at UC Berkeley, Bruce N. Ames.

A question the field at-large recognized that it had to address was how a rod-shaped bacterium, only about two micrometers in length, could sense changes in the concentration of a chemical in a gradient. Was the gauge spatial, that is, was the cell assessing the concentration of a chemical at one end and comparing it with its concentration at its other end? Or, was the mechanism for sensing temporal, that is, was the cell swimming around and comparing the increase or decrease in the concentration of a chemical over time. From a purely mathematical perspective, it seemed quite unlikely that the bacterium could perceive the minute change in chemical concentration in a spatial gradient as short as its length. In 1972, postdoc Robert M. Macnab and Koshland used the microscopy set up by Dahlquist and Lovely to track live bacteria in real time and observed that each bacterium would swim straight for a time (~1 second), but then tumble for a time (~0.1 second), thereby allowing for a change in its direction of swimming. When the cells were suddenly exposed to a large increase in the concentration of an attractant (the amino acid serine), the frequency of tumbling was noticeably suppressed. Conversely, if the concentration of serine was rapidly reduced, the bacteria tumbled more frequently. They also noted that, under their experimental conditions, the bacteria returned to the original behavior that they had exhibited prior to the drop in concentration within a dozen seconds. Thus, Macnab's findings provided evidence that the mechanism underlying the ability of the bacterial cells to sense an attractant was a biased random walk.[20] They further postulated that the bacterial cell must possess a type of "memory," in the sense that it is able to compare present and past concentrations of the attractant.

In 1968, Howard C. Berg, a physicist at Harvard University, also became fascinated by the phenomenon of bacterial chemotaxis and had entered the field, and likewise used the approach of tracking cells under the microscope. By the time of the Macnab and Koshland report, Berg had obtained similar results and reached similar conclusions. Further substantiating their hypothesis, Nora Tsang, Macnab, and Koshland published a paper entitled, "Common mechanism for repellents and attractants in bacterial chemotaxis," shortly before Nora Tsang's tragic untimely death.[21]

Looking back on this particular era of his lab's work, Dan enjoyed highlighting particular accomplishments with a shorthand he found amusing. He liked to refer to the chemical alteration of the active site residue in subtilisin as the "Neet Koshland" experiment and to the microscope system assembled to monitor chemotaxis as the "Lovely Koshland" apparatus. This trend seemed to stop, though, when he published with postdoc Philip G. Strange a study entitled "Receptor interactions in a signaling system: Competition between ribose receptor and galactose receptor in the chemotaxis response." I guess Dan found it unpalatable to refer to this publication as the "Strange Koshland" article.[22]

Dan thoroughly enjoyed his puns and parodies. For example, Ph.D. student John L. Spudich and Dan published a paper in *Nature* entitled "Non-Genetic Individuality: Chance in the Single Cell,"[23] which Dan fully intended as a Koshland-esque twist on *Sex and the Single Girl,* a then-popular non-fiction book by Helen Gurley Brown, long-time editor of *Cosmopolitan* magazine.

In the mid-1970s, bacterial geneticist John S. "Sandy" Parkinson entered the field of bacterial chemotaxis. His prowess with the genetics of *Escherichia coli* seemed to provide the impetus for nearly all the high-powered research groups investigating bacterial chemotaxis to adopt *E. coli* as their primary experimental organism. The Koshland lab resisted this trend for a while, and there certainly were some triumphs using the *Salmonella typhimurium* system, but those advances were most impactful when combined with parallel studies performed with *E. coli*. Graduate student Wayne R. Springer and Koshland identified CheR in *S. typhimurium* and *E. coli* as the *S*-adenosyl methionine-dependent methyltransferase responsible for the observed methylation of chemotaxis receptors, part of the mechanism of adaptation.[24] Postdoc Jeff Stock and Koshland identified what would be called CheB, when a unified nomenclature was accepted, as the methylesterase.[25] Postdoc Steven G. Clarke and Koshland and postdoc Elizabeth A. Wang and Koshland later established that aspartate and serine directly bound to their transmembrane receptors and did not require cognate periplasmic binding proteins, unlike the receptors for ribose and galactose.[26,27]

The term "response regulator" was introduced by Koshland in a 1977 article in *Science*.[28] It became the term of choice for describing the ultimate effector in any bacterial two-component regulatory system, such as the protein (CheY) that regulates the rotational direction of the flagellar motor in bacterial chemotaxis and the transcription factors that evoke the responses to other chemical stimuli. In the article, there is reference in the title to a "simple sensory system." This article was about midway through a series of Dan's reviews and a book article with increasingly flamboyant headlines: "Chemotaxis as a Model Sensory System" (1975)[29]; "Bacterial Chemotaxis as a Simple Model for a Sensory System (1976)[30]; "Sensory Response in Bacteria" (1977) in *Advances in Neurochemistry* (!)[31]; "A Model Regulatory System: Bacterial Chemotaxis" (1979)[32]; "Biochemistry and Behavior" (1979)[33]; "Bacterial chemotaxis in relation to neurobiology" (1980)[34]; *Bacterial Chemotaxis as a Model Behavioral System*

(1980)[35]; "Biochemistry of sensing and adaptation in a simple bacterial system" (1981)[36]; and, culminating in the aforementioned "The bacterium as a model neuron" (1983).[37] Contrast Dan's titles with the 1975 review articles by Adler and by Berg, each entitled simply "Chemotaxis in bacteria" (just like the Adler *Science* article nine years earlier).[38,39]

There were a few missteps. The Zukin and Koshland 1976 *Science* article was flawed.[40] Around that same time, Dan had a graduate student named Beverly A. Rubik, who described to Dan in typical New Age fashion how when she focused on positive thoughts, as instructed by her guru, the bacteria in her experiments swam straight, as if they were headed towards an attractant. Dan was furious. In her only publication, aside from her doctoral dissertation, Rubik (who went on to become a luminary in the "alternative medicine" arena) and Koshland reported some interesting findings, but engaged in some incorrect speculation about their significance.[41]

My first encounter with bacterial chemotaxis was indirect. Bob Macnab was one of the two professors from the Department of Molecular Biophysics and Biochemistry who taught my biochemistry course at Yale University. Although he joined the Yale faculty in 1973, five years later Macnab had one last publication with Koshland,[42] which, in fact, cleared up the misinterpretations promulgated in the earlier Rubik and Koshland paper. An aside: Macnab could often be unpleasantly acerbic and insensitive but could also be puckish. On more than one occasion, for example, he upbraided members of the Koshland laboratory, especially Jeff Stock, for "involuntarily circumcising" Shahid Khan, who was the first author on Macnab's last paper with Koshland. Apparently, Stock and others repeatedly and mistakenly cited that paper as "Kahn *et al*." Macnab's point was that authors should learn not to cite papers without having read them; far too many just reuse a reference that they have encountered elsewhere.

Chair of the Department of Biochemistry

Koshland took his five-year turn as chair of the Department of Biochemistry at UC Berkeley from 1973 to 1978. When he took the helm, he had been teaching for more than a dozen years already and found that he enjoyed the performance aspects and felt that he was good at it. He described himself as a bit of a ham. I later had the opportunity to be a teaching assistant for his undergraduate biochemistry class. Dan always changed into a suit and tie before he taught—sometimes in front of his male graduate students. His lectures were generally well crafted, although there was one time in a class on 3',5'-cyclic AMP and metabolism in which, at the end, he tried as a bonus to explain how caffeine worked to the complete befuddlement of hundreds of students in the hall. Fortunately, there was no question about caffeine on any examination.

Speaking of examinations, Dan had two guiding principles. First, at the beginning of the semester, he informed the students in the course that if anyone requested regrading of any portion of his or her exam, the whole test would be subjected to regrading, warning that as often as not such a protocol resulted in a lowering of the overall score. This procedural nuance had the desired effect of reducing the number of such regrade requests drastically. Second, if there were ever cause for Dan to confront a student about a charge of cheating, he would always have one or more of his teaching assistants present in the room with him. This concern for his safety was precipitated by the fact that in 1965, plant biochemist and UC Berkeley biochemistry professor David P. Hackett had been murdered after leaving his laboratory, and the prime suspect was a disgruntled student in Hackett's biochemistry course. We wondered whether Dan thought our presence would protect him, or whether he just wanted moral support.

As chair, Dan felt confident enough to reorganize the curriculum and assigned those who were good lecturers to teach the larger undergraduate courses and those who were not (he singled out Barker) to teach lab courses or smaller specialized courses. He also insisted that professors manage their teaching responsibilities within a course not on the basis of their deciding how much time should be spent on any particular topic, but by divvying out the chapters of a mutually accepted textbook equitably and having them cover adequately the content therein.

Dan at the National Academy of Sciences

Dan Koshland was active with the Academy Forum of the National Academy of Sciences (NAS). In 1976, he participated in a forum titled "The Citizen and The Expert." He started his address, characteristically, with a witticism. The complete quotation that follows (Dan only used the first sentence) is attributed to Georges Pompidou, then prime minister of France. "There [are] three ways for a politician to ruin his career: chasing women, gambling, and trusting experts. The first was the most pleasant and the second the quickest, but trusting experts was the surest." Dan asserted, against many in society, that the contributions of experts were essential for guiding proper public policy. He then proceeded to prescribe quantitative "credibility ratings" that could be used to evaluate expertise. He also decried the pressures that politics and the public place on scientists. Dan served as chair of the NAS General Advisory Committee from 1977 to 1979. As moderator of the 1979 Academy Forum entitled "Nuclear Radiation: How Dangerous Is It?," he reiterated his complaint about the pressures placed on scientists by the agenda of certain politicians and by a sometimes misguided public. The experiences of expert virologist, NIH investigator, and former Chief Medical Advisor to the U.S. president Anthony S. Fauci during the SARS-CoV-2 pandemic demonstrate that, in this same regard, matters in American society have not improved much since Dan raised his concerns.

