Profile of Jeffrey C. Hall

When geneticist Jeffrey C. Hall looks back on his career path, he offers praise for each of the personalities he has encountered, from his deaf undergraduate advisor to his fellow Civil War scholars—not to mention the small, elegant, and urbane fruit fly. "They're very complex organisms, quite sophisticated and interesting," he says of *Drosophila*, the neurobiology and behavior of which have occupied his research since college.

To Hall, *Drosophila* are valuable for more than just their easily manipulated genomes. As he grew to "love the fly," he also began to delve into the insect's genetics, neurobiology, and behavior at a deep level. Convinced of the worth of analyzing *Drosophila* mutants for studying behavior, Hall has dedicated his career to probing the neurobiological underpinnings of the fly's courtship and behavioral rhythms. His research with *Drosophila* genetics has elucidated the mechanisms of biological clocks and opened a window into the basis for sexual differentiation in the nervous system.

Hall, a Professor of Biology at Brandeis University (Waltham, MA), was a recipient of the Genetics Society of America Medal in 2003, the same year he was elected to the National Academy of Sciences. His Inaugural Article in this issue of PNAS (1) investigates the *fruitless* gene, which controls behavior such as the recognition by a male of whom he might "choose" to court and courtship singing behavior, by analyzing the behavioral meaning of this gene's expression within various regions of the nervous system.

Jeffrey C. Hall

Small and Simple Research

Born in Brooklyn, NY, Hall grew up in the suburbs of Washington, D.C., where his father worked as an Associated Press reporter, covering the U.S. Senate. His father's attitude permeated his consciousness in many ways, Hall says, causing him to, for example, "read more than just the sports section each morning." A good but not stellar student in high school, Hall planned to attend medical school when he entered Amherst College (Amherst, MA) in 1963. Halfway through earning his bachelor's degree, however, he found his curiosity for medicine replaced by one for basic science.

For his senior honors project, Hall hoped to gain experience in formal research and began working with Philip Ives, a genetics researcher who studied fruit flies. Ives, who had been a student of geneticist Albert Sturtevant, lost his hearing in graduate school and was relegated to a non-tenure-track research career that included shepherding undergraduate students like Hall through small projects. Yet Ives excelled as a researcher and was dedicated to his mentoring role. He exhorted his students to "love the organism," Hall says. "This sort of resonated, because I really did like the little fruit flies. They're extremely appealing, one reason being that they're small and cute, as silly as this may seem." As a model for research, *Drosophila* strike a good balance of qualities, Hall points out, in that they are small enough to handle in large numbers, large enough to facilitate observations, and simple enough to yield large amounts of data but "not so pathetically simple as to be dreary and boring."

With Ives, Hall spent a year studying recombination and translocation induction in *Drosophila*. This research project, which Hall describes as "intrinsically rather silly," turned out well, and department faculty took notice, recommending that he pursue graduate studies at the University of Washington (Seattle), which had the unusual distinction of having an entire department devoted to genetics. "I applied there, just following orders," Hall says, "but I'm glad I did, because they were absolutely right."

A Push Down the Coast

When Hall arrived in Seattle in 1967, he already knew he wanted to join the *Drosophila* laboratory of Lawrence Sandler, also a research descendent of Sturtevant's. Hall worked with Sandler on several research projects, starting with the analysis of age-dependent enzyme changes in *Drosophila* (2) but with a main focus on the genetic control of chromosome behavior in meiosis (3).

After a few years of research, Hall was summoned into the office of Herschel Roman, the department's founder, chair, and longstanding father figure. Roman took a sharp interest in the fate of his department's students, and he recommended that Hall do postdoctoral work with Seymour Benzer at the California Institute of Technology (Pasadena, CA). Hall knew Benzer to be a highly regarded geneticist who had moved from research on bacterial viruses during the 1960s to study behavioral genetics and neurogenetics. Benzer's signature approach was to induce random mutations in fruit flies, screen them for noteworthy behavioral characteristics, and then use the genes defined by these mutations to dig as deeply as possible into the neurobiology of such behaviors.

Roman phoned Benzer as Hall sat in his office, and two days later Hall was on a plane down to southern California to interview with Benzer. At the end of the brief visit, Benzer offered him a

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 16550.

spot in his laboratory, and Hall finished his doctoral work and moved to Benzer's laboratory in 1971.

