Comment

A truly titanic figure in science

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I almost had this month's column finished when I got the news; then I knew I had to write a different one. The news was that Dan Koshland, one of the truly titanic figures in American science in the past 50 years, had died of a massive stroke at age 87 on Monday, 23 July.

Dan always said that his ambition was to die young as old as possible. He succeeded: very few people, of any age, have had a younger heart or a more open mind. He went the way we should all go: suddenly, while still sharp and having fun. In fact, he called his delightful autobiographical sketch "*How to get paid for having fun*" (Koshland DE: *Annu Rev Biochem* 1999, **65:**1-13), and few scientists have enjoyed themselves more. His scientific accomplishments were vast, ranging from the development of fundamental concepts in enzymology to important advances in understanding sensory transduction through his work on bacterial chemotaxis. He managed to combine a gift for theorizing with a talent for clever but rigorous experiments - a feat that few have done so well. And throughout it all he gave the impression that he was just a kid playing with his favorite toy.

He was my friend for over 30 years. I first met him when I was a graduate student in England and he was on sabbatical there. I knew who he was, of course - he was already famous for his work on enzymes. In the late 1950s, he did a series of experiments on the enzyme hexokinase that were incompatible with the rigid 'lock-and-key' picture of how an enzyme works that had stood as dogma for half a century. To explain his results he formulated what he called the "induced fit" theory, invoking a moderately flexible enzyme fitting itself to a moderately flexible substrate. This revolutionary advance in our thinking about how enzymes work was greeted with resounding skepticism, which Dan recalled with the relish of the vindicated in his wonderful essay "*Crazy, but correct*" (Koshland DE: *Nature* 2004, **432:**447). He also had demonstrated the phenomenon of absolutely negative cooperativity (where the binding of a ligand to one subunit of a multi-subunit enzyme completely blocks binding to another, identical subunit) and had proposed an alternative model for allostery to the 'all-or-nothing', symmetrical model of Monod, Wyman and Changeux. Dan's 'sequential' model, in which some subunits can be in the tense (or T) state while others are in the relaxed (R) state is now generally acknowledged to be correct, at least for some allosteric proteins. At the time we met he had just started to

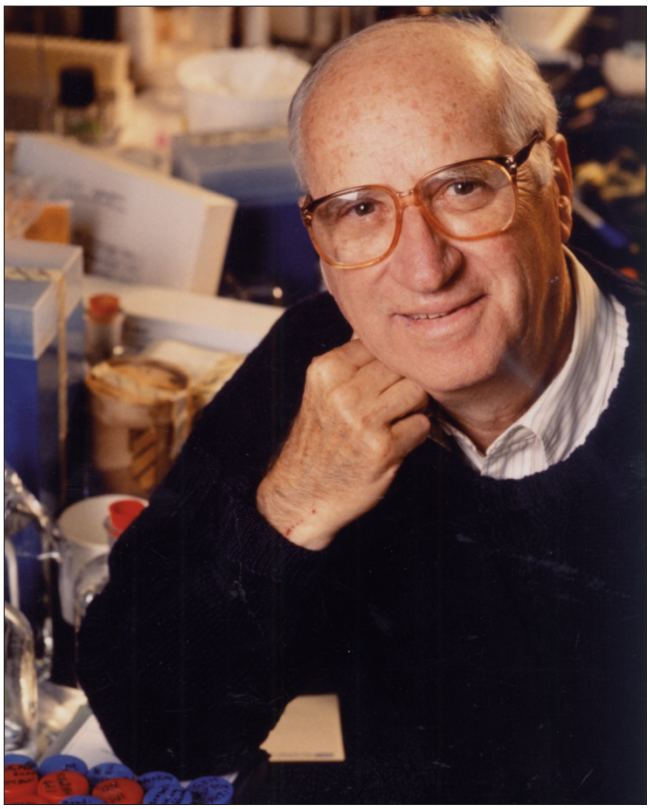

Figure 1
Daniel Koshland, circa 1991. Image courtesy of Robert Holmgren (UC Berkeley News).

work on bacterial chemotaxis, a field that had been dominated for decades by beautiful genetics from the likes of Julius Adler but which was lacking in any molecular description of how a chemical signal generated a change in behavior. Over the succeeding 20 years, Dan and his students and postdocs, bringing not just the tools but also the quantitative rigor of the enzymologist to bear on the problem, delineated the structures and mechanisms of all of the major players in this pathway. Dan's enthusiasm for this new foray into cell biology - a field seemingly light years removed from his biochemical research - made a deep impression on me, and was largely responsible for my own effort to learn yeast genetics many years later so I could study the problem of cellular quiescence. ("Petsko," he said, when I told him of my plans, "I see you have learned a valuable lesson from me: if you have no conscience whatsoever, you can ruin more than one field in your lifetime.") At the time of his death he was excited about yet a new venture, an effort to use light energy to improve the efficiency of ethanol production from plant material. Biofuels has been something of a stodgy field in recent years; can there be any doubt that it would have become much livelier - and more scientifically interesting - with Dan Koshland in it?