Dan was also the introducer at the 1977 National Academy Forum, titled "Research with Recombinant DNA."[43] He again inveighed against the pressures on policy makers to reach important decisions on scientific issues too rapidly, but mainly focused upon championing science and scientists. Dan declared: "Unlike some other areas of public policy, science tends to glorify the sacredness of a fact" and "The job of the scientist is the creation of good." He also stated, "We [in science] hope to clarify the true extent of disagreement by condensing the lofty vapors of impassioned rhetoric into the cold droplets of distilled truth"—poetry and organic chemistry combined. Koshland did, however, attribute to Alexis de Tocqueville a saying about a "simple lie" and a "complicated truth," which apparently de Tocqueville never uttered. In any event, de Tocqueville was clearly one of Dan's favorite authors. In a *Science* editorial in 1985, a quotation from De Tocqueviile's *Democracy in America* occupies more than half the text.[44] Interestingly, a *Science* editorial on biotechnology by Dan in 1986 would be a paean to another renowned Frenchman, Louis Pasteur.[45] Dan continued for the rest of his life to be a booster of biotechnology both in research and as an industry, although he did not at all ignore its potential misuse.

In 1980, Dan was appointed the editor-in-chief of the *Proceedings of the National Academy of Sciences* (PNAS) and served in that position until 1984, when he was appointed editor-in-chief of *Science* by the American Association for the Advancement of Science (AAAS).

Peregrinations in Protein Phosphorylation

Back at UC Berkeley in 1978, graduate student Jean Y. J. Wang and Dan discovered protein phosphorylation in bacteria, originally in *S. typhimurium*. This research finding would lead Dan's lab in three future directions. The first was identification of bacterial isocitrate dehydrogenase (IDH) as a substrate for regulatory phosphorylation. Postdocs David C. LaPorte, Antony M. Dean, and Barry L. Stoddard and graduate students Kenneth Walsh and Peter E. Thorsness were important contributors to the studies on IDH. In 1987, Thorsness and Koshland demonstrated that inactivation of IDH by phosphorylation of the active-site serine residue could be mimicked by substituting an aspartate residue for the serine, whereas the substitution of an alanine had no major deleterious effect.[46] With some help from me, they concluded that it was the negative charge introduced on the phosphate that was key in suppressing IDH activity rather than phosphorylation eliminating some essential role of the serine residue per se. Finally, the structure of IDH was determined by X-ray crystallography in 1989 in a collaboration of the Koshland lab with UCSF graduate student James H. Hurley and UCSF professor Robert M. Stroud. "Zero-order ultrasensitivity," a theoretical approach to cooperativity based upon covalent modification of an enzyme described by frequent Belgian guest Albert Goldbeter and Koshland in 1981, was supported by the data the Koshland lab had collected on IDH.[47]

The second avenue of research on phosphorylation in the Koshland lab was focused on protein kinase C (PKC), which in Dan's opinion was connected to memory. Former postdoc Daria Mochly-Rosen has written that apparently the argument involved some logic about phorbol esters working though PKC to promote cancer but only after a few exposures, suggesting that PKC was "remembering" the prior phorbol-ester treatments. Subsequent research on PKC by former postdoc Alexandra C. Newton over the ensuing years has been instrumental in elucidating the biochemical properties of PKCs and their biological roles. Graduate student Andrew J. Flint and postdoc Philip N. McFadden also made important contributions to the PKC research in Dan's laboratory.

The third line of investigation of protein phosphorylation was a consequence of the ongoing investigations of bacterial chemotaxis and the eventual unveiling of the mechanism by which the signal from the cell surface receptors for attractants and repellants is transduced to the flagellar motor responsible for propelling cell swimming.

Bacterial Chemotaxis—A Reprise

In 1981, Jeff Stock, graduate student Ann Maderis, and Koshland published "Bacterial Chemotaxis in the Absence of Receptor Carboxymethylation."[48] Graduate student Andrew F. Russo investigated the effects of truncating the carboxy-terminus of the aspartate receptor. Postdocs Thomas C. Terwilliger, Elena Bogonez, Elizabeth Wang and Koshland determined the sites of methyl esterification of the *S. typhimurium* aspartate chemoreceptor.

At this time, the Koshland laboratory began investigating the effects on chemotactic behavior of overexpressing components of the chemotaxis system from recombinant plasmids. Graduate student Dennis O. Clegg determined that overproduction of CheY would cause the bacterial cell to tumble, even when most of the other chemotaxis proteins were absent. Thereafter, Chilean postdoc Bernardita Mendez and I focused on the effects of overexpressing CheW. Intriguingly, as we published in 1989, overproduction of CheW led to the same behavior as found in the absence of CheW, namely continuous smooth swimming.[49] This result was different from what was observed with overexpression of the other cytosolic chemotaxis proteins, where the behavioral effect (for example, continuous tumbling) was opposite to that resulting from the genetic deletion of the gene for the protein (continuous smooth swimming). These findings suggested that CheW has an important role in properly coupling the receptors to the response machinery.

Upon first joining the laboratory, however, I was assigned to work with Tom Terwilliger, known by all in the Koshland group by the nickname "Tom Terrific," after both an animated character on the long-running *Captain Kangaroo* children's television show and the Baseball Hall-of-Famer New York Mets pitcher Tom Seaver, because Terwilliger did everything—science, writing, tennis, skiing, dancing, etc.—with consummate panache. Tom even played the cello at my wedding to my late wife, Miriam S. Hasson. Together, Tom and I investigated the kinetics of the methylesterification of the multiple sites of modification in the *S. typhimurium* aspartate receptor. The experiments involved purifying *S*-adenosylmethionine away from its contaminant, *S*-adenosylhomocysteine, incubating receptors in prepared membranes with purified CheR and our *S*-adenosylmethionine spiked with some [^{3}H-*methyl*]-*S*-adenosylmethionine, solubilizing the membranes, and treating them with proteases. The products were analyzed by high-performance liquid chromatography. Unfortunately, I came to realize that one of the sites of methylesterification had been misidentified, which affected interpretation of the results. Moreover, Dan decided that he wanted me to move to a different project.

How this transpired illustrates, I think, certain characteristics of Dan's personality and his approach to science. Dan operated his laboratory as a collective. Research typescripts were placed on the lunch table (next to the High Performance Liquid Chromatography apparatus, in those days), and each member of the laboratory was expected to read them (definitely a good thing—Dan wrote his articles by speaking into a dictation machine and then his secretary would transcribe his words). This practice expanded discussion of each other's work within the group. This in turn led to discussions about authorship. Should ideas from members of the laboratory that prompt experiments or influence interpretations be recognized by their being listed as an author? No, was Dan's answer for the members of his group.

Dan had his favorites, however, and this sometimes became a source of friction despite the collaborative nature of the lab. For example, Dan's protégé Jeff Stock maintained an unusually close relationship with the Koshland laboratory after he moved to his faculty position at Princeton University. He sometimes collaborated with and at other times competed with Dan and members of his lab group. On occasion, he sought Dan's guidance as a long-standing member of the National Academy of Sciences for publications he had submitted to PNAS. Thus, sometimes his preprints appeared on our lunchroom table. I examined one entitled "Neither Methylating nor Demethylating Enzymes are Required for Bacterial Chemotaxis,"[50] which built on the prior work of Stock, Maderis, and Koshland.[51] But I recalled that an earlier 1981 paper by Jeff and Dan had included a model that explicitly proposed that the levels and activities of the CheR methyltransferase and the CheB methylesterase constituted the signal produced by the chemoreceptors, an hypothesis that was clearly wrong.[52] I mentioned to Dan that, with some degree of irony, Jeff had decided to erase the role of CheR and CheB as essential altogether. I also noted that I found the data in the Stock, Kersulis, and Koshland preprint unconvincing, specifically with regard to whether authentic adaptation to chemical attractants was occurring when CheR and CheB were absent, as well as expressing concern about the data in another preprint from Stock on taxis to sugars that was also circulating. He was clearly worried. Dan conveyed these apprehensions to Jeff, who strongly rebuffed them. Dan, unlike some others, valued the opinions of a second-year graduate student.

The Weizmann Institute of Science

Dan Koshland had an enduring association with the Weizmann Institute of Science in Rehovot, Israel. At various times, he was a member of their Scientific and Academic Advisory Committee, their Women and Science Award Selection Committee, and their International Board of Governors. He contributed funds to establish two endowed career development chairs there, one named after his father, Daniel E. Koshland Sr., and one named after his grandmother, Corinne S. Koshland. Dan also donated $8 million to establish the Koshland Center for Basic Research, which supports the Koshland Prize for postdoctoral fellows at the Weizmann Institute. There is a large sculpture with the Koshland name in Jubilee Plaza on the grounds of the institute. The Weizmann Institute awarded Dan an honorary doctorate in 1984.

In the summer of the same year (1984), it was announced that Dan Koshland was going to be the next editor-in-chief of *Science*, the prestigious academic journal of the AAAS, replacing physicist and author Philip H. Abelson. Dan pledged to continue to operate and guide the research in his laboratory research while serving as the editor at *Science*. Given the time constraints imposed by these dual commitments, he knew something had to be jettisoned. So, Dan decided to forgo attendance at scientific conferences and to turn down invitations to give lectures. This decision clashed with some plans of the Weizmann Institute. At least partially to honor Dan, the Thirteenth Annual Aharon Katzir-Katchalsky Conference was scheduled to be on the topic of "Sensing and Response in Microorganisms" and was designed to include only a limited number of principal investigators and their spouses. The meeting was scheduled for March 1985 in

Rehovot and Kibbutz Ayelet Hashchar, and Dan was to be a featured lecturer.

Dan decided that he could not afford the time to attend. He knew that I spent time at the Weizmann Institute in 1981 as a participant in a summer program established in memory of Chicago-born actress Karyn Kupcinet, who had died under puzzling circumstances. So, very graciously, Dan asked me to take his place. Needless to say, I was both honored and thrilled. Nearly all of the major figures were present—Julius Adler, Mel Simon, Sandy Parkinson, Howard Berg, Gerald Hazelbauer, Peter Devroetes, Philip Matsumura, Lee Segal, and several others. They were mostly just amused by my serving as a stand-in for Dan Koshland.

