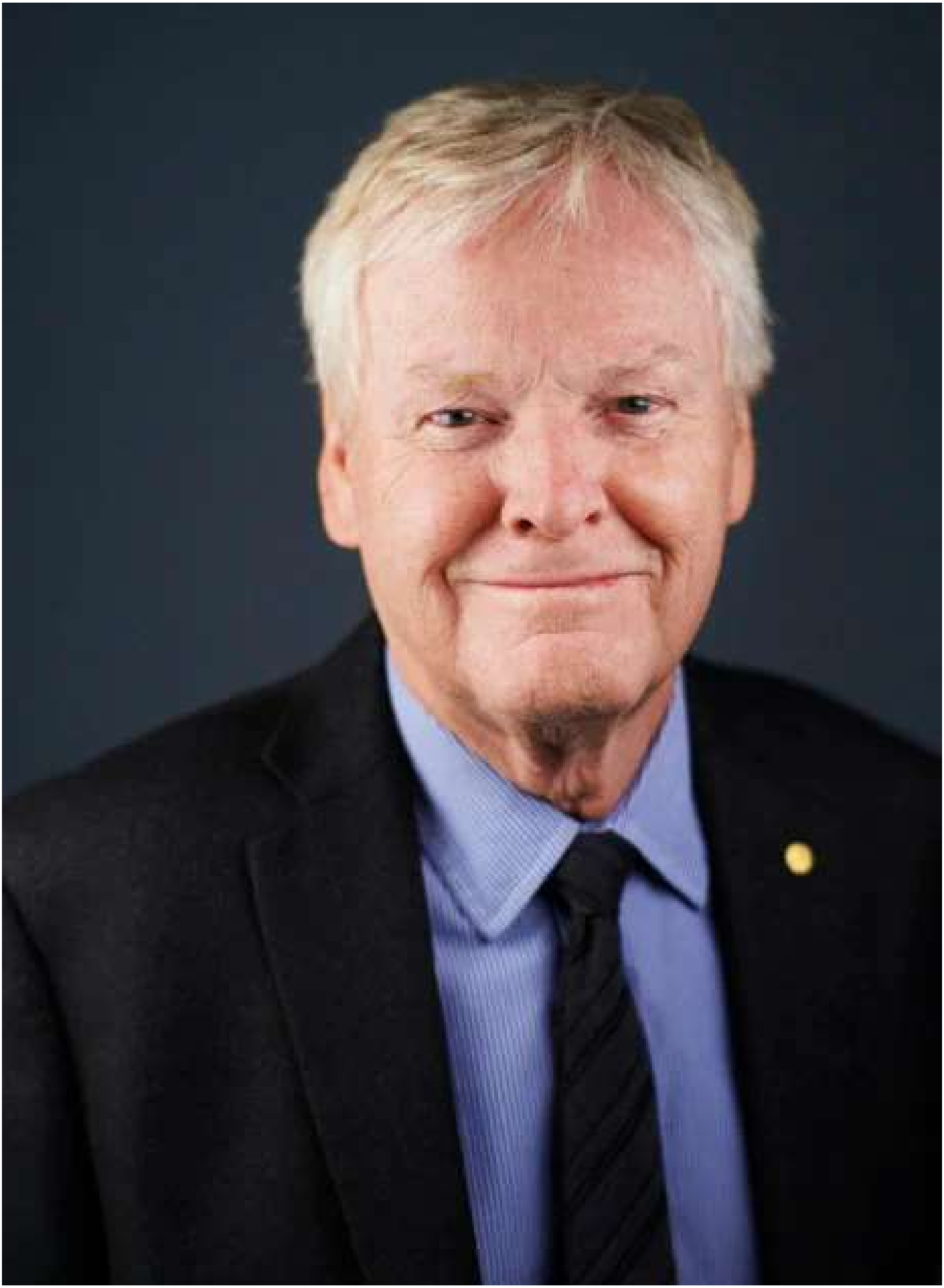

Michael W. Young
The Nobel Prize in Physiology or Medicine 2017

Born: 28 March 1949, Miami, FL, USA

Affiliation at the time of the award: Rockefeller University, New York, NY, USA

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

Prize share: 1/3

Life

Michael W. Young was born in Miami, Florida, and his family later moved to Dallas, Texas. He studied at the University of Texas and received his doctor’s degree there in 1975. After a stay at the Stanford University School of Medicine, in 1978 he moved to Rockefeller University in New York, which he has been associated with since then. Michael Young is married and has two daughters.

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.

