

A Nobel Pursuit May Not Run like Clockwork

Living in rural Maine, Jeffrey Hall's own rhythm has been thrown upside down after he received a very unexpected call one morning on the award of this year's Nobel Prize in Physiology or Medicine. Together with Michael Rosbash and Mike Young, they were recognized "for their discoveries of molecular mechanisms controlling the circadian rhythm." *Cell* editor Marta Koch caught up with Jeff on a calm Sunday morning, when electricity at his house had just returned after recent storms. Annotated excerpts from their chat about behavior, misbehavior, and the challenges and joys of working with fruit flies, are presented below.

Marta Koch: Thank you so much for making the time to speak with me. Is this a good time to chat? I hope electricity is back on?

Jeff Hall: Yes. For a while at least.... I'm used to having no electricity often around here. Very close to the middle of nowhere.

MK: You were born in Brooklyn, New York, and now you live in rural Maine. What are you really? A city boy or a country man?

JH: Well, I almost always lived near cities. I didn't really plan specifically to become a rural person. It was just a kind of a fluke that happened several years ago when I was visiting some old friends who live in this community, and I became aware of a home for sale nearby. I imagined that it might be a little more interesting to retire to here, compared with retiring to this doleful suburb near Boston where I lived for many years. And if I was gonna be retired, I didn't need to necessarily have access to civilization (laughs).

MK: Yeah, (laughs). But it's always handy to have electricity!

JH: And I don't. Living here there's no civilization. It's kind of uncivilized.

MK: On behalf of the *Cell* team, my sincere congratulations on being awarded this year's Nobel Prize in Physiology or Medicine, and a big thank you for chatting with me despite, I'm sure, being bombarded with similar requests since the big announcement.

JH: Yeah. That is correct. The whole thing is unexpected and even all the bombardment, it's not really expected either.

MK: I'm sure you were asked this question many times, but how did you react when you got THE call?

JH: Well, I was in my usual situation, which old people like me tend to get sleepy in the early evening and they go to bed, and then they wake up very early.

MK: How your circadian rhythm works nowadays....

JH: Yeah. Your circadian clock changes with age and the cycle duration speeds up and that logically means that the so-called phase, like sleep onset and wake time, shift to earlier times. So anyway, I was, as usual, awake and then this call came in ... and the person apologized for waking me, and I said "No, you didn't wake me." ... But I thought it was a prank. And he said, "No, it's not a prank."

MK: That's funny!

JH: You know, being in almost in a near stupor for many years post-retirement, it was something that had never

occurred to me that might happen ever. This is in contrast to several people who I've known in my time who have been hoping to receive the Nobel Prize. They've said so... I would say "Hey, Seymour, you know, it might happen you gotta hang in there. You gotta stay alive". And he was aware of that rule. But then eventually he died 10 years ago when he was well into his 80s. [Referring to Seymour Benzer, with whom Jeff pursued post-doctoral work at the California Institute of Technology, Pasadena, California]. But it's very subjective. You know, it's like the Oscars.

There's vast numbers of scientists and others for whom it might have been deserved, but they never got it. If you're working yourself up every fall about this, and it doesn't happen, then that can be negative. You might be giving yourself an ulcer or something. If, on the other hand, it never occurred to you (it never occurred to me) then it's a very pleasant surprise

MK: (laughs) So, who was the first person you told the news to?

JH: I didn't tell anybody.

People started calling me and even coming by At the local grocery store, which is many miles away, they knew too. "How in the world did you hear about this?" I asked them. And they said, "Oh, it's Facebook."

MK: This year's Nobel Prize is a big shout-out for *Drosophila* research!

JH: Yes, it is. I don't know if a lot of biologists realize that in the early decades, research in *Drosophila* didn't have anything to do with biological phenomena. It was pure genetics.... When I was a graduate student, the head of the department, a pioneer yeast genetics researcher and a wonderful person and chairman [Referring to Herschel Roman] used to poke fun at people in the fly lab (only in a jocular manner!), that we were working in a dying system.

Drosophila had been so successful to study higher organismal genetics that it almost did away with itself, because of successes as exemplified by Nobel Prizes given to Thomas Hunt Morgan and students. They had done so well that the field seemed to have disappeared by success, but then, half way through graduate school, I started to realize that a small number of people were beginning to use the fruit fly's genetic potential to study biological phenomena. And that resurrected *Drosophila*.