Back to Chemotaxis

Shortly after I returned from Israel, Dan greeted me with a few questions. "Did you enjoy Israel?" "Have I treated you well?," I answered with a smile, and "Yes" to both. "Okay, then," said Dan, "I need a favor from you." He wanted me to reinvestigate adaptation in the absence of methylation. I was not happy. The aspartate receptor methylation site project would proceed without me, and I was now supposed to investigate what a postdoctoral fellow Robert M. "Bob" Weis had deemed an "epiphenomenon." Reviewing the data indicated to me that some of the confounding results were likely the consequence of leaky mutations. As it happens, it was fortuitous that I was in charge of demonstrating to Bob some of the behavioral assays we employed; my growing unease led to his assuming responsibility for the project. Bob had two nicknames in the lab; one was "Herbie" because of his uncanny resemblance to an elf character in the TV cartoon *Rudolph the Red-Nosed Reindeer* (the character was actually named "Hermey," but we had it wrong), and the other was the "Prince of Mischief" for reasons that are likely obvious. I am eternally grateful to Bob; he did a far superior job on Dan's pet project and also revived some ancient apparatus for his experiments, including a helium/neon laser. Moreover, Bob also saved me when I cut the palm of my hand badly enough to expose the muscle when the arm of a chipped filter flask broke off. I went into partial shock, and Bob took charge and rushed me to the hospital. This incident illustrates another characteristic of Dan Koshland's lab management style—he hated waste and was reluctant to discard anything, even if it was no longer fully functional. After my palm healed (I still have quite a visible scar), I went through the lab and discarded into the sharps receptacle every item of broken glassware I could find. As for Bob Weis, he remained a close friend until his untimely death.

During this time, postdoc Joseph J. "Joe" Falke devised a method to probe the structure of, and ligand-induced conformational changes in, the *S. typhimurium* aspartate receptor by substituting cysteine for the existing native residues at various pairs of positions and analyzing the efficiency with which they were able to form disulfide bonds. Graduate student Daniel L. Milligan and I were each able to use the disulfide-bond formation that occurred with some of those mutant receptors for our published studies.

Protein Phosphorylation and Signal Propagation in Bacterial Chemotaxis

Several exciting and rapid developments instigated the third foray of the Koshland lab into protein phosphorylation in the 1980s. Ann Maderis Stock (now married to Jeff), Koshland, and Jeff Stock recognized that CheY was homologous to the amino-terminal domain of CheB and to the N-terminal domains of certain transcriptional regulators.[53] At MIT, postdoc Alexander J. Ninfa and Boris Magasanik demonstrated that one such transcriptional regulator, NtrC, was phosphorylated in a reaction promoted by NtrB.[54] At Caltech, the laboratory of Melvin Simon made major initial discoveries about the role of phosphorylation in bacterial chemotaxis. They found that CheA, which is homologous to NtrB, was phosphorylated.[55] They then showed that the phosphate in CheA could be transferred to CheY, but that the phosphorylation of CheY was transient.[56] They also discovered that CheA was phosphorylated on a histidine residue.[57]

Except with respect to studies of the chemotaxis receptor themselves, our team was being trounced with respect to figuring out the molecular mechanism of post-receptor signal transmission. Although our laboratory had studied the phenotypic/behavioral consequences for the bacterial cells of overexpressing in them the Che gene products from recombinant plasmids, we had not devoted resources to the purification of the overexpressed proteins. Dan recognized that it was clearly time to expand our approach. The transience of the phosphorylation of CheY was intriguing. Using purified CheA and CheY proteins (the latter was produced with the assistance of Gideon Bollag), we found that the CheY phosphorylation was stabilized by denaturation, indicating that its lability was a consequence of the native structure of the protein. Relying on a 1951 article[58] about the properties of acetyl-phosphate by none other than Daniel E. Koshland Jr., I determined that the CheY phosphate was hydrolyzed under either acidic or basic conditions, suggesting that it was an acyl-phosphate.

Phosphorylation of the CheA protein required magnesium ion as a catalyst. If phosphorylated CheA was incubated with sufficient ethylenediamine tetraacetic acid (EDTA) to chelate all the magnesium ion, then transfer to CheY could still occur, but dephosphorylation of the resulting product (CheY-P) was inhibited. Conversely, if the CheY were pre-incubated with the EDTA, no transfer would occur. These data indicated that the magnesium necessary for catalysis of CheY phosphorylation and dephosphorylation was provided by CheY itself and that CheY catlyzed transfer of the phosphoryl group from the phospho-His in CheA to CheY.

Using methods devised by Degani and Boyer,[59] we identified the site of phosphorylation in CheY by reductive cleavage of the acyl-phosphate with radioactive sodium borohydride, protease degradation of the labeled protein product, analysis of the resulting peptides by HPLC, and sequencing of the radio-labeled peptide by tandem mass spectrometry (MS-MS). This analysis, a collaboration with Beth Gillece-Castro and Alma L. Burlingame at UCSF, showed that the labeled peptide contained a single aspartate residue that had been reduced to homoserine, thereby pinpointing the site of phosphorylation. Sequence alignments demonstrated that the aspartate residue was conserved in the family of response-regulators to which CheY belongs. In toto, our studies identified the second components in the two-component regulatory systems as enzymes that catalyze the phosphotransfer from the first protein, that is, protein histidine phosphatases with a covalent (Asp-P) intermediate.[60] Consequently, it is formation of that enzymatic intermediate that changes the conformation of the response regulator so that it gains a function, such as, for CheY, the capacity to alter the direction of rotation of a flagellar motor or, for NtrC, to promote gene transcription.

The Stocks, in their turn, persuaded Dan that there might be a second site of phosphorylation, so we repeated the experiment with NtrC, which led to identification of the equivalent aspartate residue as its site of phosphorylation. Two-component regulatory systems are the dominant means by which bacteria respond to environmental changes, so the delineation of a common phosphotransfer pathway by our lab and others was a major advance. This work also contributed to the recognition that many more enzymes than previously appreciated possess a nucleophilic active-site aspartate residue that forms a covalent intermediate.

In other studies, which were mostly focused on the aspartate receptor, Gregory R. Moe, Gideon Bollag, and Dan investigated signal transduction by a chimera of the aspartate receptor and the insulin receptor. Dan Milligan demonstrated that aspartate-receptor dimers wherein only one of the two subunits had a cytoplasmic domain could still display increased methylation upon binding aspartate, although the interpretation of the results would later be revised because of subsequent findings. Graduate students Peter Dunten, Constance J. Jeffery, and Michael J. Shapiro and postdocs Berkley A. Lynch, Hans-Peter Biemann, Hervé Le Moual, and Karen Ottemann each made important contributions to the understanding of receptor signaling. Achieving a long-time goal, Koshland and UC Berkeley colleague and X-ray crystallographer Sung-Hou Kim were able to determine the three-dimensional structure of the periplasmic ligand-binding domain of the *S. typhimurium* aspartate receptor at atomic resolution.[61]

Food and Fun

Turning to the atmosphere abroad in the Koshland lab in my day, it should first be emphasized that it was fun. Dan attracted intelligent, generally hard-working, and collegial researchers to his group, and Dan authentically cared about them. He always made sure that visiting scientists (who tended to be well-known investigators) spent time with lab members. Once, two-time Nobel Prize-winning chemist turned Vitamin C evangelist Linus Pauling paid a call. Dan asked him to sign a large bottle of Vitamin C tablets. Pauling, although somewhat miffed, obliged, and the bottle remained in the lab providing what we all said, with tongue in cheek, were life-saving nutritional supplements to group members for quite some time.

Dan would regularly take people from the lab to meals, with or without other guests. He could get a table at Alice Waters's Chez Panisse restaurant at short notice, but his favorite place, it seemed, was just one block away from the Biochemistry Building—Oscar's, a greasy hamburger joint. After sixty-five years at the same location, Oscar's closed in October 2015 and has been replaced, I regretfully report, by the first outpost in Northern California of Washington, D.C.-based salad salon chain Sweetgreen. Dan would be heartbroken. For laboratory celebrations, Dan would take the entire lab out to the Yenching (later Mandarin Garden) Chinese Restaurant, where the waiters were embarrassingly deferential to him. I'm sorry to report that it too is gone—it burnt to the ground in December 2015.

After it first opened in March 1986, Greg Moe, Gideon Bollag, Andrew Flint, and I regularly patronized Triple Rock, a microbrewery located just two blocks from the Biochemistry Building that I'm happy to report still exists, making it one of the oldest brewpubs in the United States. This establishment was founded initially as Roaring Rock Brewery and Alehouse but was forced to change its name in 1989 at the insistence of Latrobe Brewing Co., owners of the (rather tasteless) beer brand Rolling Rock.

In January of each new year, the Biochemistry Department would hold a research retreat at the state-owned Asilomar Conference Center, whose initial buildings were designed by architect Julia Morgan, in Pacific Grove, California. Most years, the members of the Koshland laboratory would stop on the way down in the small agricultural town of Castroville and meet at the Giant Artichoke Restaurant, so-called because its entrance was graced with a twenty-foot-tall, green plaster artichoke and because every item on the menu was or contained artichoke. The Asilomar retreat itself was always a great occasion. There was a mixture of presentations by professors, postdocs, or graduate students and evening social events, with accompanying afternoon walks along the oceanfront or to see the grove of trees laden with monarch butterflies. Especially memorable was the comedic jousting between Dan Koshland and Randy Schekman, which Koshland would inevitably win. Schekman joined the faculty of the Biochemistry Department at UC Berkeley in 1976 while Dan was chair. Randy would later follow Koshland as editor-in-chief of PNAS (2006–11) and would be awarded the Nobel Prize in Physiology or Medicine in 2013 for his work on protein secretion. Dan would always tease by saying that Randy studied "excretion." Schekman once charged Koshland with being "almost a dilettante," and, interestingly, at one point, Dan had leveled the same accusation against me.

An indelible display of Koshland's comic genius at Asilomar was the time that he declared that one of his colleagues in the department was a "real slave driver." To prove it, he had three of the male students of said colleague who were facing the audience from the stage lift up their shirts while Dan walked behind each one of them and declared how awful were the gashes on their backs, which were not visible to the audience. Of course, everyone laughed, assuming Dan was just feigning that they had actual lacerations. He then said, "You don't believe me, do you?" We didn't. He then had them turn around—each of them had huge red welts across their backs (made with lipstick, it turned out). Dan's delivery and timing were perfect.

As mentioned, our Asilomar retreats corresponded to the wintering of migrating monarch butterflies in Pacific Grove. Back then, several trees in several locations were completely covered with butterflies. Sadly, that is no longer the case. In the ensuing years, the population of these insects has declined more than 80 percent due to habitat loss, pesticide use, and other degradations of the environment along their migratory route. Similarly, during our trips to and from Asilomar, we would often stop to visit the Santa Cruz Beach Boardwalk or to hike in Big Basin Redwoods State Park, but in 2020 much of Big Basin was so dried out and weakened by global warming that it was devastated when struck by wildfire. Likewise, the historically harsh winter storms of 2023, also reflective of global warming, destroyed many parts of the Santa Cruz pier and promenade, but the Giant Dipper (the old wooden roller coaster that rattled as if it were going to fall apart) is still operational.