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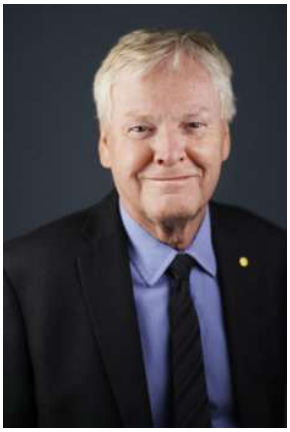
Michael W. Young

Biographical



I remember reading this big book, *The Wonders of Life on Earth*, when I was eleven or twelve. It said bird migration was controlled by some kind of internal timer, some kind of clock. Some birds, it explained, use the position of the sun to orient their migration, and the clocks in their heads are able to track time in order to assume the same direction of flight even as the position of the sun moves throughout the day. I thought that was both mysterious and fascinating. It was my first exposure to the notion of biological clocks.

I was born in Miami, Florida on March 28, 1949, into an environment where biology was all around. The neighborhood kids spent a lot of time running around each other's backyards together. Many of the families had greenhouses with an array of exotic plants that always interested me. We were close to tourist attractions: the Parrot Jungle, the Monkey Jungle, the Serpentarium, the Orchid Jungle. The Parrot Jungle was especially close and a lot of the birds weren't caged, so toucans and parrots would sometimes arrive in our yard. You'd see native wildlife, too. One time, my sister, Denise, and I caught a small alligator in the creek behind our grandmother's house. The local newspaper published a photograph. But my favorite place was the "Rockpit". This covered an area of about 50 acres and was the source of the landfill under our elementary school, David Fairchild. The excavations left scattered hills of coral rock that we would climb to survey the ponds below. The place had plenty of reptiles and the ponds were full of tadpoles. There was a "No Trespassing" sign next to the narrow gravel road into the Rockpit that said "Violators will be Prosecuted", which to my eight year old mind meant electrocuted.

At the local hobby shop they sold models of all sorts of things. You could build model airplanes or cars, but you could also build model biological systems, like of the brain or something called the Visible Man. These were a mix of colored and transparent plastic that came in boxes just like those for model cars and airplanes and with similar price tags. You'd get these things and put them together, and they were a pretty reasonable representation of real anatomy. The other kids, especially my sister's friends, thought I was really weird for putting people together, taking them apart, and have them sitting on the desk. But for me, although inert representations, the models were ways I could explore biology a bit more formally, beyond just observing nature as it was around me.

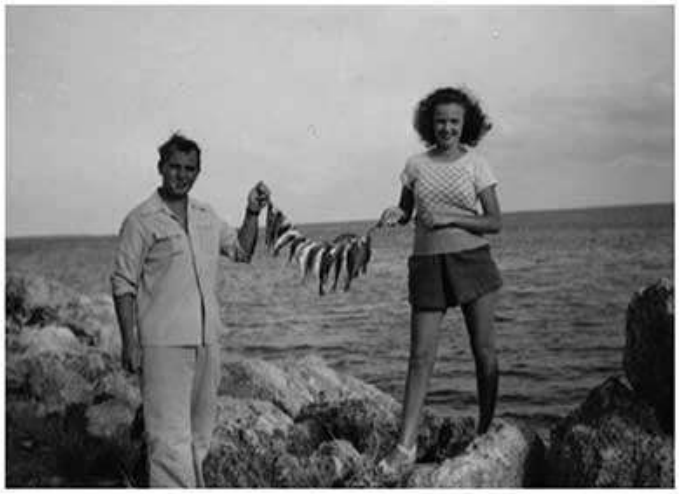


Figure 1. Michael and his sister Denise (1954). *Figure 2.* Michael's parents, Lloyd and Mickey, vacationing in the Florida Keys (~1947).

I was interested in chemistry, too. I got a chemistry set at one point and set up a lab in the back room of our house. We had this beautiful terracotta tile floor. You'd do things like use potassium chlorate to generate some oxygen and hold a match to it and get it to explode. But I also would just mix and match things kind of carelessly. I never blew myself up, but I did create something that bubbled over and shot small droplets onto the floor that left lots of little white stains. After that, my parents confined my chemistry lab to the garage.

There was a kid down the street whose father worked at Porsche, and he was always bringing home these sports cars and dissecting them while the neighborhood kids watched. Mechanics interested me and we started building our own vehicles – the most typical starting point was a lawnmower engine – for running around in the neighborhood. I built a go-kart. It's amazing that I survived that, but it taught me a lot about the way things can be put together to work. Biology and motorized machinery are obviously not equivalent, but it was useful to think about what makes something work and to see what vehicles look like on the inside.