Jeff Hall at Brandeis in 1994. Photo courtesy of the Robert D. Farber University Archives & Special Collections Department, Brandeis University.

MK: And later, you arrived at Brandeis as a professor of biology, pretty much at the same time as Michael Rosbash. Tell us about it.

JH: We met during the first part of my first year at Brandeis, when Rosbash came to visit to make a preliminary visit to anticipate joining the faculty a half year later. He told me what he was studying, and I was aware of it 'cause I knew some other molecular biologists studying similar phenomena, which I thought was very interesting. And Michael said, "Well, okay, so you're a *Drosophila* geneticist, I'm a molecular jock. Maybe some time in the future we could join forces on something." And I said, "Sure. Maybe we could." We had no clue that we ever would, or let alone be what it might be about. But as of the early toward mid-80s, we did in fact do what he thought might conceivably happen.

We had, you might say, complimentary backgrounds and knowledge, and maybe even skills. So, about half of my lab was working with about half of his lab on this *Drosophila* rhythm, what became known as chronogenetics of the monumental biogenetic enterprise which was rolling along as of late '70s, '80s, and '90s, culminating in the mid-90s when three developmental geneticists using *Drosophila* were awarded the prizes you know. [Referring to the Nobel Prize in Physiology or

Medicine awarded to Edward Lewis, Christiane Nüsslein-Volhard, and Eric Wieschaus in 1995, for their discoveries concerning "the genetic control of early embryonic development"].

And this was yet another prize devoted to people studying *Drosophila*, although in this case, it was taking a genetic approach to study biological phenomena. I knew all three of them, especially Lewis who started out as a hardcore geneticist. He was actually the grandson of Morgan.

It was extremely beneficial and interesting to me, and enjoyable to get to know Ed Lewis when I was a postdoc. We had a lot of mutual understanding of our activities. And Ed, I'll never forget, Ed was the most obscure biologist you could ever imagine in those days.

MK: (laughs) In what sense?

JH: He was at Caltech! He was disparaged as somebody who was a full professor, but hadn't done anything in years. And, some people who knew that that was so, said, "Oh, this is great. Ed Lewis hasn't published a primary paper since the mid-50s." "That's terrific. He doesn't publish because, well, in these days, even if you're not productive in the literature, you can still sustain grant support." It's no longer possible....



Jeff Hall and Michael Rosbash (left) at Halloween party around 1981 (photo courtesy of Jeff Hall) and (right) in the late '70s (photo courtesy of Michael Rosbash).

MK: That's right, things have certainly changed in that sense.

JH: But they said that he doesn't publish because he's a perfectionist. He demands some absolutely thorough meaningful something. And Ed told me "I hear people say that about me," he said, "That's complete bullshit. I haven't published anything in years because I haven't got anything done... at all!"

Ed was always a straight forward, full disclosure type of guy, very nice guy, a real gentleman. And I said, "Ed, I know that's so. I know what you've been doing. Nothing's really working." "So that's why you don't have anything to publish." He said, "It's refreshing to hear somebody who's a little bit self-effacing about reality."

He kept plugging away at this intriguing genetic factor for all those decades, getting not far as he said, but then, he burst forth. At the very end of the '70s, David Hogness at Stanford, with Lewis' close collaboration, isolated key elements of this gene, which became a famous Hox gene in all animals on the planet— as opposed to just an insect-bound developmental factor. And so, this was really the first truly biologically interesting gene, actually gene complex in that case, which was molecularly identified. And then, through the '80s, even later, it was very common to do a zoo blot: taking your piece of DNA cloned from some organism like fruit flies or a nematode, and asking if that piece of DNA will anneal to pieces of DNA extracted from other species. And they found again and again that these fruit fly genes seemed to have molecular relatives in other organisms. They were potentially saying something about how other animals developed under genetic control, as opposed to just insects.

MK: This was a turning point, right?

JH: Yes, all of these early decades biogeneticists realized that their work became far more significant in later years, often

from the work of others, who went to school on their accomplishments in *Drosophila* and had these probes available to ask, "Might there be an analogous or even a homologous factor in my organism?" *Drosophila* developmental genetic research became far more significant than anybody would have ever imagined....