Asilomar was also the site of a symposium to honor Dan's sixty-fifth birthday. Former and current members of the Koshland laboratory gathered, along with some of Dan's prominent scientific colleagues. It was a wonderful occasion. The reminiscences of the postdocs and graduate students who proceeded me were particularly rewarding. One story harked back to the Vietnam War. As noted before, Dan had disagreements with some of his lab members about opposition to the war and some of the social changes that the United States was undergoing, although it would be unfair to characterize Koshland as being to the right on the political spectrum. One former postdoc reminisced about advice Dan provided him when the postdoc was preparing to give a seminar at an institution where he was being considered for a faculty position. Dan gave him some advice before he left—Dan told him to shave off the beard he had sprouted in the style of the times, because it was unprofessional. Of course, he followed Koshland's advice. He concluded this story with the fact that at his interview, which was for a job at the Albert Einstein College of Medicine (until 2015, a part of the Yeshiva University of New York City), he was the only man there without a beard! While on the subject of Dan's counsel to his juniors, many of us have had the experience of Dan advising us that, "Assistant Professors shouldn't tell jokes," and, to some, adding, "But, I can."

Returning to food, Dan used to host pool parties at his stately home in Lafayette, California, an upscale community situated about twelve miles due east from the UC Berkeley campus. There were games on the lawn, concluding, in one famous episode, with Bunny's beloved flower garden getting trampled. There was an orchard on the grounds, and Dan would bring peaches into the laboratory for us to eat. They were the most mottled and ugliest-looking peaches ever, but they were delicious. Andy Russo used to say that you could always tell the ripest, best-tasting peach by finding one that had a maggot or two on it.

No discussion of Koshland comestibles would be complete without mentioning Saturday pizza. Whenever not away on travel, Dan always came into the lab on Saturdays. To reward laboratory members who joined him there on that day of the week, he would provide pizza. There was an unspoken expectation that any serious Koshland lab researcher would be there on Saturdays, unless that person had family obligations. If Dan were away for the weekend, he would give someone some cash to pay for the pizza; on these occasions, the lab was more inventive with regard to the toppings that were ordered. There were also some Saturday arrival and departure times that were scheduled around the pizza delivery. It will come as a shock to many Koshland alumni and alumnae that there was apparently a brief time in the late 1970s or early 1980s when pizza was displaced by Kentucky Fried Chicken. It will not come as a shock that many former Koshland trainees have instituted some variant of Saturday pizza in their own laboratories.

When someone was leaving the laboratory, Dan would always write a limerick for them that would capture some aspect of their research. Many former Koshland lab members still cherish their limericks. The last line of the poem for Dennis Clegg, whose project, as mentioned, involved high-level overexpression of CheY, was "Am I becoming too extremely Ys?"

A Decade as Editor-in-Chief of *Science*

The day in 1984 that it was announced that Dan would become the new editor-in-chief of *Science*, he came into the lab to discuss his new adventure. He declared that his children always said that he should be the publisher of a small-town newspaper, so that he could promulgate his opinions. Becoming editor-in-chief of *Science* would fit the bill in spades and provide an even greater forum than he had during his preceding four-year stint as editor-in-chief of PNAS. His secretary then came into the laboratory to say that U.S. senator John H. Glenn Jr. (D-Ohio), the decorated Marine aviator and former U.S. astronaut, was on the phone and wanted to congratulate Dan. In a display of Bunny Koshland's dry humor, she shared with the media at that time a bon mot that she had used on us, the members of Dan's laboratory, namely that the Koshland men all worked until they were ninety and then dropped dead. Dan was annoyed, he said, because he was planning to live to one hundred and thus was upset by the loss of ten years in Bunny's prognostication.

Dan had agreed to be editor-in-chief of *Science* only after negotiating an arrangement whereby he would need to spend only one week out of each month in the AAAS offices in Washington, D.C., and the remaining three weeks continuing to teach, supervise his laboratory, and reorganize the biological sciences at UC Berkeley. For the same reasons, Dan also reduced his other travel. So, we actually saw more of him after he became editor of *Science* than beforehand. He used his airplane time for writing; he said that engaging in that activity gave him a solid excuse to avoid speaking with anyone seated next to him.

Dan's main priorities were to enhance the reputation of *Science* and increase both domestic and international readership by raising the quality of the published scientific articles. He created a Board of Reviewing Editors made up of a distinguished panel of scientists, with select groups of them giving an initial review to determine whether the article would be sent out for full peer review. Not only did this protocol speed the response to authors, but it also gave more researchers a stake in the success of *Science.* He also made certain to staff all the full-time editor positions at *Science* with individuals who had science Ph.D. degrees.

Dan's attitude was that the authorship of an article was as consequential as what the article had to say. With this in mind, Koshland took two actions. First, flouting the past precedent at *Science*, Dan insisted that the list of authors be moved from the end of an article to the beginning because, in Dan's eyes, one's initial judgment about the impact of any article (and whether one should take the time to read it) was greatly influenced by the identity of its authors. Second, he beat the bushes to encourage colleagues and friends to submit their "best stuff" to *Science* and not some other journal. To quote Dan himself on this early initiative, "At the beginning, I had to plead with people to send articles in—frequently friends of mine who were either at Berkeley or other places. They were going to send them in to *Nature*, and I said, 'Please send it in to us.' I got them to do it." Indeed, regular readers of *Science* noted a shift in the source of the preponderance of the articles—authors from West Coast establishments outnumbered those affiliated with East Coast institutions, at least at the start of his tenure as editor.

Koshland made other noteworthy decisions at *Science*. He changed the content of the "Research News" section so that it had more punch and was situated at the front of each issue. He also introduced the "This Week in *Science*" feature, which highlighted the most significant articles in each issue and provided a short synopsis that could be understood by non-specialists—this feature was especially well received by journalists. In 1988, Koshland added a news feature called "Random Samples"—twenty-two years later, that section reported on an interview I'd done during my ultimately unsuccessful run for U.S. House of Representatives from my congressional district in Indiana, in which I stated that the most pressing and underappreciated scientific issue faced by society was access to clean fresh water.

Dan often clashed with the executive officers at the AAAS, first William Carey and then Richard S. Nicholson, who technically were his bosses, but Dan, with his wit, wisdom, and self-confidence, usually prevailed. He also had disagreements with his staff, but most remember him with great fondness because they realized that he just enjoyed the intellectual stimulation of a good argument.

Koshland used the forum provided by his position as editor-in-chief to express his viewpoints in frequent editorials. He hailed the development in the mid-1980s of genetic fingerprinting in the laboratory of Alec J. Jeffreys in the Department of Genetics at the University of Leicester in the United Kingdom because this DNA analysis method was exonerating wrongly accused prisoners. He denounced the spread of lawsuits that interfered with the manufacture and distribution of life-saving vaccines. He repeatedly insisted that more judicial decision-making should be based on science. He raised the alarm about the danger of antibiotic-resistant bacteria. Dan championed women in science; he declared, "As society searches for solutions to the horrendous global problems in need of scientific input, we cannot afford to lose the potential of women's brainpower"—and, in the same mouthful, he reiterated his faith that science could and should provide solutions to our most pressing problems. He commended the work of Mothers Against Drunk Driving; we shared a conviction that curbing driving while intoxicated should be a major public-health objective.

In his defense of embryonic and fetal tissue research against so-called "pro-life" critics, Dan asserted that work on such tissue did not promote abortion any more than research using cadavers was "pro-death." Koshland was also, in general, a strong advocate for protecting the environment; he proposed that the price of an object should include the cost of disposing of it in an environmentally friendly manner and championed the preservation of biodiversity. In 1990, Dan advocated for national health insurance. He asserted that U.S. hegemony in science and technology would replace natural resources as the fountainhead of American wealth. In an editorial on teaching, Dan contended that true teacher evaluation was difficult because "a highly demanding, tough-grading professor is usually appreciated by top students who want to be challenged, but disliked by those whose records are less impressive. The more lenient professor gets ratings that are usually high…." Dan expressed his concerns about "Big Science" (substantially, physics) until the Human Genome Project was proposed and implemented, and then he became a supporter.

Koshland was not a fan of animal-rights activists. In February 1989, during construction of the Genetics and Plant Biology Building immediately adjacent to Barker Hall, six protesters took over a construction crane. They were protesting the construction of a different building (the Northwest Animal Facility) and were masquerading as a group called something like Berkeley Coalition Against Toxics, claiming that they were trying to save the local populace from toxic chemicals that would leak out during an earthquake. The Alameda County Superior Court issued an order mandating that the demonstrators return to earth, and eventually they did. Dan wrote about the incident in a March 10 editorial in *Science* titled, "Animal Rights and Animal Wrongs."[62]

On October 17, 1989, the Loma Prieta Earthquake struck. This 6.9-magnitude event had its epicenter on the San Andreas fault close by Mt. Loma Prieta in the Santa Cruz Mountains, roughly fifty-six miles south of San Francisco. Despite the distance, this disturbance caused building collapses and fires in the Marina District of San Francisco, failure of a section of the upper deck of the Bay Bridge, pancaking of an elevated freeway (the Cypress Structure) in Oakland, and halting of the third game of the 1989 World Series in Candlestick Park (torn down in 2015), which just happened to be between the San Francisco Giants and the Oakland Athletics. Despite the widespread damage elsewhere, no toxic chemicals were released on the UC Berkeley campus and, in 1992, two years after completion of its construction, the Genetics and Plant Biology Building was renamed Koshland Hall.

