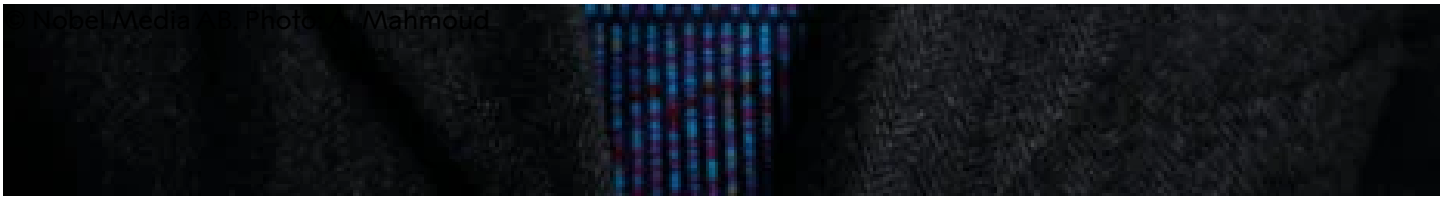

Jeffrey C. Hall
The Nobel Prize in Physiology or Medicine 2017

Born: 3 May 1945, New York, NY, USA

Affiliation at the time of the award: University of Maine, Maine, ME, USA

Prize motivation: “for their discoveries of molecular mechanisms controlling the circadian rhythm”

Prize share: 1/3

Life

Jeffrey Hall was born in Brooklyn, New York, and grew up outside of Washington, DC. After studies at Amherst College, he went on to the University of Washington in Seattle, where he earned his doctor’s degree in 1971. After a stay at the California Institute of Technology in Pasadena, he began work in 1974 at Brandeis University in Waltham, Massachusetts.

Work

In our cells an internal clock helps us to adapt our biological rhythm to the different phases of day and night. Jeffrey Hall, Michael Rosbash and Michael Young studied fruit flies to figure out how this clock works. In 1984 they managed to identify a gene that encodes a protein that accumulates during the night but is degraded during the day. They also identified additional proteins that form part of a self-regulating biological clockwork in the fruit fly's cells. The same principles have been shown to apply to other animals and plants.

To cite this section
MLA style: Jeffrey C. Hall – Facts. NobelPrize.org. Nobel Prize Outreach AB 2023. Tue. 29 Aug 2023. <https://www.nobelprize.org/prizes/medicine/2017/hall/facts/>

Nobel Prizes and laureates

Nobel Prizes 2022

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Jeffrey C. Hall

Biographical

Jeffrey C. Hall was born in Brooklyn, New York, near the end of World War II (in Europe). His parents, fortunately for him, were among rare young adults in the U.S. who achieved college educations during the Depression. Hall's father used his higher education credentials to become a journalist, his mother a school teacher. These are arguably mindful vocations, and they promoted a mindful atmosphere in Hall's home when he was growing up, without there being any indoctrination and probably without Hall himself necessarily being aware of this salutary environment.

Eventually, what Hall's father achieved vocationally caused him to work in Washington, D.C., covering the United States Senate along with presidential campaigns. Thus his offspring were raised mostly in a Maryland suburb of Washington. The aforementioned intra-home atmosphere (enhanced by how interesting it was for Hall to absorb information from his father about politics, society, and their historical contexts) made it axiomatic that he and his two siblings would attend college. Hall

did so, beginning in 1963, and became a Biology major at Amherst College (Amherst, Massachusetts). A key element of this experience stemmed from his desire to do "Senior Honors" research. This caused Hall to be assigned, as his Honors supervisor, Dr. Phillip T. Ives. The latter had, by then (mid1960s), been a longstanding *Drosophila* geneticist. Though Hall was unaware of the following during his college stint: Ives was a distinguished such geneticist then and later, as Hall learned during his post-undergraduate time.