I think in some cases people were hoping that you wouldn't find that the fruit fly pieces of DNA were potentially significant elsewhere. They said, "Let's just rule it out." And with regard to this first so-called clock gene that was cloned by Rosbash and me, and independently by Mike Young, [referring to the cloning of the gene period]. I vividly remember, people were asking the obvious question, "Is there a similar gene in other animals?" And I knew everybody was doing it, even personally.

They kept looking and finding nothing. And they said, "Ah, so this clock factor seems to be a bona fide clock factor in *Drosophila*, but this is gonna be an insect bound phenomenon only." I heard people say that constantly "There's no intraspecific homology, unlike all these other cases, like in development especially." And I would hear this and I would nod and say, "Thank you for sharing. I don't believe you. I think that you people are not looking hard enough or well enough."

Sure enough, more than ten years later, two labs, one in Japan, one in Houston, Texas, independently found evolutionary molecular relatives of the fruit fly's first clock gene. And that helped kick-start this enormous molecular chronobiological enterprise in mammals, which once again made our work, thanks to the efforts of others, including people we had never heard of and functioning far away, more significant than we would have imagined ourselves back in the mid-80s.

MK: But it did take quite some effort and perseverance.

JH: Yeah. But by the way, that's the whole history of science... way beyond genetics, way beyond biology,

chemistry, physics, you name it. If your work is gonna stand the test of time, it's often because the significance gets expanded without one individual lab being able to affect the expansion. It usually takes many other labs which become aware of the early stage studies in some particular systems.

There was one remarkable clock mutant which was stumbled into by a young fellow working in Oregon [Referring to Martin Ralph and the tau mutant]. It was a single gene factor which sped up a hamster clock and it's a fascinating mutant. And the head of the lab, Joe Takahashi, told me one dark night at some meeting. "You know, you *Drosophila* people, you, Rosbash, Young, you guys seem to be on to something." I said, "We are?" He said, "Yeah. I'm a convert. ... I'm gonna try to do mammalian chronogenetics." And then he started to do it very shortly after that, and he made it work.

And so, he and his team isolated this hamster gene molecularly, which was an absolute tour de force. They cloned it and could have been anything molecularly, biochemically. It was nothing other than a bona fide molecular evolutionary relative of Mike Young's doubletime gene!

And then, Martin started doing what the great Ron Konopka had done in flies in Benzer's lab.

MK: You're referring to Konopka's landmark 1971 *PNAS* paper, right?

JH: That's right. That was the greatest paper in the history of rhythm related research. It was an incredible tour de force then and it has stood the test of time, like you wouldn't believe.

Anyway, this mammalian guy treated genetically normal mice with a chemical mutagen and screened among the offspring for a rhythm anomaly. And he found one. And then he was able to map it and isolate the gene. Once again, not having any clue as to what the gene would be like. He did it by its genetic map position. That's the best way to get at a novel gene because it's value free. You're not making an assumption that the gene will have certain molecular properties. You're cloning the gene based on pure genetics. And he called this gene clock. And then we, at Brandeis, found two mutations which made the adult fly have no behavioral rhythms. We cloned the gene and turned out it was a bona fide evolutionary relative of the mouse clock gene. I said, "Whoa, we have re-identified clock!" So, it's not just that the period gene exists in other mammals, but these additional clock genes of *Drosophila* have molecular relatives in other animals—actually in all other animals! Of course the clock gene in mouse and *Drosophila* are not identical—they have diverged, but the fundamental nature of these genes and how they operate, and how their products operate, is strongly analogous across animals.

MK: But in the early days things got pretty competitive, right? I mean when you and Rosbash were working on cloning period, and Mike Young was leading a similar enterprise

JH: So, when we started we knew Young was trying to do it. And Michael and I wondered about the possibility of doing it. And I said, "No, let's not do it. It's gonna be unpleasantly competitive."

But then we started to do it at Brandeis, also. And that, as you say, became very competitive up through the most of the 1980s.

MK: And the two groups ended up publishing in the same year—1984; you and Michael in *Cell*, Mike Young in *Nature*....