When I was in the fourth or fifth grade, I remember putting my books together in my desk with the science book on top and thinking somehow, I'm going to do something that involves the sciences. That evolved over the next couple of years into medicine. I had no idea how you could become a scientist. That was something else completely. But if you had an interest in the sciences, then becoming a doctor seemed like a reasonable path.

No one in my family shared my interest in science, but my parents, each with a high school education, were very supportive of my interests. My father was a bomber pilot in World War II. His plane was shot down in 1944 (he crash-landed in a potato field in Holland) and he was in a prisoner-of-war camp for the rest of the war. I have a copy of a letter a woman in the mid-west sent to my grandmother, saying that she had heard my father on a short-wave radio, asking that someone contact his mother to say he was alive and ok.

My parents met when my father came home to Knoxville, Tennessee. I think because of his war experience, he was not averse to taking risks, so when they went to Miami for their honeymoon in 1946, they just decided to stay. We went to church until I was about 10, but it was a very soft touch. And I don't remember a particular political bent to any of the discussions in our family. I think an advantage of this was that I didn't come out of a mold with a set of ideas that I'd eventually have to undo, because I became very irreligious in high school. I was much more enchanted by what you could prove to yourself than by having to put your faith into something.

In 1966 my father's job changed and we moved to Euless, Texas, a small town near Dallas. I went to LD Bell, the local public high school, and later to the University of Texas at Austin, where the tuition was $50 a semester, still expecting to study medicine eventually. Having grown up in the Great Depression, my father was always concerned that I needed to work at developing a career, by which he meant something tangible, a well-established profession. Medical doctor was something he understood.

Figure 3. My little league base-ball team. I'm kneeling on the lower right. We made it to the Miami-wide playoffs, but lost when I struck out (~1962).

But my path quickly took a lasting turn, first with my father's sudden death (he had a heart attack on a business trip during my first year of college) and then when I took a course in genetics with Burke Judd in my senior year. Burke was very contemporary in the way he thought about genetics – his course looked ahead to the questions on the horizon – and I went to speak with him on several occasions because I really liked the class. I learned from him that I could sign up to do a summer research project in his lab and see how I liked research. I hadn't even known that this kind of thing was possible. That's when I first began to realize how you could train to be a scientist.

It's also how I ended up with my first mentor. Until then, the notion of having an advisor was foreign to me. Neither of my parents had gone to college, so although I took a lot of interesting courses, I didn't have a way of thinking about how to make decisions about the future. Burke's support and positive feedback very early on were very important in showing me this whole new world.

And I met my wife, Laurel Eckhardt, in Burke's course. I had tried to introduce myself to her, but she paid no attention to me at all. Later, when we met again in Burke's office I guess she realized maybe I was legitimate. I later learned that Burke and his course had also introduced her to the idea of a scientific research career. Like me, she was clueless about where scientific discoveries were made.

So I did spend that summer in the lab and it was a great time. The lab was a classical genetics lab and was focused on cytogenetics, that is, looking at chromosomes. There were two postdocs in the lab, Lenny Robbins and Ron Woodruff, who took me under their wings and seemed to think that I was serious enough to invest some time in. Lenny, especially, helped me learn more about biology, particularly molecular biology.

This was the early 1970s, and everybody was thinking about the new molecular biology. Burke's lab was very interested in understanding the genetic complexity of eukaryotes using *Drosophila*, the fruit fly, as a model. Fruit flies have these enormous chromosomes in their salivary glands and it's very easy to tell one chromosome from the other and even to tell

specific regions apart. They have these striations that were thought at the time to be visible markings of the genes. You could count off the striations and you were just counting genes. But the tools were still too dull to go much further, to bring that down to a real understanding of the organization of these genes or other information in the chromosomes.

That summer, my project was to use genetic screens to look for sterile mutations in the X chromosome region on which Burke's lab was focusing. But I could do other things. If I wanted to use the microscope to look at my own chromosome preparations, I could do that. It was like stepping all the way back to my chemistry and biology sets, but here was a real laboratory at my disposal. I'd spend hours talking with the postdocs in the lab and those in adjoining laboratories, just dreaming up experiments that we might want to do. I began pushing to introduce molecular biology into Burke's lab so we could do some of the experiments that might get us to a better understanding of how eukaryotic genes and chromosomes are put together. By the end of the summer of 1971, I had made a career choice – to pursue genetics – and I had decided to stay on as a graduate student in Burke's lab.

The lab was focused on a short part of the X chromosome and how many genes there were in that region, which included enough DNA to include about 400–500 genes the size of those in a bacterium like E. coli. The first sweep through had given us something like twenty genes, so what's all the rest of that DNA doing? If knocking a gene out resulted in lethality, you wouldn't miss that gene. But how do you know what you've missed? We knew that knocking some genes out led to a much more subtle phenotype, so that was a real question.

