

Douglas Koshland



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Doug Koshland lives by his father's observation that, "scientists overestimate their worldly fame. If you really want to be famous, you should become the mayor of a small town in Iowa with a population of 10,000. Then if you measure strictly by number counts, you would be far more famous as mayor than almost any scientist in the world." An HHMI Investigator at the Carnegie Institution of Washington's Department of Embryology in Baltimore, Koshland admits to minor fame only in the close-knit, global "village" of cell biologists interested in chromosome cohesion and condensation.

Yet the field is an important—and hotly contested—one today, in no small part, according to Koshland's friends and colleagues, because of Koshland's pioneering efforts. "In the early-to-mid 1990s, Doug helped to define and crack open the field of chromosome condensation and cohesion, first in yeast, by developing methods to watch yeast chromosomes, and then by applying genetic screens to identify the molecules involved," says Dan Gottschling, who was a post-doc contemporary in Seattle with Koshland.

"Doug was one of the first to understand that chromosome condensation was a real problem that could be separated from everything else that was going on during cell division," affirms Marc Kirschner. Koshland did his second post-doc in Kirschner's UCSF lab. When Koshland first took on chromosome condensation, Kirschner says, he was wading into deep waters. "We've always known that something was making chromosomes stick together until just the right moment, but most people thought that the mechanism was probably so complicated that there was no feasible way to get at it. But with his genetic screens and analysis, Doug led us to the view that you could study the problem of cohesion as an independent piece. You didn't have to understand all aspects of chromosome function. Because of Doug's work and the work of others, we've made rapid progress."

As obscure as it may seem outside scientific circles, understanding chromosome cohesion and condensation is critical to human health and development, says Gottschling. "Condensation is the idea of taking a string that's six feet long down to about three inches. Cohesion is the idea that if you have a string—a chromosome—six feet long and replicate it, the two strings have to hang onto each other until mitosis when they get dragged in opposite directions." Among other things, condensation is what allows chromosomes to roll and unroll the yards of DNA within the nucleus so their genetic instructions can be implemented. Cohesion is what binds sister chromosomes as error-free copies until the precise moment in cell division when they can be safely separated. Mistakes, mutations or damage in these fundamental chromosome functions are thought to be at the heart of many diseases, including cancers.

The medical implications are important and immediate, says Koshland, in understanding, for example, multi-drug resistance or breakdowns in DNA repair. But chromosome function is so fundamental, it offers insight into wider biological

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Doug Koshland's own chromosomes are full of science. His father, Daniel E. Koshland, Jr., worked on the Manhattan Project, served on the faculties of Brookhaven, Rockefeller University, and UC Berkeley, and won renown (and the Lasker Prize) for his "induced fit" theory of enzyme interaction. He also served as Editor-in-Chief of *Science*, from 1985 to 1995. Doug's mother, the noted UC Berkeley immunologist

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Marian Elliott Koshland (also a Manhattan Project and Brookhaven veteran) discovered that antibodies differ in their amino acid composition, helped elucidate the assembly of IgM antibodies, and settled forever the question of antibody diversity through “selection.” (The recently opened Marian Koshland Science Museum at the National Academy of Sciences in Washington, DC, is Daniel Koshland’s tribute to his wife, who died in 1997.)

Douglas Koshland was born in 1953 on Long Island. He moved when he was 12 to the San Francisco Bay Area when his parents took up faculty positions at Cal. The youngest of their five children, Doug Koshland recalls that, “My parents didn’t want any of us to become scientists.” They succeeded with his older siblings (although one sister did become a kinesiologist later in life) but, says Koshland, with him, “My mom got too tired trying to direct the fifth child into something else.”

Doug Koshland attended Haverford, a small liberal arts college in Pennsylvania. There, he found his own style as a scientist and, just down the road at Bryn Mawr, he also found his future wife, biology student Mary Porter. When Koshland became a graduate student of David Botstein’s at MIT, Porter took a job as a lab technician with Harvey Lodish. It was in Botstein’s lab that Koshland first learned the ingenious uses of genetics in parsing cell structure and mapping genetic linkages.

So it was not surprising that Koshland took a post-doc in the genetics-based lab of Leland Hartwell at the University of Washington. There, Mary Porter switched disciplines, enrolling in a graduate program in landscape architecture. Today, Porter helps direct capital improvement programs for the City of Baltimore’s Parks & Recreation Department. They have three children: Eliza, 21, who is finishing her degree in architecture and urban planning at Barnard; Sophia, 18, who is exploring her interests in chemistry and art at Haverford, and Benjamin, 15, who is a sophomore at Baltimore City College High School, a public school magnet program, where he pursues “anything involving a ball—basketball, baseball, football,” says his father, who admits to similar jock tendencies at 15.

An ASCB member since 1992, Koshland serves on the Society’s Public Policy Committee. He remembers, “When I joined the Committee, I didn’t have a particular axe to grind. The

other members assured me that I would soon develop one.” Today Koshland works on the Committee’s full range of issues, from stem cells to NIH funding, but, true to premonitions of his colleagues, he has developed special concerns about the future of science education and about protecting “small science.” He believes that cultivating creativity and independence in small research settings pays off in scientific breakthroughs. He notes that while many Nobel laureates eventually have large labs, the seminal work that led to their prize was almost invariably done when their groups were small. Koshland feels that his home institution exemplifies the tremendous success of “small” science. The Carnegie is a one-of-a-kind place, says Koshland, which suits his personal and scientific style perfectly.

While continuing its cohesion and condensation work, Koshland’s lab has recently taken a new tack to examine chromosome integrity in the context of genome evolution, by using yeast hybrids to create artificial chromosomes of non-existent—until now—yeast species. Koshland hopes for insights into disperse repetitive DNA, whole-genome duplication, sequence divergence, and protein buffering. He also expects some collegial needling. “When you say that you’re going to work on evolution, a lot of people take it as an indication that you’re over-the-hill and approaching the end of your career. Still, I think the value of these experiments is that they may tell us interesting things about cell biology, even if they don’t tell us much about evolution. If you look at cell biology through a different set of glasses, you may see things that no one ever noticed before.”

Evolution research aside, Dan Gottschling doesn’t see his friend winding up his career anytime soon. “Doug is one of the good guys in science today,” says Gottschling. “As this business of biological research has become more and more competitive, I’ve never seen him do or even hint at doing anything self-serving. Doug remains genuinely interested only in the advancement of science and in the advancement of other people. He’s a great role model.” ■

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