JH: Exactly. This was good enough for *Cell* at the time. But not anymore! All we did was clone DNA, and we could infer where within the stretch of cloned DNA was the period gene. Somewhere in there... but we hadn't definitively yet identified it. In fact, some of the early results from both Rockefeller and Brandeis were wrong. Mistakes were made, but they eventually got corrected. That was part and parcel of being very competitive. There was a lot of mutual anxiety, which isn't the best way to be thorough and accurate ... but we didn't intend initially to compete with Young. We just eventually broke down and began to do. And my worry that it was gonna be unpleasant and competitive, with zero communication, that's what happened. Young always acts very placid and polite. That's actually part of his genuine nature. But Rosbash and I were more overtly anxious about the whole deal, you know, in the mid-80s, even toward the late '80s. One thing that actually helped, which was ironic, was that our approach to study circadian clocks was disparaged by other rhythm researchers, in public! They said, "These guys are wasting their time" ... and this was kind of unpleasant, but I realized, "You know, this is good, 'cause to hear this negativity, are we gonna abandon?! No, we're not. We're gonna keep going!!"

Not aiming to disprove it. We'll just keep going because we want to do it. We know how to do it and we think it's worth doing. And partly, I think, because it was regarded as silly and maybe even worthless, there was almost no other competition! Young and I muttered, when we got to know each other much better than in the early days, "This is almost like Nirvana!". We had two labs near Boston and one in New York, and that's it! Nobody else is doing it. If we're gonna muddle along, and even make mistakes, we're not gonna be demolished by a competitive situation that involves a whole score of labs.

There's is something I'll never forget: This is very early '90s at a meeting ... a grad student in Young's lab approached me to ask me a minor question about some chronogenetics something [Referring to Leslie Vosshall, now a Professor at Rockefeller University]. I tried to answer as best I could. And she kept conversing with me. This had never happened before. People in the separate labs, Boston versus New York, communicate.... I don't know if this was her intention, but boy, did it work—a day later, people from the competing labs were interacting personally and enjoying each other's company ... and then, there was regular communication between New York and Boston, and zero secrecy or paranoia—the opposite. Even public collaborations, which began through the '90s and thereafter.

MK: Collaborations are so important.... perhaps even more so nowadays for a young researcher who's just setting up his or her own lab in a very competitive field.

JH: I don't know how these youngsters do...., it's so difficult because you're utterly dependent on your own fund raising. You can't just operate according to your education and training skills and interests....

I'm glad that I did in the early days. I wrote grants which I thought were good, they were not regarded as good as I thought they were; they got low scores, but the low scores still

got you grant money in those days. I quit because I was running out of grant money.... And I said "I'm not gonna stay at the university as a pretentious pompous ass, full professor, just phoning it in 18 hours a week on campus with no more research doable." "I don't wanna quit because I wanna do research, but I can't, I won't be able to do it in upcoming years." And fortunately for me, I started in the '60s when it was possible to initiate and sustain a career of that sort. And I did so for 40 years....

I know a lot of people who've just actually given up 10 years after their PhD, 10 years of horrible struggles. And they said, "I give up." They can't do it without money... Universities still assume everybody will get a grant and start to be productive... The vast majority of newly minted PhD's and postdocs, I think, could do great things. There's vast numbers of amounts of biological knowledge which is waiting to be elucidated.

MK: That's absolutely true.

JH: I've known people who almost have admitted. "I would give up my first born child to get a paper into *Cell*, *Nature*, or *Science*." They're only half joking. Many people are evaluated not by the content of their papers, but on where the papers appear. How about reading the papers, wherever they're published? Publishing is very competitive... and the competition; imagine getting up in the morning and going to work with a sense of foreboding. I mean, I loved to go to work!! It was easy to get grant money; I loved working with the little flies and thought it was very enjoyable to study behavior and neurobiology, which at the time, when I started, was regarded as silly.

MK: And you were also very active in fly courtship research, right?

JH: Absolutely. And that was regarded as frivolous and trivial and esoteric. And I said, "But gee, these are highly evolved animals and their sex related behavior is very interesting and sophisticated. Of course, fly phototaxis is very study-able. But fly courtship is a more important behavior because, no courtship, no next generation, (laughs).

MK: (laughs) That's right! Game over!