In any event, Ives was an excellent mentor, who not only instructed his small number of undergrad supervisees superbly, but also imbued them with a fervent interest in basic research generally and *Drosophila* genetics in particular. As Hall was performing a low-level genetics project at that college, his Biology Department superiors (including Ives) recommended that he try to become a graduate student at the University of Washington in Seattle. This advice came Hall's way in the context of an incipiently well-regarded Genetics Department having been established at "U-Dub" (W = double U). Hall took heed of those college-based recommendations and enrolled at U-Dub in 1967. Soon after joining the Genetics Department there, he joined (in turn) the laboratory of Prof. Larry Sandler. The latter was an excellent *Drosophila* geneticist, who like Ives happened to be a direct descendant of Thomas Hunt Morgan. Morgan, along with his students at Columbia University in New York, were pioneers who founded, sustained, and expanded the fruit-fly genetics "system," during the 19-teens and subsequent decades.

Within U-Dub's Genetics Department, Sandler's – and Hall's – leader was Professor Herschel Roman, founder and longstanding Chair of that department (1959–1980). Roman fostered departmental norms that promoted high-quality instruction, training, and mentoring. In this regard, "Hersch" was well acquainted, professionally and personally, with almost all members of his department. The interest he took accordingly caused him to pull Hall aside, albeit not by singling him out. In any case, Hersch recommend that Hall try for a postdoctoral position in the laboratory of Seymour Benzer, California Institute of Technology (CalTech, a.k.a. CIT) in Pasadena where, more than incidentally, Morgan's lab had moved from New York in the late 1920s. For Benzer's part, by the early 1970s, he had established a second career, after initiating his genetically-based vocation via "pure" genetic studies of microbes. Along with Seymour *also* moving to CalTech in the mid-1960s, he shifted his interests and activities into the nascent sub-field of behavioral-cum-neuro-genetics. Benzer chose *Drosophila*, possibly influenced by the famed "fly group" that had long been ensconced there. Morgan was dead – as was one of his famed students, Calvin Bridges (Columbia -> CalTech) – but the equally famed Alfred Sturtevant remained alive, as was the latter's student (then CIT Professor) Edward Lewis.

Back to Roman's intra-departmental office at U-Dub: That Chair's recommendation – in person to Hall *and* on the telephone to Benzer – about the former doing a postdoc in the latter's lab led to Hall joining that CIT group during the late summer of 1971.

For a few months thereafter, Hall was fortunate to overlap with one of Benzer's senior grad students, Ronald (Ron) J. Konopka. That investigator had made himself into a "chrono-geneticist," taking a genetic approach to study biological timing, viz. daily rhythms. Thus, as Konopka was completing his thesis project (PhD, 1972), Hall became vividly aware of what Ron had been doing and spectacularly accomplishing: Induce from scratch, via application of a chemical mutagen, novel mutants in *Drosophila melanogaster* that would potentially manifest abnormalities or anomalies of such rhythmicity (including that which is exhibited at the level of fruit-fly adult behavior: rest/activity cycles, normally manifested via ca. 24-hour cycle durations). Ron's mutant hunting, followed by high-quality analysis of the rhythm-based phenotypes *and* mutational genotypes, was stunningly successful. This was based in large part upon Konopka inducing and identifying a magnificent trio of novel mutants: one that displayed only 19-h daily cycles (in constant darkness), a 29-h mutant, and a third (the original) that was arrhythmic, a.k.a. aperiodic. Ron named these variants *period* mutants, formally justified, for he demonstrated that each of the three mutations involved newly induced changes within *one D.* melanogaster *gene* (famously abbreviated *per* and pronounced "purr" as opposed to "peer").

During these heady days of the early 1970s, Hall could not help become a fan of Konopka's research, owing to the findings themselves, and against a recent background that caused him previously to become aware of daily rhythmicity in *Drosophila*. Exposure to the relevant phenomena – including that fly cultures maintain daily rhythms in constant darkness, in which condition they display what are known as a "circadian" rhythm" – occurred when Hall was a student in a college course; its instructor happened to include a module about circadian rhythms manifested by "emerging flies" (metamorphosis ->