For some reason he took a liking to me, and to my ideas. I wasn't his student - there was nothing in it for him - but nevertheless he became one of my biggest supporters over the years (I suppose he has that to answer for, somewhere). Time and time again something good would happen to me and I would find out later that Dan was behind it. From the day we met in England until the day he died, I always felt like he was there for me, and I can't describe how important that was. We often don't realize the influence we have over others. We're supposed to be supportive of the people who work with us, but sometimes it's the support we give the stranger, the casual scientific acquaintance, that has the greatest influence. When a senior scientist, especially one of any eminence, takes an interest in a younger colleague, it can have a transforming effect on that person's life and career. I've been fortunate to have had several such supporters in my life, and they've made a huge difference. It doesn't take much, really: the right words at the right time, a phone call or e-mail, a remark dropped in the right ear, a willingness to write that letter or visit that poster or attend that talk. Who knows what, if anything, I meant to Dan Koshland? I sure know what he meant to me.

I didn't know for many years that Dan was fabulously wealthy - he was one of the heirs to the Levi-Strauss clothing fortune. Everybody was surprised when they learned that, because he was among the most down-to-earth people you would ever meet. He wore his wealth like he wore his scientific distinction: casually, unostentatiously. He used it well, too: he helped build several buildings - at Berkeley, where he taught since 1965, and in Washington, where he provided a major gift to endow the Marian Koshland Science Museum of the National Academy of Sciences, named after his wife Marian (Bunny), herself a distinguished scientist (in immunology). The couple were also the lead donors to the Marian E Koshland Integrated Science Center at Haverford College, which their two sons attended.

In 1985 he accepted the position of editor-in-chief of the journal *Science*. These days, when *Science* is considered one of the highest-profile places in which to publish biological research, it's hard to believe that it was once not even on the top twenties list, but that was indeed the situation when Dan took over. If you wanted to publish basic life sciences research in a high-impact journal, you published in *Nature*. Dan set out to change that, and did so, spectacularly. He created a board of reviewing editors with heavy emphasis on the biological sciences, brow-beat (charmingly, of course) his friends (including me) into publishing their hottest stuff there, and so changed the perception of the biological community that, by the time the first genome sequence of a free-living organism was completed, in 1995 by Claire Fraser, Craig Venter and their associates, *Science* was considered the most prestigious place for US life scientists to publish earth-shaking discoveries - as in fact, they did (Smith *et al.*: *Science* 1995, **269:**495-511). *Science* continued to lead the way in publishing new genome sequences for some time, although *Nature* soon caught up. But Dan had changed the journal completely, and much for the better.

He told me that the only reason he took the job, which required him to fly to the East Coast almost every week for ten years, was so that he would have a place where they had to publish his little musings on any subject that took his fancy. Numerous times each year, he wrote editorials for the front of the journal - remarkable short essays on topics ranging from spousal abuse to the Clinton Administration's science appointments. They were always a delight to read - still are, after all these years. They're funny, insightful, irreverent, and candid. Dan never hesitated to speak his mind but managed to do it in an offhand, witty way that was both charming and effective. His style and fearlessness had a big influence on me when I decided to do this column (so I guess that's something else he has to answer for). Here's an excerpt from an editorial he wrote on the scientific funding crisis of 1990: "What is important is to think big about 'little science'. There will undoubtedly be some megaprojects, but what the nation and the world really need is a major expansion of investigator-initiated science, because that historically has been the source of great discoveries that have opened new frontiers." (Is anybody in Washington listening today?)

Dan was a big supporter of genomics, including the human genome project. In 1989, when support for this biological Manhattan Project was highly controversial, this is what he said in one of his *Science* editorials: "We must be vigilant

about ethical concerns but not paralyzed by outlandish scenarios. The belief of biologists that studying simple organisms such as *Escherichia coli*, flies, and rats is relevant to human physiology and behavior has been brilliantly confirmed. But there are differences. One cannot extrapolate carcinogenic potency from the mouse to the rat with precision, and even less to the human. Some diseases involve speech and mental states unique to man. Sequencing the human genome puts us on the threshold of great new benefits and some real but avoidable risks. There are immoralities of commission that we must avoid. But there is also the immorality of omission - the failure to apply a great new technology to aid the poor, the infirm, and the underprivileged. We must step boldly and confidently across the threshold."

Dan was the doyen of biochemistry but nevertheless always behaved like, and loved, the maverick. "Later in life," he wrote a few years ago, "when I became editor-in-chief of the journal *Science*, my early experience allowed me to keep a friendly eye out for the non-conformist. But does science have any lessons for non-conformism in other spheres, such as politics and religion? Non-conformity is looked on with more hostility by religion, government and culture than by science - because each of them is more vulnerable to change than science is. The other segments of our society have yet to find a better mechanism for encouraging non-conformity to achieve progress, while still controlling non-conformity to prevent chaos. Science has achieved the best balance, but it must fight to preserve this and serve as a beacon to other sectors of our society." He was 85 when he wrote that.

I last saw him a month ago, at a dinner in New York. "Petsko," he said when he saw me (he never called me Greg, not once in 35 years), "what mischief are you up to now?" He actually looked disappointed when I told him I was being good.

I loved him greatly. I can't imagine what my life would have been like without his encouragement, enthusiasm, and interest. I know it would have been poorer. After he started to show his physical age a few years ago, I made it a point, every time I saw him, of telling him how much his friendship meant to me. Now I think I still didn't say it often enough.