JH: So, I thought it was ecstasy. "They pay me a little bit to go to work and do something that I like to do!" But for the great majority of my career, people didn't know about it, or care, or, if they knew a bit about it, thought it was silly. I mean Bambos, [Referring to Charalambos Kyriacou, Professor at the University of Leicester, UK] who went to many, many conferences, as did I, said, "You know, it's always that the behavioral session is always the last one at the meeting. Most people have gone home or they're hung over from the banquet the night before."

It's just regarded as the caboose of the train, the candy store....

MK: In his speech at Brandeis the day of the Nobel announcement, Michael Rosbash thanked you for introducing him to the field of circadian behavior. He said, "Jeff is a larger than life figure whose humor and wit and whose ability to walk narrowly on the line of social convention, and occasionally fall off, is and was unparalleled." (laughs)

JH: Yeah. Michael and I misbehaved very frequently. Sometimes planned, sometimes spontaneous. And we often worked ourselves mutually into moments of untoward

behavior. Even before we met, we both had a little bit of a studied loose cannon-type mentality. But, you know, because Michael was interested in what, just from afar, I was doing in my lab in the early days, and I was interested in what he was doing.... So I couldn't help mention to him the spectacular paper of the great Ron Konopka. And so, well before we began to work together on chronogenetics, Michael knew about this incredible chronogenetic coup made by Konopka.

I learned a lot about molecular genetics from him, and he learned about fruit fly genetics from me.

MK: You obviously had a very strong scientific partnership! But how about falling off the line of social conventions? (laughs) Any concrete examples you can tell us about?

JH: We would pull these ridiculous stunts, sometimes planned, and we thought they were gonna be hilariously funny, and one or two of the younger faculty would chuckle a little bit and all the older faculty would go, "You, you, you immature jerks." Which we were. One of the most memorable things was spontaneous: One of the chores as a faculty member was to entertain visitors once a week to one's campus who would come for a two-day visit and give a seminar. So we were involved in hosting all these visitors. Michael had been asked to be one of the faculty who would go out to dinner with one of these visitors in the evening after the seminar. And he had agreed to do it. I ran into him and he told me that he had agreed to do it. He realized he didn't wanna do it. The visitor was a dull tool, which is not a nice word... and he said, "Would you PLEASE go with me so I'll have somebody at the dinner table to interact with." ... I said, "No, c'mon man, of course I don't wanna go to dinner with the speaker." Mercifully nobody had asked me to, thank god...! But he kept begging me to do it. And finally, we were standing out in the middle of this large lab area in this building, and he got down on his knees and started humping my leg spontaneously. And I said, "Michael, you got me. That is a good argument." (laughs)

MK: (laughs) So, but you two will have to behave at the Nobel ceremony, right?

JH: Well, I've warned them! The Nobel people keep contacting us about all these events.... We have to go here, go there.... And I said, "Well, beware!" But both of us are prone. "This is not gonna be necessarily the most typical awardees." We may, without planning to do, go off the rails. We wouldn't necessarily realize it, 'cause we don't realize much about these matters.

It's not gonna be very politically correct. And some people may say, "These distinguished visitors to Stockholm, why are they behaving this way?" ... I have no idea if any of that's gonna happen, but I won't be surprised....

MK: I'm very looking forward to hearing all about it (laughs). So, where are you gonna place your Nobel medal?

JH: I have a little office, which I never use. ... I put my various diplomas up on the wall in that office. Nobody knows or cares... If anybody's ever in my home, I say, "Do you wanna see my diplomas?" And they say, "Are you kidding?"

I'll probably put it in that office. ... the Brandeis people begged me to order copies of this circular thing ... "Because we're gonna display them here at Brandeis, where all this work did happen." And they said, "We're gonna like post one of

these copies outside your former lab.” I said, “Are you kidding? Within the few years of me leaving Brandeis, the whole building was demolished!” The building, including what used to be my lab, (laughs) it’s gone! It was deliberately destroyed. And if it hadn’t been destroyed, it probably would have just collapsed. It was the worst building I’ve ever worked in....

MK: Oh, no...! (laughs)... I could talk to you forever, but I really don’t want to take up more of your time. It’s been a great chat!

JH: I appreciate your interest. You got it. Thanks for calling.

MK: All right. Thank you so much. Have a great day. Bye!