adulthood = “eclosion”). That Assistant Professor at Amherst College had recently completed his PhD thesis research in the laboratory of Colin Pittendrigh (Princeton University, New Jersey), whereby the latter was becoming one of the “grand old men” of rhythm-related research. However, neither Pittendrigh nor anyone else had brought any definitive *Drosophila* genetics to bear on studies of these eclosion rhythms. At all events Hall was fortunate, by coincidence, to be attuned to the way that Ron Konopka pioneered a genetic approach to asking “what is a circadian clock?” That quoted phrase alludes to the notion that Konopka’s novel variants seemed for all-the-world to be *clock* mutants, as the relevant publication, co-authored by Benzer, was entitled. Implicitly, if a mutation (actually two) can change the circadian-cycle duration in a constant environmental condition, that smacks of a “pacemaker” problem. The noun just quoted had been invoked in context of organisms of all kinds displaying daily rhythmicities of all kinds, including behavioral; and that such biological (physiological, biochemical, etc.) cycling persists in the absence of daily earth cycles, notably light:dark ones. Implication: Central pacemakers harbored *within organisms* underlie such rhythmicity. This kind of pacemaker can be regarded as synonymous with “the circadian clock,” as it was initially inferred to exist via a plant experiment (-> animal studies, including of invertebrates and mammals, -> microbes as well).

Aside from the rhythm-related sub-enterprise extant within Benzer’s lab, Hall’s own research there from fall 1971 to the end of 1973 did not involve time-based phenomena. Instead: neurochemical ones as well as a project involving genetic “mosaics.” The latter genotype entailed *Drosophila* that were each part-male (one X chromosome)//part-female (XX) and with the two kinds of chromosomal genotype marked phenotypically via “histochemical” genetic marking (one-X cells, including CNS neurons, unstained for an enzyme reaction; 2X ones stained). Hall’s mentor, trainer, and co-worker for these projects was a fellow postdoc in the laboratory of Benzer, whose supervisory actions tended toward *laissez-faire,* named Douglas Kankel (Brown University, Providence, Rhode Island -> CIT, -> Yale University, New Haven, Connecticut). Doug taught his labmate a whole lot about *Drosophila* biology, including neurobiology, against a background of Hall having previously done genetic (qua genetic) studies alone. The latter did manage to bring to his pair of Benzer-lab projects genetic expertise, involving a heavy dose of *chromosome manipulations* in the context of many types of such being afforded by the “lore of *Drosophila*,” harking back to Morgan and his students.

Shortly after Hall’s postdoc stint entered its third year, by which time his co-worker Kankel had moved to Yale as noted above, he received invitations to interview for Assistant Professorships at two U.S. universities: U. Missouri (Columbia) and Brandeis U. (Waltham, MA). These invites were promoted by none-other-than Herschel Roman, who had recently visited those two institutions and recommended that his former mentee be considered for faculty-level jobs. So Hall can never forget nor fail to appreciate how meaningful to him was Prof. Roman’s career-sponsoring support (1967–1971; then intra-1973).

After traveling for the interviews just referred to, Hall received job offers from both of the universities in question, initially from Brandeis. That offer led him to begin an Assistant Professorship there, winter 1974. Hoping to get some research going there – at this near-Boston locale – he continued the pair of projects that had been maturing at CalTech around the time when Kankel and then Hall moved across the United States from Southern California (U.S.). This collaborative association continued for a while, “Back East,” facilitated by both fledgling faculty members being located in New England. These two former Benzer lab members put forth publications presenting the neurochemical-genetic and nervous-system mosaic findings in 1976. Yet Hall and Kankel had published zero primary papers during their postdoc stints, during an era when that kind of ostensible non-productivity could nonetheless lead to faculty jobs; nowadays, applications for such must be accompanied by massive publication-ridden CVs.

One aspect of Hall’s lab studies at Brandeis University involved *courtship* behavior in *Drosophila*. The starting point was to observe and quantify courtship capacities of the aforementioned sex mosaics: Which portions of the neuro-histochemically marked CNSs had to be genetically male (or female) if a given mosaic would perform one or more elements of the sex-specific, courtship-behavioral sequence? This category of behavioro-neuro analysis proceeded to a merger of genetic-mosaic principles and practices with neurochemically *disrupting* mutations, stemming from the other project Hall and Kankel had performed, starting at CalTech. The rather complex “mosaic dissection” experiment in question, based at Brandeis, was initiated in Hall’s lab by him and a postdoc who joined it during the late 1970s: C.P. (Bambos) Kyriacou. A key reproductive-behavioral phenotype recorded during this study was a male-like courtship song (normally produced by a standard XY fly’s wing vibrations, put forth when he follows a female, ramping up toward eventually attempting to mate with her). Bambos’s and Hall’s question: Which types of mosaics – set up to be each all-male, but with some tissues neurochemically mutated,