Dan loved to come into the laboratory, toss out a provocative, often outrageous, idea, and then have the members of the group challenge him. We, in turn, would provide our proposals on topics in science and/or society, and Dan would appraise them. At one point, he critiqued California's Proposition 65, which voters approved by a 63-to-37 margin and became law in Nov. 1986. This measure requires businesses to provide warnings to Californians about significant exposures to chemicals that cause cancer, birth defects, or other reproductive harm. These chemicals can be in the products that Californians purchase, in their homes or workplaces, or are released into the environment. The prior in-lab back-and-forth likely influenced how Dan handled this subject in his *Science* editorial about it in 1989.[63]

In an editorial entitled "Scientific Literacy," Dan advocated for introduction of not only scientific findings (as if that would not already be a great enough achievement), but also application of the scientific method itself into public policymaking.[64] He argued for inclusion of methodology that requires a "control" group. He declared that he "attended a school board meeting at which a new math program was proposed. A board member (Dan himself, no doubt, given that we know Dan was school board president when he was at Brookhaven) made the suggestion that students be divided by lot into two groups," with one being taught the new math curriculum and the other in the traditional manner, and thereby determine in a properly controlled manner whether the new math led to greater math competency. "He was denounced … because one should not conduct 'a lottery with the students' lives'." In the same article he reiterated his credo, writing "The scientific method has been the most effective means of overcoming poverty, starvation, and disease." It is a good thing that Koshland did not use an example that he discussed with me before the editorial was published. In taking his argument about the importance of control groups into the realm of reductio ad absurdum (although it appeared to me at the time that he was serious), he suggested that we could test the efficacy of the death penalty as a deterrent to crime by taking two similar states—he named Arizona and New Mexico—and impose the death penalty for a few years in one but not in the other, and then compare their crime rates. As a vigorous opponent of the death penalty since my childhood, I was taken aback and convinced Dan not to use that scenario.

The editorial just described was not the only one wherein Dan would refer obliquely to himself as the protagonist of the story. In another article, relating how spanking of a child who was comporting himself properly (not misbehaving) was a deliberate paternal lesson in how capricious and irrational the world can be, Koshland claimed that he heard the tale from "an exceedingly logical friend." In another context, however, he intimated that the incident involved himself and his father.

In 1986, Koshland implemented a wholesale redesign of *Science*. Dan showed the lab the proposed new logo before it was publicized. Apparently, he had solicited the opinions of many graphic artists about it. It featured the title in majuscule, but with the S larger than the other letters and with a dot over the otherwise capital I. We thought it was silly. Dan was not dissuaded. He waxed poetic in his editorial announcing the changes, comparing the dot to a sky-bound balloon, "a hole in an argument that must be plugged," the Big Bang, and the first wheel, among other things.[65] It was called an "offense to orthography" by the *The New York Times.* Someone told Dan that the best solution was to make the dot smaller and smaller each issue until it vanished.

Editorials written under Dan's pseudonym, Dr. Noitall—who acknowledged fulsome praise with the response, "A vast understatement of my true value," (or some variant thereof)—first appeared in summer 1989. In a June 1989 issue, Dr. Noitall held forth about one of Dan's favorite hobby horses, namely the general inability of people to base their actions on impartial quantitative evaluation of risk (in another editorial, he discussed the risk associated with the consumption of a favorite food of his, peanut butter).[66] The article ended with another Koshland self-reference. His paternal ancestors lived by the motto "Eat, drink, and be merry" and "died prematurely, in their early nineties," and he would be unlikely to "escape the family curse," in concordance with the prophecy of Bunny Koshland noted earlier. Dr. Noitall reappeared in "Interview with a Disaster Expert."[67] Then, in "The Addictive Personality," Dr. Noitall described the compulsion of scientists for science.[68] Dr. Noitall subsequently pontificated on waste, stress, and gloom.[69-71] He mocked public relations experts with a description of how he would sell the concept of a dam in Death Valley to the populace[72]; yet, he expounded on the virtue of projecting science with more charisma. Dr. Noitall's piece titled "A Campaign for Science," about "reforms" to journal publication, is particularly effective.[73]

Dan was an outspoken and unabashed defender of science against detractors in the media who decried the fact that fraud and misconduct occurred in research. On the other hand, in a January 1987 editorial, he correctly recognized the dangers of the era of increasingly interdisciplinary research—"when no one person has expertise in all aspects of the research, there can be dangers."[74] He also decried inadequate supervision and the competition that led "entrepreneurs" to be "intent on the next grant or big success" to the detriment of their critical reasoning. Contrariwise, against the fervent remonstrance of his laboratory, he asserted, seemingly without concern, that "we must recognize that 99.9999 percent of reports are accurate and truthful." Regrettably, and dependent on the discipline, current estimates of the incidence of scientific misconduct in published scientific reports (fabrication, falsification, or plagiarism) is significantly higher than the rosy view held by Dan.

In this same regard, Koshland testified before the Subcommittee on Oversight, Space, and Technology of the U.S. House of Representatives on June 28, 1989. In his oral testimony, he asserted that "one of the real duties of the scientific journals is to publish retractions, corrections, criticisms, when they do exist." He nevertheless minimized the frequency of "major fraud" and maintained that such misconduct is readily discovered because a bedrock practice in science is independent verification, validation, and corroboration. For these reasons, Dan said the effect of frauds on the progress of science is "relatively small." But he also raised the concern that journals or universities might be hesitant to take action to confront misconduct because of fear of litigation. He concluded that "When you deal with 'a high consequence, but low incidence, type of problem' (a favorite Koshland expression), such as scientific misconduct, the way to do it is to punish the people who do it severely." In his written statement, he again declared his belief that even minor fraud is rare. He defended peer review, paraphrasing Winston Churchill, saying that it "is like democracy—it has many imperfections but, when compared with the alternatives, it is clearly the best device." On honorary authorship, he wisely averred that "the scientific community should be tougher than it has been in agreeing that those who benefit from the praise when work goes well should suffer when error or fraud is found. In some cases, heads of large groups have protested that they didn't know about co-workers' failures. If that alibi were greeted with the condemnation it deserves, the 'honorary author' problem might become a thing of the past."

Peer Review Can Have Its Shortcomings

Events that occurred when Koshland was editor-in-chief at *Science* would bring the national and congressional outrage about fraud in science to his doorstep. In July 1986, Robert Rando and colleagues at Harvard University submitted a manuscript on the isomerization of rhodopsin retinoids to PNAS. John E. Dowling, an NAS member (also at Harvard), sent the article for evaluation to C. David Bridges, a rhodopsin researcher then at the Baylor College of Medicine, who returned the manuscript after a month's delay, stating that he could not review it because he was conducting similar research. In November 1986, Bridges submitted a manuscript to *Nature* on experiments that resembled those in the Rando paper, but it was rejected for publication. Bridges then submitted the same work to *Science*, where it was accepted and scheduled for publication in June 1987.[75]

Rando learned of the claims of Bridges and, through Dowling, that Bridges had been sent Rando's manuscript to evaluate for PNAS. Rando contacted both PNAS and *Science* about his concerns. At this point, the dispute was being treated as one of priority of discovery, and *Science* decided to go forward with publication of the Bridges article. Soon, however, the issues became both violation of the confidentiality of the peer review process and plagiarism. Indeed, in May 1989, an investigatory panel of the NIH found that Bridges had plagiarized Rando's PNAS manuscript. Bridges, who had moved to Purdue University, consistently denied the charges. *Science* reported on the matter, and Koshland was forced to defend the magazine's decision. U.S. Representative John D. Dingell Jr., a Democrat representing Michigan's 12th district who was conducting an investigation into scientific misconduct, directed some of his fire towards Dan. Koshland's previous remarks apparently minimizing the frequency of scientific misconduct were the subject of comment in the media. Nevertheless, Dan was able to defend the initial acceptance of the article. Despite the NIH finding, it has never been retracted.

In the end, it was with great prescience that Dan asserted, "a press that equates a peer-reviewed experiment with a public relations document should expect the public to equate *Time* with the *National Enquirer*."

Genesis of the "Molecule of the Year"

One day in either 1988 or 1989, I walked into the laboratory and announced that if *Time* magazine had a "Man of the Year" (it was later renamed "Person of the Year"), then *Science* magazine should have a "Molecule of the Year." The response to my proposal was the expected ridicule from my lab colleagues. Nevertheless, Dan was listening.

I left the lab in the middle of 1989 to take a brief position as a visiting scientist at the University of California, San Francisco School of Medicine (UCSF) working jointly with Frank McCormick and the late Henry R. Bourne to produce two major reviews about the superfamily of GTPases that were published in *Nature*.[76,77] Towards the end of the year, Dan called me and said: "Guess what is going to be in the end-of-the-year issue of *Science*?" I surmised that it was something related to chemotaxis, or the GTPases. "No," he replied gleefully, "Molecule of the Year!"

As Dan stated in his Dec. 22, 1989, editorial announcing the award, part of the rationale for implementing such recognition was that it should be "the process of progress rather than a personality" that should be acknowledged.[78] Selecting a molecule for kudos, rather than any individual, would permit everyone in the field to take pride in the designation. Koshland again proclaimed a full-throated devotion to the belief in societal advances through time and the central role that science plays in such progress. Much to Dan's dismay, after he stepped down as editor-in-chief, the name of the award was changed to "Breakthrough of the Year."

In a clear parody and hat-tip to Molecule of the Year, Koshland lab members, *Science* writers, friends, and family concocted a faux issue of *Science* in March 1990, entitled "Man of the Decade." It is a loving and hilarious tribute to Daniel E. Koshland Jr. published by Bunny Koshland on the occasion of Dan's seventieth birthday. There are references to the tussle with Representative Dingell (involving the "Purified Muscle Proteins and the Walking Rate of Ants" article), the commandeering of the crane by the animal-rights protestors, and Dan's penchant for peanut butter. There is even an allusion to "overexpression is equivalent to absence."

Some people ponder what Dan might have had to say about SARS-CoV-2 and the COVID-19 pandemic. His 1987 editorial in *Science*, entitled "Epidemics and Civil Rights," provides the answer.[79] Public health should supersede individual rights when such purported privileges include "the 'freedom' to infect others." It is possible that his faith in the soundness of the scientific literature might be shaken, but not his belief in the ultimate triumph that results when the fruits and methods of science are applied for the common good.