Universal Slices of Courtship

Hall soon realized that Benzer ran "a lab where you make your own way," in which students and postdoctoral fellows were encouraged to pursue research independently. Benzer's main suggestion to Hall was to work with Doug Kankel, another postdoctoral fellow in the laboratory. Hall found Kankel to be replete with detailed knowledge of *Drosophila* biology that extended to neuroanatomy and neurochemistry, all of which Hall gratefully absorbed. The pair began collaborating on two projects, both of which progressed surprisingly well, Hall says (4, 5).

Hall left Benzer's laboratory before publishing any results, however. During Hall's third postdoctoral year, Roman called from Seattle to say that he had been lobbying on Hall's behalf for open faculty positions at the University of Missouri (Columbia, MO) and Brandeis University. Such promotion was a generous act of faith on Roman's part, Hall says, because Roman was unfamiliar with Hall's research in California. Brandeis University offered Hall a faculty position, and he joined the university as an Assistant Professor of Biology in 1974.

At Brandeis, Hall carried forward the momentum of his work with Kankel, who by that time was working at Yale University (New Haven, CT). A particularly intriguing research thread sprang from an offhand suggestion from Kankel during Hall's last months in California. They had been generating fruit fly sex mosaics—organisms part male and part female—and staining them to determine which nerve cells were male and which were female. Kankel mentioned that they should be examining each mosaic before dissection to see whether male or female courtship patterns were present. From such observations, they would have been able to correlate courtship behaviors with genetic sex in various regions of the nervous system, which Hall eventually accomplished during his early years at Brandeis.

That casual comment triggered Hall's interest in this area, and his subsequent career path of investigation into the neurogenetics of *Drosophila* courtship was born. Before long, Hall saw that findings from this research could carry greater significance beyond insight into insect rituals. "The male gets interested in the female, gropes her with his forelegs, follows her around and sings to her, and licks her posterior region," he says. "When you describe *Drosophila*

Male *Drosophila* following and courting a female by singing to her.

courtship, anybody who is listening instantly knows what you're talking about." Yet Hall was mindful of the conservative academic nature of many biologists at the time, and he kept these inchoate hopes for greater human significance largely to himself.

Transatlantic Songs

Hall's study of *Drosophila* courtship behavior eventually encompassed the male's courtship song, a pattern of sounds emitted from a male's vibrating wings as he follows a female. In the mid-1970s, Hall began collaborating with Florian von Schilcher at the University of Munich to correlate song qualities with genetic sex. Hall generated *Drosophila* mosaics and shipped

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them to von Schilcher, each housed with a bit of food in its own glass vial. von Schilcher recorded and analyzed the flies' songs before sending them back to Hall. Hall then dissected and stained the flies that survived the double cross-Atlantic journey. It was an arduous experiment, Hall says, but it allowed them to map nervous system regions that helped contribute to the regulation of courtship song (6).

Hall decided to bolster the song component of his laboratory's research. "I realized from this study that courtship singing behavior is one of the exquisitely quantifiable features of courtship, well worth delving into further," he says. In the late 1970s, Bambos Kyriacou joined Hall's laboratory as a postdoctoral fellow from England to work specifically on the neurogenetics of singing behavior. Kyriacou's analyses revealed that the *Drosophila* courtship song is produced rhythmically with a normal periodicity of about one minute. When Hall saw these findings, he recalled the *period* mutants generated by Ronald J. Konopka in the late 1960s in Benzer's laboratory. Konopka's mutants displayed daily sleep–wake rhythms deviating from the 24-hour cycle, and so Hall suggested to Kyriacou that they check whether these mutants had altered courtship song cycles as well. In basketball terms, this suggestion was "throwing up a prayer," Hall says. "It was crazy. There was no reason to think that the control of this one-minute rhythm would have anything to do with the regulation of daily rhythms."

To their surprise, Hall and Kyriacou found that the *period* mutations affected the courtship song just as they changed the circadian rhythms, by stretching, shrinking, or obliterating both cycles similarly (7). Using the then-emerging tools of molecular genetics, Hall, Kyriacou, and Michael Rosbash, a colleague at Brandeis University, set out to isolate the *period* gene.

Cracking the Case of Circadian Rhythms

Hall and his colleagues used fruit fly molecular genetics to study biological clocks, but traditional circadian rhythm researchers had long preferred a nongenetic approach using a variety of organisms. "Many of them loudly and publicly denounced the genetic approach to study rhythms," Hall says. He now considers this a mixed blessing, in that the distaste of some researchers for molecular genetics kept the number of competitors to a minimum. The only other group also hunting for the *period* gene was Michael Young's laboratory at The Rockefeller University (New York), which had been prompted by Young's previous analyses of *Drosophila*'s chromosomal region in the vicinity of the *white* gene, near which *period* is located.