others normal – might sing abnormally, putatively correlated within intra-CNS locations of the neurochemical deficit? But this project ended up dying on the vine, because of the following: Kyriacou and Hall also recorded (with microphones and magnetic tape) the singing behavior of *control* males: siblings of the mosaics, whereby such XY controls were uniformly normal for their neurochemistry. Analyzing visually appreciable renditions of the auditory recordings led to their inability to discern supposedly canonical "song parameters," previously but cavalierly reported by the early song recorders, who had been working mostly in the U.K.

By virtue of enhanced labor, Bambos broke down and analyzed the entirely of each several-minute recording; thus he pulled-out long series of relevant computations, concentrating on a key song parameter: rate of tone-pulse production (per series of 10-second bins). He therefore discerned that that singing element seemed to be fluctuating systematically. Further analyses revealed, indeed, that the rate in question oscillated rhythmically: speeding up, slowing down, speeding up again; with a cycle duration of about one minute for *D. melanogaster* free of behavioral/neural mutations. Next step, during the micro-era in question (late 1970s): Kyriacou and Hall wondered whether the only known rhythm-affecting mutations in "our" species might by-some-chance alter song rhythmicity. Hall, especially, knew that those variants were Ron Konopka's *circadian* mutants (n=3, harking back to the latter's PhD thesis project). So Hall wrote Dr. Konopka, asking for culture copies of Ron's mutants, even though the Brandeis researchers were aware that circadian rhythmicity and song such are defined by cycle durations three orders of magnitude different from each other. Yet, Konopka's *per* mutations – two of which caused altered cycle durations, the third causing arrhythmicity – were found to alter courtship-song cycling in ways paralleling effects of these genetic variants on daily rhythms.

So Hall's admiration for Konopka's chrono-genetic accomplishments and a coincidental matter of the former being instructed in a college course about biological rhythms in *Drosophila*, prompted that lab head at Brandeis, and others there, to enter an arena defined by actual chronobiological lab work. Meanwhile, a close colleague of Hall in Waltham, MA – then Associate Professor Michael Rosbash – had previously become aware of the Konopka mutants. After Hall and Rosbash met during 1974, the former could not help mention that banner study (emanating from his former postdoc lab) and speak highly of it; even though neither Hall nor Rosbash had any mid-'70s interest in doing anything about *per* mutants or the gene defined by them. Nonetheless, Rosbash also became well acquainted with Bambos Kyriacou, as the second half of the 1970s unfolded, enhancing the former's appreciation for the *period* gene's existence.

A few years later in the early 1980s, an experimental question suggested itself, whereby the *per* gene would have to be identified and isolated at the DNA level.

To make a medium-length story short as to how that question arose: We fantasized about "cloning *per*" from *D. melanogaster* (*mel*), using that DNA readily to do the same for *per* in the close interspecific relative *D. simulans* (*sim*), then transferring the latter into *mel* to ask whether such a single-gene infusion would bring with it regulation of *sim*-like singing rhythmicity. As of the early '80s, Kyraicou and Hall had found that *sim* and *mel* males generate species-specific song-cycle durations *and* that the genetic etiology of this difference mapped to the same chromosome on which *per* is located.

Therefore, and initially *not* based on a specific interest in *circadian* rhythmicity in *Drosophila*, the researchers at Brandeis with material help from Kyriacou and from Konopka himself, set out to isolate *period*-locus DNA and identify it via behavioral bioassays: introduction of putative *per* DNA into *per*-mutant "hosts" carrying the arrhythmia-inducing mutation. This new project was rooted in an incipient, close collaboration between the laboratories of Hall and of Rosbash at Brandeis, augmented by the two sending behaviorally-pertinent strains to professional locations where the "two K" guys had ended up as of the mid-'80s.