Reorganization of Biology at UC Berkeley

The reorganization of the biological sciences at UC Berkeley is one of Dan Koshland's most remarkable achievements. It began in early 1980 with a characteristically blunt comment from Bunny Koshland. At a cocktail gathering at the Faculty Club, when asked by plant biochemist and dean of Biological Sciences (and soon to be vice chancellor) Roderic B. Park about the state of the life sciences at UC Berkeley, Bunny responded, "Terrible." There was a metaphorical fire in the edifice of biology at UC Berkeley, and it would take a wholesale administrative and physical rebuilding to restore it to its glory. When Park became vice chancellor later that year, he remembered his conversation in the Faculty Club, and he persuaded law professor and chancellor Ira Michael Heyman to take action. They appointed Dan Koshland to spearhead this effort. Through the assessments of external review panels of eminent scientists representing the full spectrum of the life sciences, the input of a series of in-house review committees composed of Berkeley life sciences faculty hand-picked by Dan, and the establishment of a Chancellor's Advisory Committee on Biology (CACB), Koshland accomplished what Wendell Stanley could not four decades earlier. Deftly overcoming entrenched academic boundaries and outmoded thinking, Koshland amalgamated hundreds of faculty

Figure 6 Dan, flanked by three of his protégés—Randy Schekman (left) and Gerry Rubin and Bob Tjian (right), was honored by the Cal Alumni Association with its 1991 Alumnus of the Year Award, which was bestowed at a banquet held at the St. Francis Hotel in San Francisco on March 13, 1992. *Image courtesy of Randy W. Schekman.*

members from well over a dozen former academic units into just three new and large departments—Molecular and Cell Biology; Integrative Biology; and, Plant Biology (now Plant and Microbial Biology). Forging this new organizational structure was no simple matter; it had plenty of initial opposition from some on campus (at one point, bacteriophage expert Richard L. Calendar referred to the plan as the "Disorganization of Bugology at Berserkeley"). In the end, the process took nine years. Formal establishment of the three new life sciences departments (and official dissolution of all the predecessor academic units) occurred on July 1, 1989. The reorganization was accompanied by the construction of new research buildings and the refurbishment of existing buildings. Since then, implementation of these changes achieved its goals of enhancing enormously the reputation of the life sciences at UC Berkeley, thereby promoting the recruitment of top faculty and outstanding graduate students.

In this same regard, Dan also played a critical role in persuading the Howard Hughes Medical Institute (HHMI) to support life sciences faculty pursuing fundamental biomedical research at UC Berkeley, even though the institution has no medical school per se. Until Dan convinced them otherwise, all previous HHMI investigators were ensconced at medical schools. In 1987, however, Robert Tjian became the first HHMI investigator at UC Berkeley. Tij, as he's known by one and all, had been an undergraduate in Dan's laboratory from 1969 until receipt of his baccalaureate degree in 1971 and had been hired back to the Department of Biochemistry faculty in 1979. Also in 1987, Gerald M. Rubin became the second HHMI investigator at UC Berkeley. Gerry had been recruited to the biochemistry faculty at Berkeley in 1983 from his prior position at the Carnegie Institution of Washington in Baltimore. In 1991, the future Nobelist Randy W. Schekman, a UCLA graduate who received his Ph.D. with Arthur Kornberg at Stanford, became the third UC Berkeley scientist to be appointed as an HHMI investigator.

In the ensuing years, Tij not only succeeded Dan as chair of the CACB, he also served as the third president of the HHMI (2009–16). Rubin left Berkeley to become the longtime director of the HHMI Janelia Farm Research Campus in Ashburn, Virginia. As of this writing (August 2023), and in addition to Tjian and Schekman, twenty other UC Berkeley faculty in the life sciences are currently HHMI Investigators, including two other Nobel Prize winners, R. Eric Betzig (Chemistry, 2014) and Jennifer A. Doudna (Chemistry, 2020).

In 1998, the Albert Lasker Special Achievement Award in Medical Science was awarded to Daniel E. Koshland Jr. It cited Dan as "the key faculty leader" in convincing the California legislature (building presumably on the experience he had in the early 1960s testifying before the U.S. Congress) to fund the three building projects that were integral, at the time, to the success of the life sciences reorganization at UC Berkeley. In 2008, shortly after Dan's passing, this same recognition was renamed the Lasker-Koshland Special Achievement Award in Medical Science in Dan's honor. In 1999, Koshland headed the Health Sciences Initiative at UC Berkeley, a capital campaign that was responsible for increased investment in life-science infrastructure. Fundraising was propelled by a $50 million gift from an "anonymous" donor.

The Marian Elliott Koshland Museum and *The Mikado*

Bunny Koshland died of lung cancer on October 28, 1997. Dan was devastated. In her memory and honor and based on discussions with Bruce M. Alberts (then-president of the National Academy of Sciences), Koshland underwrote establishment of the Marian Koshland Science Museum in Washington, D.C. Dan oversaw every aspect of the museum; he wanted the exhibits to be entertaining, topical, and aimed at "Joe Six-Pack." The museum opened in 2004, but in 2017 the decision was made by the NAS to close the museum and replace it with a different emporium with exhibits on modern science and scientific issues that would engage the general public in an accessible way, which the NAS dubbed LabX.

In 2000, Dan married Yvonne San Jule (née Cyr), his classmate from his undergraduate bacteriology class, becoming her third husband. Their first date was seeing the movie *Topsy-Turvy,* about the premiere of Gilbert and Sullivan's *The Mikado* (from which Dan had quoted in his 1996 *Annual Review of Biochemistry* article, "How to Get Paid for Having Fun").[80] Dan did not know that Yvonne came from a family who were great Gilbert and Sullivan fans, but it was fortuitously an excellent choice for their first night out. Yvonne died ten years after Dan on March 29, 2017, at age 94.

Closing Thoughts

According to Dan Koshland, the Seven Pillars of Life are Program, Improvisation, Compartmentalization, Energy, Regeneration, Adaptability, and Seclusion. These words of wisdom were first promulgated by Dan in a *2002 Science* editorial accompanied with a cartoon of the "Temple of PICERAS."[81] Unfortunately, not too many acolytes seem to have stepped forward to worship at this particular shrine.

Dan and I stayed in close contact in the years after I left his laboratory. Dan was glad to hear that I had continued my work on phosphoryl transfer, including determining, with my wife Miriam Hasson, the structure of exopolyphosphatase (one of the favorite enzymes of Dan's close friend Arthur Kornberg) and that of an acetate kinase from a methanogen. He was keen to listen to my ideas about how it might be possible to couple photosynthesis by cyanobacteria to methane generation as the means to produce a clean energy source that could substitute for fossil fuels.

In the late spring of 2007, accompanied by my two youngest sons, Akiva and Yinnon, I visited Dan in his office in Barker Hall. The Dan Koshland I knew and admired was on full display. Dan tried to convince the fifteen-year-old Akiva that he should attend UC Berkeley, and our chat was briefly interrupted by Dan engaging in an animated interview over the telephone with someone from *Wired* magazine about alternative energy (I cannot find any evidence of it being published). Having just seen him so recently, I was heartbroken to learn that Daniel Edward Koshland Jr. died of a massive stroke on July 23, 2007. He was working until the last, doing his utmost to fulfill the prophecy of his first wife, Bunny. It was a privilege to attend the memorial service and the symposium held in Dan's honor, "Induced Fit: The Science and Wit of Daniel E. Koshland Jr.," held on September 16, 2007, at UC Berkeley. Representatives of the campus and all of the attendees displayed their great affection for Dan.

In an article published posthumously in *Science* on August 10, 2007, Dan attempted to propound one last theory and to coin one last new expression.[82] It was entitled the "Cha-Cha-Cha [Charge, Challenge, Chance] Theory of Scientific Discovery." The "charge" component seemed a bit forced, but the "challenge" aspect of science was clear. Tellingly, the "chance" element relied on one of Dan's favorite quotations, an off-hand remark made by the great French chemist and microbiologist Louis Pasteur, whom Dan so admired: "By chance, you might say, but remember that in the fields of observation chance only favors prepared minds." Dan was always one of the "prepared minds."

Note

This biographical memoir is based largely on information taken from several sources. They include Randy Schekman's tribute, "The Nine Lives of Daniel E. Koshland, Jr. (1920–2007)," in PNAS (*Proc. Natl. Acad. Sci. U.S.A.* 104:14551–14552); Robert Tjian's tribute, "Daniel E. Koshland, Jr. 1902–2007" (*Cell* 130:579–580); and the University of California Senate's tribute by Robert Tjian and G. Steven Martin, "In Memoriam: Daniel E. Koshland Jr., Professor of Biochemistry, Emeritus, UC Berkeley, 1920–2007" (Berkeley, Calif.: University of California; https://senate.universityofcalifornia.edu/_files/inmemoriam/html/danielkoshland.html). Additional information came from the UC Berkeley Regional Oral History Office's interview with Daniel Koshland (https://archive.org/details/reorgbiounical00hughrich) and Marian Koshland (https://digitalassets.lib.berkeley.edu/rohoia/ucb/metadata/oralhisttransretro00maririch.html), and his own 1996 retrospective on his life and work, "How to Get Paid for Having Fun" (*Annu. Rev. Biochem.* 65:1–13).

References

1 Guyer, R. L. 2007. Marian Elliott Koshland, 1921–1997. National Academy of Sciences Biographical Memoir, http://www.nasonline.org/publications/biographical-memoirs/memoir-pdfs/koshland-marian-e.pdf.

2 Koshland, M. E., F. Englberger, and D. E. Koshland. 1959. A general method for the labeling of the active site of antibodies and enzymes. *Proc. Natl. Acad. Sci. U.S.A.* 45(10):1470-5.

3 Westheimer, F. H. 1987. Why nature chose phosphates. *Science* 235(4793):1173–1178.

4 Fischer, E. 1894. Einfluss der Configuration auf die Wirkung der Enzyme. *Ber. Dtsch. Chem. Ges* 27(3):2985–2993.

5 Koshland, D. E., Jr. 1958. Application of a theory of enzyme specificity to protein synthesis. *Proc. Natl. Acad. Sci. U.S.A.* 44:98–104.

6 Koshland, D. E., Jr. 1959. Mechanisms of transfer enzymes. In: *The Enzymes,* eds. P. D. Boyer, H. Lardy, and K. Myrback, pp. 305–346. Cambridge, Mass.: Academic Press.

7 Koshland, D. E., Jr., N. S. Simmons, and J. D. Watson. 1958. Absence of phosphotriester linkages in tobacco mosaic virus. *J. Am. Chem. Soc.* 80(1):105–107.

8 Levy, H. M., N. Sharon, and D. E. Koshland Jr. 1959. Purified muscle proteins and the walking rate of ants. *Proc. Natl. Acad. Sci. U.S.A.* 45:785–791.

9 Koshland, D. E., Jr. 1983. The bacterium as a model neuron. *Trends Neurosci.* 6:133–137.

10 Koshland, D. E., Jr., G. Nèmethy, and D. Filmer. 1966. Comparison of experimental binding data and theoretical models in proteins containing subunits. *Biochem.* 5:365–385.

