Cell

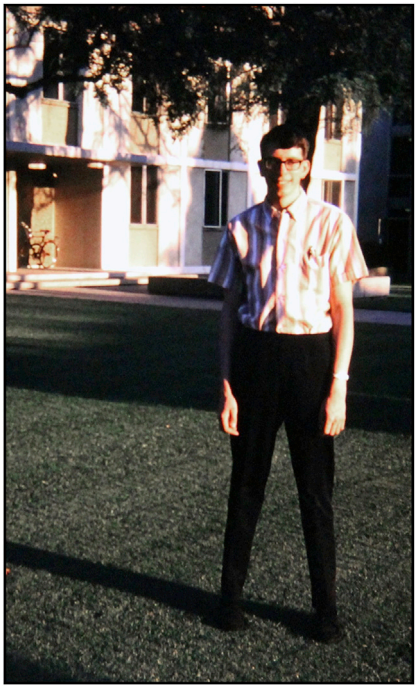
Ronald J. Konopka (1947–2015)

Ron Konopka was found dead of an apparent heart attack in his Pasadena, CA home on February 14, 2015. Konopka was my close contemporary and began graduate school at Caltech in 1967. He published his thesis work along with his mentor Seymour Benzer in what is perhaps the single most influential paper in circadian rhythms (Konopka and Benzer, PNAS *68*, 2112–2116). The field has spent much of the subsequent 45 years deciphering the meaning and validating (over and over again) the importance of this Rosetta stone. It began the modern era of circadian biology and is the cornerstone of my own circadian career. As if this were not enough, it is arguably *the* landmark paper in behavioral genetics writ large.

Benzer moved from Purdue to Caltech in the mid-60s and began this field; the physical move paralleled an intellectual move from prokaryotic genes to the underpinnings of behavior. He is properly credited with combining simple behavioral screens with the power of *Drosophila* genetics. The strategy could associate single mutations and the underlying genes with a behavioral phenotype. Although Benzer accumulated a coterie of talented students and post-docs to join him in this grand adventure, Konopka was the first. Moreover, he brought the circadian problem to Benzer rather than vice versa, and Ron designed as well as carried out the primary screen used to search for circadian mutants. The clock causes adult flies to eclose (emerge from the pupal case) at or shortly after dawn; this rhythmic emergence continues in constant darkness, with about 24 hr periodicity. The screen therefore searched for mutant flies that eclose in aberrant fashion and was remarkably successful. Ron found a short period mutant (about 20 hr), a long period mutant (about 30 hr) and an arrhythmic mutant.

Three striking features of the 1971 Konopka and Benzer paper led them to propose that the mutants were central to circadian rhythms. First, the three mutants affected not only the eclosion rhythm but also an independent circadian rhythm feature, locomotor activity, which also exhibited a short period, a long period, or arrhythmicity. Second, genetic analysis indicated that all three mutations were alleles of a single gene, which they named *period.* The more expected result would have been three different genes each giving rise to the very different circadian phenotypes of fast, slow, or no rhythm; the finding of a single gene suggested that only a small number of gene products might be running the circadian clock. Third and most intriguingly, the results indicated that this single protein was of key importance for circadian timing, as it could mutate to a fast-running protein (short period) or a slow-running protein (long period) as well as being necessary for rhythmicity.

It took another 15 years for recombinant DNA and DNA sequencing to allow molecular characterization of the *period* gene and its protein, which verified some of these much earlier implications. For example, the short and long period alleles were determined to be missense mutations that altered the protein, whereas the arrhythmic mutation was a stop codon that prevented synthesis of the protein. Subsequent dynamic assays from many labs continue to this day and show that the short and long period alleles really do speed up and slow down the clock pace in ways that are being understood in considerable mechanistic detail. The *period* protein is also conserved in mammals. Although there are certainly some functional differences between the mammalian *period* proteins and the fly protein, one cannot overstate the extent to which the conclusions from Konopka and Benzer (1971)—drawn strictly from phenotypic and genetic studies—were prescient for the entire circadian field and all of its subsequent molecular sophistication.



Ronald J. Konopka

Konopka did a post-doc at Stanford with the circadian biology pioneer Colin Pittendrigh and then was hired back at Caltech as an Assistant Professor in 1974.

Although publication requirements were much less onerous 40 years ago than today, Konopka was denied tenure based on his thin publication record from those assistant professor years. Nonetheless, important work from his lab was published at the end of his Caltech stay. Although these papers substantially added to the characterization of the *period* gene and its importance to circadian biology, they were deemed too late or insufficient to impact the tenure decision.

Konopka moved to Clarkson University in the early ’80s. He had maintained a warm relationship with my long-time Brandeis collaborator Jeff Hall since their Caltech days and was important to our initial efforts to clone and identify the *period* gene. We were amateurs in the assays of locomotor rhythms, and Ron made sure that our first transgenic flies with wild-type *period* DNA constructs were indeed rhythmic. So we had truly rescued the arrhythmic behavior of the mutant host strain and had the gene in hand. Konopka continued to publish and was on track to receive tenure at Clarkson, but his promotion was apparently derailed by changed academic priorities at the university. He returned in 1990 to the small Pasadena house he had purchased while at Caltech.

Although Ron spent his last 25 years out of academic science, he began tutoring high school students in math and science after his return to Pasadena. According to his friend and former Benzer post-doc Larry Kauvar, “he was genuinely

fascinated by what makes science hard for some people and easy for others.'' This long-standing commitment to teaching, along with a sardonic wit and broad interests, also contributed to his popularity as a Caltech professor, including by non-biologists. His hobbies included a first-rate butterfly collection as well as perhaps a thousand Grateful Dead concert tapes.

Few people know that Ron also played a seminal role in the beginnings of the Hereditary Disease Foundation. Milton Wexler, a psychoanalyst in Los Angeles, had begun to search for ways to attack Huntington's disease (HD), an illness that affected his wife's family. Wexler consulted with Benzer, who proposed in 1971 that Wexler hire his then 23-year-old graduate student Konopka. His task was to seek out talented people to attend a workshop and potentially pursue research on HD. Konopka was so successful that Wexler hired him as the first Scientific Director of the organization that eventually became the Hereditary Disease Foundation. According to Alice Wexler, ''Ron filled this post with his characteristic imagination and intelligence for several years. He played a wonderfully creative role in the history of the Hereditary Disease Foundation, and his legacy lives on to this day.''

Although Konopka participated only marginally in the molecular revolution that overtook behavioral genetics and fueled the remarkable progress of the circadian field since the mid-80s, his initial work was essential. The same is true for precious few researchers. Indeed, most scientists would fail the ''deletion-test,'' a term coined by Gerry Rubin to describe a scientist's contributions by imagining what the field would be like had he/she not existed. The same cannot be said of Konopka and his bold, revolutionary screen. That paper proved a very hard act to follow.

Sydney Brenner, and apparently J.D. Bernal before him, compared science to chess. They emphasized that the two games most worth playing are the opening game and the end game. Konopka and Benzer played the ultimate opening game. As Benzer died in 2007, Ron Konopka's death closes this remarkable and singular chapter in the history of circadian rhythms, sadly the end of the beginning.

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