This multi-lab effort eventually ballooned *as* its interests shifted mainly into the *daily*-rhythm arena. The researchers began to so study via multi-pronged approaches: behavioral genetics, cyto-genetics (application of chromosome aberrations), molecular genetics, and neuro-genetics. For Hall's and Rosbash's part, it was meaningful that they had become close not only professionally but also personally: respectively, related to co-awareness that Hall was a generic fruit-fly geneticist; and Rosbash was a generic molecular biologist, initially studying vertebrates and yeast from the mid-'70s into the '80s. In addition, these two faculty members shared various personal interests, mostly revolving round low-culture stuff. Might their

association – including separate, seemingly complementary, scientific backgrounds – promote a fruitful joining of forces: chrono-genetics deepening into the molecular-genetic area?

As this bi-lab collaboration at Brandeis got started and proceeded, the two were operating in competitive parallel with *per*-molecular studies performed in the lab of Mike Young (Rockefeller University, New York). Mike had become at least marginally interested in circadian rhythms affected by *period* mutations back when he was a graduate student in the 1970s, mainly studying other bio-genetic phenomena in *Drosophila*.

The *tri*-lab deal – a pair of collaborating groups plus one competing with the former two – began to work out. As of approximately the mid'80s, a quartet of publications (two from Massachusetts, two from New York) reported *probable* cloning of *per*, followed by nailing that matter via DNA-mediated "rescue" of the relevant *per*-mutational effects, as alluded to above. Hall maintains that a companion piece in this volume, based on his Nobel Prize lecture in late 2017, usefully recounts sufficient additional features of these early-days stories, along with presenting the requisite background information from the 1970s and earlier.

No doubt the lecture-based articles by Profs. Rosbash and Young will flesh out all additionally relevant aspects of this history. Meanwhile, some quasi-editorial remarks, partly coming under the header of Hall tooting his own biographical horn; as well, what follows may usefully divulge some historical stuff, referring to the post-'80s era: In this respect, and in Hall's experience plus opinion, it is possible to get carried away with "the primacy of *per*": yes, the first clock gene cloned in any organism. Gene #2 of this type was identified at that level in *Neurospora* five years later. Could one clock factor, the PER protein, tell the whole fruit-fly story insofar as the circadian-pacemaker mechanism was concerned? A priori, no. Realizing this, Hall and associates such as Rosbash and Young "did Konopka's" of their own, spearheading renewed searches for rhythm-related genes in *Drosophila*, whose products could be gleaned to contribute materially to said mechanism. Such mutant hunting was set-up to involve chromosomes extending beyond the one where *period* is located.

As elaborated citationally within Hall's "lecture article," this tri-lab endeavor led to identification of Young's *timeless* (*tim*) gene, which encodes a PER companion; and *doubletime* (*dbt*), whose encoded enzyme influences the dynamics of PER protein "cycling." Now *per* and *tim* must be transcriptionally activated, of course, before their first-stage products (mRNAs) can go up and down each day. Indeed, although perhaps anti-climactically, the Hall/Rosbash crew – including several valued co-workers (grad students, post docs, and others) – induced behavior-arrhythmia-inducing mutations at loci named *Clock* (*Clk*) and *cycle* (*cyc*), which also lead to very low levels of *period* and *timeless* products. Neither *Clk* nor *cyc* mutations (loss-of-function "alleles") kill developing *Drosophila*; same for *per* or *tim* "nulls," but unlike *dbt* ones, the latter gene being a developmentally vital one with pleiotropic effects. Thus, *Clk* and *cyc* – whose transcrioton-factor products co-associate to turn-on both *per* and *tim* transcription – can be regarded as semi-dedicated to rhythm-regulating processes.