11 Kirtley, M. E., and D. E. Koshland Jr. 1967. Models for cooperative effects in proteins containing subunits. Effects of two interacting ligands. *J. Biol. Chem.* 242:4192–4205.

12 Neet, K. E., and D. E. Koshland Jr. 1966. The conversion of serine at the active site of subtilisin to cysteine: A "chemical mutation." *Proc. Natl. Acad. Sci. U.S.A.* 56:1606–1611.

13 Levitzki, A., and D. E. Koshland Jr. 1969. Negative cooperativity in regulatory enzymes. *Proc. Natl. Acad. Sci. U.S.A.* 62:1121–1128.

14 Levitzki, A., and D. E. Koshland Jr. 1971. Cytidine triphosphate synthetase. Covalent intermediates and mechanisms of action. *Biochem.* 10(18):3365–3371.

15 Haber, J. E., and D. E. Koshland Jr. 1970. An evaluation of the relatedness of proteins based on comparison of amino acid sequence. *J. Mol. Biol.* 50:617–639.

16 Storm, D. R., and D. E. Koshland Jr. 1970. A source for the special catalytic power of enzymes: Orbital steering. *Proc. Natl. Acad. Sci. U.S.A.* 66:445–452.

17 Mesecar, A. D., B. L. Stoddard, and D. E. Koshland Jr. 1997. Orbital steering in the catalytic power of enzymes: Small structural changes with large catalytic consequences. *Science* 277(5323):202–206.

18 Adler, J. 1966. Chemotaxis in bacteria. *Science* 153(3737):708–716.

19 Dahlquist, F. W., P. Lovely, and D. E. Koshland Jr. 1972. Quantitative analysis of bacterial migration in chemotaxis. *Nature New Biol.* 236:120–123.

20 Macnab, R. M., and D. E. Koshland Jr. 1972. The gradient-sensing mechanism in bacterial chemotaxis. *Proc. Natl. Acad. Sci. U.S.A.* 69:2509–2512.

21 Tsang, N., R. Macnab, and D. E. Koshland Jr. 1973. Common mechanism for repellents and attractants in bacterial chemotaxis. *Science* 181:60–63.

22 Strange, P. G., and D. E. Koshland Jr. 1976. Receptor interactions in a signalling system: Competition between ribose receptor and galactose receptor in the chemotaxis response. *Proc. Natl. Acad. Sci. U.S.A.* 73(3):762–766.

23 Spudich, J. L., and D. E. Koshland Jr. 1976. Non-genetic individuality: Chance in the single cell. *Nature* 262:467–471.

24 Springer, W. R., and D. E. Koshland Jr. 1977. Identification of a protein methyltransferase as the cheR gene product in the bacterial sensing system. *Proc. Natl. Acad. Sci. U.S.A.* 74(2):533–537.

25 Stock, J. B., and D. E. Koshland Jr. 1978. A protein methylesterase involved in bacterial sensing. *Proc. Natl. Acad. Sci. U.S.A.* 75(8):3659–3663.

26 Clarke, S., and D. E. Koshland Jr. 1979. Membrane receptors for aspartate and serine in bacterial chemotaxis. *J. Biol. Chem.* 254:9695–9702.

27 Wang, E. A., and D. E. Koshland Jr. 1980. Receptor structure in the bacterial sensing system. *Proc. Natl. Acad. Sci. U.S.A.* 77:7157–7161.

28 Koshland, D. E., Jr. 1977. A response regulator model in a simple sensory system. *Science* 196:1055–1063.

29 Koshland, D. E., Jr. 1974. Chemotaxis as a model for sensory systems. *FEBS Lett* 40:S3-S9.

30 Koshland, D. E., Jr. 1976. Bacterial chemotaxis as a simple model for a sensory system. *Trends Biochem. Sci.* 1(1):1–3.

31 Koshland, D. E., Jr. 1977. Sensory response in bacteria. In: *Advances in Neurochemistry,* eds. B. W. Agranoff and M. H. Aprison, pp. 277–341. New York: Springer.

32 Koshland, D. E., Jr. 1977. A model regulatory system: Bacterial chemotaxis. *Physiol. Rev.* 59(4):812–855.

33 Koshland, D. E., Jr. 1979. Biochemistry and behavior. *Bull. Am. Acad. Arts Sci.* 32(8)49–57.

34 Koshland, D. E., Jr. 1980. Bacterial chemotaxis in relation to neurobiology. *Annu. Rev. Neurosci.* 3:43–75.

35 Koshland, D. E., Jr. 1980. *Bacterial Chemotaxis as a Model Behavioral System.* Distinguished Lecture Series of the Society of General Physiologists, Vol. 2. New York: Raven Press.

36 Koshland, D. E., Jr. 1981. Biochemistry of sensing and adaptation in a simple bacterial system. *Annu. Rev. Biochem.* 50:765–782.

37 Koshland, D. E., Jr. 1983.

38 Adler, J. 1975. Chemotaxis in bacteria. *Annu. Rev. Biochem.* 44:341–356.

39 Berg, H. C. 1975. Chemotaxis in bacteria. *Annu. Rev. Biophys. Bioeng.* 4:119–136.

40 Zukin, R. S., and D. E. Koshland Jr. 1976. Mg2+, Ca2+-dependent adenosine triphosphatase as receptor for divalent cations in bacterial sensing. *Science* 193:405–408.

41 Rubik, B. A., and D. E. Koshland Jr. 1978. Potentiation, desensitization, and inversion of response in bacterial sensing of chemical stimuli. *Proc. Natl. Acad. Sci. U.S.A.* 75:2820–2824.

42 Khan, S., et al. 1978. Inversion of a behavioral response in bacterial chemotaxis: Explanation at the molecular level. *Proc. Natl. Acad. Sci. U.S.A.* 75(9):4150–4154.

43 Koshland, D. E., Jr. 1977. Introduction. In: *Research with Recombinant DNA: An Academy Forum, March 7–9, 1977,* pp. 1–3. Washington, D.C.: National Academy of Sciences.

44 Koshland, D. E., Jr. 1985. Associations and democracy. *Science* 229(4715):711.

45 Koshland, D. E., Jr. 1986. The biotechnology issue. *Science* 232(4756):1313.

46 Thorsness, P. E., and D. E. Koshland Jr. 1987. Inactivation of isocitrate dehydrogenase by phosphorylation is mediated by the negative charge of the phosphate. *J. Biol. Chem.* 262:10422–10425.

47 Goldbeter, A., and D. E. Koshland Jr. 1981. An amplified sensitivity arising from covalent modification in biological systems. *Proc. Natl. Acad. Sci. U.S.A.* 78:6840–6844.

48 Stock, J. B., A. M. Maderis, and D. E. Koshland Jr. 1981. Bacterial chemotaxis in the absence of receptor carboxylmethylation. *Cell* 27(1, Part 2):37–44.

49 Sanders, D. A., B. Mendez, D. E. Koshland Jr. 1989. *J. Bacteriol.* 171(11):6271–6278.

50 Stock, J., G. Kersulis, and D. E. Koshland Jr. 1985. Neither methylating nor demethylating enzymes are required for bacterial chemotaxis. *Cell* 42:683–690.

51 Stock, J. B., A. M. Maderis, and D. E. Koshland Jr. 1981.

52 Stock, J. B., and D. E. Koshland Jr. 1981. A cyclic mechanism for excitation and adaptation. *Curr. Top. Cell. Regul.* 18:505-17.

53 Stock, A., D. E. Koshland Jr., and J. Stock. Homologies between the *Salmonella typhimurium* CheY protein and proteins involved in the regulation of chemotaxis, membrane protein synthesis, and sporulation. *Proc. Natl. Acad. Sci. U.S.A.* 82:7989–7993.

54 Ninfa, A. J., and B. Magasanik. 1986. Covalent modification of the glnG product, NRI, by the glnL product, NRII, regulates the transcription of the glnALG operon in *Escherichia coli*. *Proc. Natl. Acad. Sci. U.S.A.* 83(16):5909–5913.

55 Hess, J. F., et al. 1987. Protein phosphorylation is involved in bacterial chemotaxis. *Proc. Natl. Acad. Sci. U.S.A.* 84(21):7609–7613.

56 Hess, J. F., et al. 1988. Phosphorylation of three proteins in the signaling pathway of bacterial chemotaxis. *Cell* 53(1):79–87.

57 Hess, J. F., R. Bourret, and M. Simon. 1988. Histidine phosphorylation and phosphoryl group transfer in bacterial chemotaxis. *Nature* 336:139–143.

58 Koshland, D. E., Jr. 1951. Kinetics of peptide bond formation. *J. Am. Chem. Soc.* 73(9):4103–4108.

59 Degani, C., and P. D. Boyer. 1973. A borohydride reduction method for characterization of the acyl phosphate linkage in proteins and its application to sarcoplasmic reticulum adenosine triphosphatase. *J. Biol. Chem.* 248(23):8222–8226.

60 Sanders, D. A., et al. 1989. Identification of the site of phosphorylation of the chemotaxis response regulator protein, CheY. *J. Biol. Chem.* 264(36):21770–21778.

61 Milburn, M. V., et al. 1991. Three-dimensional structures of the ligand-binding domain of the bacterial aspartate receptor with and without a ligand. *Science* 254(5036):1342–1347.

62 Koshland, D. E., Jr. 1989. Animal rights and animal wrongs. *Science* 243(4896):1253.

63 Koshland, D. E., Jr. 1989. Blank check laws. *Science* 243(4891):585.

64 Koshland, D. E., Jr. 1989. Scientific literacy. *Science* 230(4724):391.

65 Koshland, D. E., Jr. 1986. A new look. *Science* 231(4733):9.

66 Koshland, D. E., Jr. 1989. Interview with a risk expert. *Science* 244(4912):1529.

67 Koshland, D. E., Jr. 1989. Interview with a disaster expert. *Science* 246(4935):1221.

68 Koshland, D. E., Jr. 1990. The addictive personality. *Science* 250(4985):1193.

69 Koshland, D. E., Jr. 1991. Waste not, want some. *Science* 252(5005):485.

70 Koshland, D. E., Jr. 1991. Stress for success. *Science* 252(5011):1353.

71 Koshland, D. E., Jr. 1992. The attractiveness of gloom. *Science* 255(5042):265.

72 Koshland, D. E. Jr. 1991. The land of the dammed. *Science* 254(5034):917.

73 Koshland, D. E., Jr. 1992. A campaign for science. *Science* 258(5087):1419.

74 Koshland, D. E., Jr. 1987. Fraud in science. *Science* 235(4785):141.

75 Bridges, C. D., and R. A. Alvarez. 1987. The visual cycle operates via an isomerase acting on all-trans retinol in the pigment epithelium. *Science* 236(4809):1678–1680.