In 1984, Hall and his colleagues found and isolated the *period* gene (8), roughly at the same time as did Young's group (9). Soon after the *period* gene was cloned, its protein product was found not to be a homolog of any known protein. "It was just this total mystery sequence of amino acids," Hall says. "We had to keep plugging away experimentally, not just descriptively, to try to figure out what it was about." Eventually, Hall's group, working closely with that of Rosbash, started to understand the role of the pacemaker cells in the fly's brain and the oscillation of *period*'s protein in them. They elucidated the selfsustained autoregulatory feedback loop that provided the core of the circadian clock mechanism (10, 11). A few years later, the gene was found to have homologs in many other animals, including humans.

Cloning *period* provided the spark that ignited current circadian rhythm research. "Molecular, neurobiological, and behavioral studies of *period* ended up cracking the case of circadian rhythms," Hall says. "The outcome of these studies made circadian rhythms no longer one of these strange biological mysteries on the Third Rock."

Behind *fruitless* Courtship

Hall's studies of sex-specific behavior have prominently involved the *fruitless* gene. The *fruitless* mutant was identified in the 1960s but had been neglected until Hall began studying it during his last few months at the California Institute of Technology. This mutant was behaviorally sterile: a *fruitless* male would court both females and males indiscriminately but not try to mate with either. "They're not homosexual, as some think. They're bisexual," Hall says.

From the late 1970s through the early 1990s, Hall's group studied the *fruitless* gene solely from behavioral genetic and anatomical perspectives (12–14). Then, in the early 1990s, Bruce Baker at Stanford University (Stanford, CA) proposed to Hall that they collaborate with Barbara Taylor at Oregon State University (Corvallis, OR) and clone *fruitless*. They isolated the gene in the mid-1990s (15), at about the same time as did Daisuke Yamamoto's laboratory in Japan (16).

Cloning *fruitless* paved the way, showing it acted as what might be termed a master regulator gene for courtship (17). "Taking into account effects of the several *fru* mutations, almost every feature of male courtship is controlled by this gene," Hall says. "Moreover, a portion of nearly every region of the nervous system is making the *fruitless* gene product. For example, *fruitless* expressed in the brain almost certainly influences whether a *Drosophila* male can discern that a companion fly is an appropriate courtship object."

Hall's PNAS Inaugural Article takes a step toward probing the behavioral significance of *fruitless*'s expression within various portions of the central nervous system (1). Adriana Villella, a senior research scientist in Hall's laboratory, led the study, which manipulated the function of *fruitless* neurons within defined subsets of the nervous system. "It's trying to take the case of *fruitless* and analyze the behavioral meaning of the gene product's presence in various neural regions a little bit deeper than just descriptive inferences," Hall says.

Historical Back Roads

Hall is spending the summer and fall of this year on sabbatical at the University of Maine (Orono, ME), living in a house "in the middle of nowhere." Whenever possible, he makes the journey to campus on his Harley-Davidson motorcycle, one of a series of different models he has owned over the last decade. Not only does it make this 100-mile round-trip commute "infinitely less doleful than trundling along" in a car, Hall says, the hazards of motorcycle riding force him to concentrate on the road "moment by moment," leaving no time to worry about the usual grinding agonies that might await in the laboratory.

At Brandeis University, some students encounter Hall only through the history department, where he has been teaching a course devoted to the Battle of Gettysburg. Hooked on the subject after a family trip to the battlefield in 1983, Hall plunged into 19th-century history books and became acquainted with several Civil War historians. In 1994, he achieved minor celebrity among the Civil War set when he enticed a group of 250 visiting Princeton University molecular biologists to take a full-day tour of the battlefield with him, complete with a packet of accompanying maps. The incongruous scene seemed to aptly characterize Hall, and it was recounted in Jonathan Weiner's popular science book *Time, Love, Memory*, which chronicled the career of Seymour Benzer and his research descendents (18). After this tour, Hall's Civil War interests continued apace with guest lectures, the Brandeis University course, and even a textbook on Gettysburg, published in 2003 (19).

Hall's passionate approach to the Civil War is not unlike his genetic investigations. By way of explaining the appeal of Gettysburg, Hall quotes a letter from his acquaintance and prominent Civil War historian James McPherson, "You [Hall] . . . like me, apprehend viscerally as well as intellectually the meaning of the Civil War. And nowhere can this . . . be grasped more meaningfully than at Gettysburg." Hall might claim the same sentiment about *Drosophila* and his scientific research: nowhere can the deeply conserved behaviors of courtship and circadian rhythms be better understood than in the humble fruit fly.

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