Discovery of all these core clock factors in *Drosophila* was rooted in mutant hunting. Yet, extending beyond that core, circadian clocks must also receive inputs from the environment, e.g., so that these only *circa*-dian pacemakers can be subjected to daily re-sets, thus underpinning 24.0-hour cycle durations in natural conditions. One conspicuously acting input factor in *Drosophila* came to the fore thanks to yet another hunt for mutants performed by Hall and co-workers, which resulted in identification of a light-absorbing molecule called CRY. It is encoded by the mutationally defined *cry* gene, whose encoded protein – when activated by photic stimuli – "touches" TIM to promote the latter's degradation during the falling phase of *tim*-product cycling. Now the core clock also has to do more than spin its internal wheels, plus be sensitive to external stimuli. Therefore *output pathways* must project from central-pacemaking functions, ultimately to mediate revealed rhythmicity (behavior, physiology, and much more overall). Starting with performance of *molecular*-genetic tactics, many output-gene candidates in *Drosophila* were uncovered at Brandeis and Rockefeller, plus within farther-flung research groups. One such gene, which encodes a brain neuropeptide, comprised a fruit of such searching at Brandeis; contributed to gaining insights about "outputs from the clock;" then was exploited molecular-genetically, neuro-genetically, and behaviorally by Hall's research group and several others. The latter came to be composed of an ever-expanding venture, extending well beyond investigative activities occurring originally at only a small number of institutions. This swelling phenomenon included a variety of "other-directed" investigators, referring to how their careers started, dropping much of what they had been doing in order to start studying *Drosophila* chronobiology and that of other-organismal rhythms.

Hall could not help summarize elements of this post-*per* research, although the meaning of that seminal gene continued to be elucidated well past the mid-1980s. At a minimum, successful searching for further factors – notably at Brandeis and Rockefeller during the 1990s – signifies that these (dare we say) molecularly pioneering labs were serious about their hope to flesh-out rather robust understandings of the overall rhythm-related deal.

By analogy to entering what he just did, Hall comes near the end of this biog by inserting a partly personal coda: He has long regarded the *genetic* side of the overall enterprise to be extremely consequential, exemplified by what was just outlined within recent passages: so many "clock players" found in *Drosophila* via pheno-genetic screenings. So the attack on fruitfly chronobiology has had a lot to do with variant genotypes and associated *pheno-genetics* (to re-invoke an arcane term, meaning rhythm-related effects of genic variants, chromosomally based ones, and molecular "clones"). Conversations between Hall and Rosbash, and among other associates, have stimulated Rosbash to say that "the molecular biology made all the difference."

Fair enough: Truly no one could have anticipated, for example, what *period*-gene products are about, absent "cloning *per*" then empirically analyzing the encoded RNA & protein (involving way more than sequencing the gene and describing PER protein on paper, hoping forlornly that that description alone would divulge much at first-blush). *In addition*, genotypic and phenotypic elements of the eventual extravaganza (momentarily factoring out molecular matters as a *gedanken* consideration) have been rate-limiting investigatively, in Hall's opinion. For his part, and in order potentially to "do anything" chrono-wise, he relentlessly sensed appreciation for genetically based interactions with and mentoring by his early-career associates: Ives, Sandler, Roman, Lewis, Kankel, and Konopka.

If Hall had not been fortunate enough to come straight out of the T.H. Morgan tradition of *Drosophila* genetics, he wonders in retrospect whether he could have contributed to the overall behavioral/neurobiological/chronobiological enterprise in some sort of meaningful manner. Prof. Young *might* sense something similar. Although he was not a molecular-geneticist in his early pre-postdoc days, he too is a direct descendant of Morgan, via Young's PhD research in a laboratory headed by an academic great-grandson of a fruit-fly-genetics pioneer. Hall has noticed, for instance, that Young merged with élan his molecular-genetic expertise with *Drosophila* cyto-genetics (matters revolving round the latter having been absorbed by that student of the fruit-fly in advance of Young beginning to focus heavily on biological rhythms and circadian clocks). Maybe Hall, as well, was able to tap into the aforementioned "lore of *Drosophila*," influencing ways that he helped sustain the chronobiological endeavor at hand, in part via some sort of genetic diligence.

From *The Nobel Prizes 2017*. Published on behalf of The Nobel Foundation by Science History Publications/USA, division Watson Publishing International LLC, Sagamore Beach, 2018
This autobiography/biography was written at the time of the award and later published in the book series *Les Prix Nobel/ Nobel Lectures/The Nobel Prizes*. The information is sometimes updated with an addendum submitted by the Laureate.

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To cite this section
MLA style: Jeffrey C. Hall – Biographical. NobelPrize.org. Nobel Prize Outreach AB 2023. Tue. 29 Aug 2023.
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