76 Bourne, H. R., D. A. Sanders, and F. McCormick. 1990. The GTPase superfamily: A conserved switch for diverse cell functions. *Nature* 348:125–132.

77 Bourne, H. R., D. A. Sanders, and F. McCormick. 1991. The GTPase superfamily: Conserved structure and molecular mechanism. *Nature* 349:117–127.

78 Koshland, D. E., Jr. 1989. The molecule of the year. *Science* 246(4937):1541.

79 Koshland, D. E., Jr. 1987. Epidemics and civil rights. *Science* 235(4790):729.

80 Koshland, D. E., Jr. 1996. How to get paid for having fun. *Annu. Rev. Biochem.* 65:1–13.

81 Koshland, D. E., Jr. 2002. The seven pillars of life. *Science* 295(5563):2215–2216.

82 Koshland, D. E., Jr. 2007. The cha-cha-cha theory of scientific discovery. *Science* 317(5839):761–762.

Selected Bibliography

1949 With J. C. Kroner and L. Spector. Peroxides of plutonium and thorium. *National Nuclear Energy Series* 14B(Pt. 1):731. Washington, D.C.: United States Atomic Energy Commission.

With F. H. Westheimer. Fermentation of glucose-1-C^{14}. *J. Am. Chem. Soc.* 71:1139.

1952 Effect of catalysts on the hydrolysis of acetyl phosphate. Nucleophilic displacement mechanisms in enzymatic reactions. *J. Am. Chem. Soc.* 74:2286–2292.

1953 With E. Clarke. Mechanism of hydrolysis of adenosine triphosphate catalysed by lobster muscle. *Nature* 171:1023.

1958 Application of a theory of enzyme specificity to protein synthesis. *Proc. Natl. Acad. Sci. U.S.A.* 44:98–104.

1959 With M. E. Koshland and F. Englberger. A general method for the labeling of the active site of antibodies and enzymes. *Proc. Natl. Acad. Sci. U.S.A.* 45:1470–1475.

With H. M. Levy and N. Sharon. Purified muscle proteins and the walking rate of ants. *Proc. Natl. Acad. Sci. U.S.A.* 45:785–791.

1961 Mechanisms of transfer enzymes. In: The Enzymes, Rev. Ed., eds. P. D. Boyer, H. Lardy, and K. Myrback, pp. 305–346. Cambridge, Mass.: Academic Press.

1962 The comparison of non-enzymic and enzymic reaction velocities. *J. Theor. Biol.* 2:75–86.

With J. A. Yankeelov Jr. and J. A. Thoma. Specificity and catalytic power in enzyme action. *Fed. Proc.* 21:1031–1038.

1964 With M. Burr. Use of "reporter groups" in structure-function studies of proteins. *Proc. Natl. Acad. Sci. U.S.A.* 52:1017–1024.

1965 With H. R. Horton. A highly reactive colored reagent with selectivity for the tryptophan residue in proteins. 2-hydroxy-5-nitrobenzyl bromide. *J. Am. Chem. Soc.* 87:1126–1132.

1966 With G. Nèmethy and D. Filmer. Comparison of experimental binding data and theoretical models in proteins containing subunits. *Biochem.* 5:365–385.

With K. E. Neet. The conversion of serine at the active site of subtilisin to cysteine: A "chemical mutation." *Proc. Natl. Acad. Sci. U.S.A.* 56:1606–1611.

1967 With M. E. Kirtley. Models for cooperative effects in proteins containing subunits. effects of two interacting ligands. *J. Biol. Chem.* 242:4192–4205.

With J. E. Haber. Relation of protein subunit interactions to the molecular species observed during cooperative binding of ligands. *Proc. Natl. Acad. Sci. U.S.A.* 58:2087–2093.

1969 With A. Levitzki. Negative cooperativity in regulatory enzymes. *Proc. Natl. Acad. Sci. U.S.A.* 62:1121–1128.

1970 With J. E. Haber. An evaluation of the relatedness of proteins based on comparison of amino acid sequence. *J. Mol. Biol.* 50:617–639.

1970 With D. R. Storm. A source for the special catalytic power of enzymes: Orbital steering. *Proc. Natl. Acad. Sci. U.S.A.* 66:445–452.

1972 With F. W. Dahlquist and P. Lovely. Quantitative analysis of bacterial migration in chemotaxis. *Nature New Biol.* 236:120–123.

With R. M. Macnab. The gradient-sensing mechanism in bacterial chemotaxis. *Proc. Natl. Acad. Sci. U.S.A.* 69:2509–2512.

1973 With N. Tsang and R. Macnab. Common mechanism for repellents and attractants in bacterial chemotaxis. *Science* 181:60–63.

1974 With P. Lovely, F. W. Dahlquist, and R. Macnab. An instrument for recording the motions of microorganisms in chemical gradients. *Rev. Sci. Instrum.* 45:683–686.

1976 Bacterial chemotaxis as a simple model for a sensory system. *Trends Biochem. Sci.* 1:1–3.

With J. L. Spudich. Non-genetic individuality: Chance in the single cell. *Nature* 262:467–471.

With R. S. Zukin. Mg2+, Ca2+-dependent adenosine triphosphatase as receptor for divalent cations in bacterial sensing. *Science* 193:405–408.

1977 A response regulator model in a simple sensory system. *Science* 196:1055–1063.

1978 With B. A. Rubik. Potentiation, desensitization, and inversion of response in bacterial sensing of chemical stimuli. *Proc. Natl. Acad. Sci. U.S.A.* 75:2820–2824.

With S. Khan, R. M. Macnab, and A. L. DeFranco. Inversion of a behavioral response in bacterial chemotaxis: Explanation at the molecular level. *Proc. Natl. Acad. Sci. U.S.A.* 75:4150–4154.

With J. Y. J. Wang. Evidence for protein kinase activities in the prokaryote *Salmonella typhimurium. J. Biol. Chem.* 253:7605–7608.

1979 With S. Clarke. Membrane receptors for aspartate and serine in bacterial chemotaxis. *J. Biol. Chem.* 254:9695–9702.

1980 With E. A. Wang. Receptor structure in the bacterial sensing system. *Proc. Natl. Acad. Sci. U.S.A.* 77:7157–7161.

1981 With J. B. Stock. A cyclic mechanism for excitation and adaptation. *Curr. Top. Cell. Regul.* 18:505–517.

With J. B. Stock and A. M. Maderis. Bacterial chemotaxis in the absence of receptor carboxylmethylation. *Cell* 27(1, Part 2):37–44.

With A. Goldbeter. An amplified sensitivity arising from covalent modification in biological systems. *Proc. Natl. Acad. Sci. U.S.A.* 78:6840–6844.

1983 The bacterium as a model neuron. *Trends Neurosci.* 6:133–137.

With A. F. Russo. Separation of signal transduction and adaptation functions of the aspartate receptor in bacterial sensing. *Science* 220:1016–1020.

1984 With T. C. Terwilliger. Sites of methyl esterification and deamination on the aspartate receptor involved in chemotaxis. *J. Biol. Chem.* 259:7719–7725.

With D. O. Clegg. The role of a signaling protein in bacterial sensing: behavioral effects of increased gene expression. *Proc. Natl. Acad. Sci. U.S.A.* 81:5056–5060.

1984 With A. Goldbeter. Ultra-sensitivity in biochemical dystems controlled by covalent modification. Interplay between zero-order and multi-step effects. *J. Biol. Chem.* 259:14441–14447.

1985 With J. Stock and G. Kersulis. Neither methylating nor demethylating enzymes are required for bacterial chemotaxis. *Cell* 42:683–690.

With A. Stock and J. Stock. Homologies between the *Salmonella typhimurium* CheY protein and proteins involved in the regulation of chemotaxis, membrane protein synthesis, and sporulation. *Proc. Natl. Acad. Sci. U.S.A.* 82:7989–7993.

1987 With P. E. Thorsness. Inactivation of isocitrate dehydrogenase by phosphorylation is mediated by the negative charge of the phosphate. *J. Biol. Chem.* 262:10422–10425.

With J. J. Falke. Global flexibility in a sensory receptor: A site-directed cross-linking approach. *Science* 237:1596–1600.

1988 With R. M. Weis. Reversible receptor methylation is essential for normal chemotaxis of Escherichia coli in gradients of aspartic acid. *Proc. Natl. Acad. Sci. U.S.A.* 85:83–87.

With D. L. Milligan. Site-directed cross-linking. establishing the dimeric structure of the aspartate receptor of bacterial chemotaxis. *J. Biol. Chem.* 263:6268–6275.

1989 With G. R. Moe and G. E. Bollag. Transmembrane signaling by a chimera of the Escherichia coli aspartate receptor and the human insulin receptor. *Proc. Natl. Acad. Sci. U.S.A.* 86:5683–5687.

With D. A. Sanders and B. Mendez. Role of the CheW protein in bacterial chemotaxis: Overexpression is equivalent to absence. *J. Bacteriol.* 171:6271–6278.

With D. A. Sanders et al. Identification of the site of phosphorylation of the chemotaxis response regulator protein, CheY. *J. Biol. Chem.* 264:21770–21778.

1990 With J. H. Hurley et al. Regulation of an enzyme by phosphorylation at the active site. *Science* 249:1012–1016.

With A. C. Newton. Phosphatidylserine affects specificity of protein kinase C substrate phosphorylation and autophosphorylation. *Biochem.* 29:6656–6661.

1991 With M. V. Milburn et al. Three-dimensional structures of the ligand-binding domain of the bacterial aspartate receptor with and without a ligand. *Science* 254:1342–1347.

1992 With D. A. Sanders, B. L. Gillece-Castro, and A. L. Burlingame. Phosphorylation site of NtrC, a protein phosphatase whose covalent intermediate activates transcription. *J. Bacteriol.* 174:5117–5122.

1997 With A. D. Mesecar and B. L. Stoddard. Orbital steering in the catalytic power of enzymes: small structural changes with large catalytic consequences. *Science* 277:202–206.