I was in the process of mapping mutations I had found that affected female fertility when Burke came in waving around a paper from Ron Konopka and Seymour Benzer, published in *Proceedings of the National Academy of Sciences (PNAS)* in September 1971, describing *Drosophila* circadian clock mutants that they had discovered. The gene they had found, which they named *period*, was in an area that seemed to be within, or very close to, the region we were studying in Burke's lab. I thought these were pretty interesting mutations: in addition to their relevance to the general question Burke's lab had about how many genes there were in the region, they affected wake-sleep behavior, a behavior with very solid properties.

So, I wrote to Ron and Seymour to ask for the mutations. One of the things about the *Drosophila* community is the unspoken agreement that if you discover something, once you publish it, you should give any mutations, any materials that you've produced, freely to anyone who asks for them. Ron sent the mutants right away.

I did experiments that proved that *period* was, in fact, a new gene and that it lived between two genes we already knew about. Missing *period* raised big questions about how we were counting genes, but there was only so far anyone could push with the tools we had. We needed to be able to really look at a gene, to actually have the DNA corresponding to a gene and map the mutations affecting that gene so we could understand how those mutations affected the gene's activity and/or the gene's protein product.

We weren't in a position to do that work yet, but it was thinking ahead – where will this field be in five or ten years – that was exciting to me. That's what you want to be thinking about, those are the questions you want to have in mind.

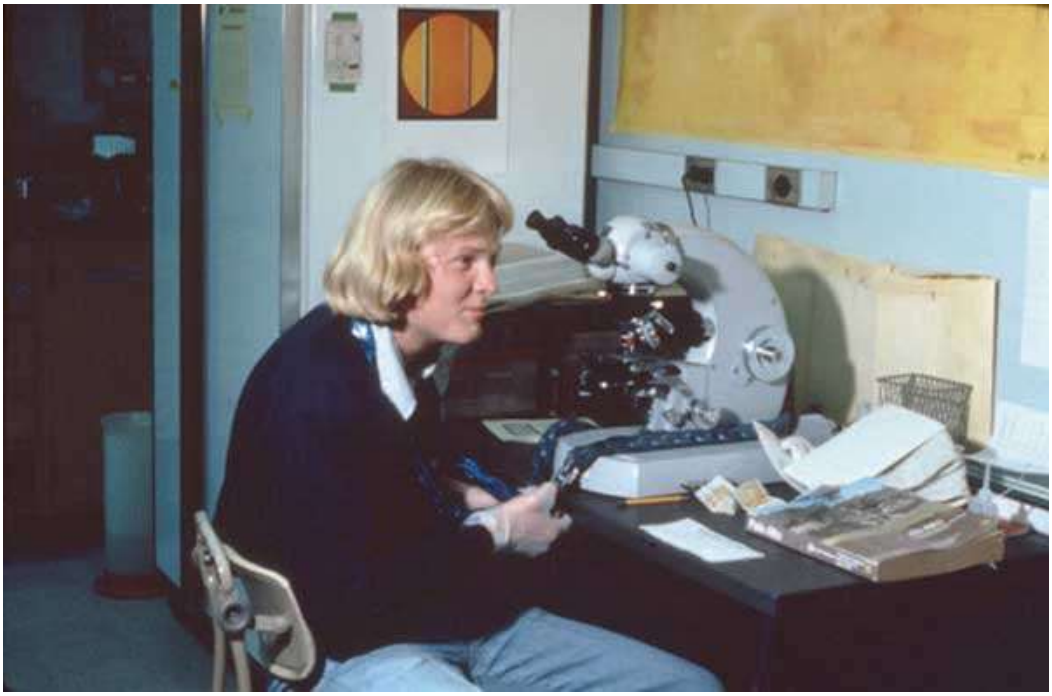


Figure 4. I had just arrived at Stanford in the fall of 1975. My two fellow postdocs, Gerry Rubin and David Finnegan, chained me to a microscope until I mapped the chromosomal locations of their backlog of in situ hybridizations.

While I was working on locating *period*, I found two deficiencies that seemed to overlap, each of which eliminated the *period* gene and appeared to be missing only the *period* gene. That was a lucky find. But an even luckier find was a translocation – an inter-chromosomal exchange – that occurred right in the *period* gene, knocking out some of the gene's activity. Because deleting *period* eliminated circadian rhythmicity without producing any other visible consequences, I began to think *period* was central to whatever larger process was involved in biological timekeeping. It could be a mainspring or a gear, by analogy, to a mechanical clock.

The question of the relationship between genes and behavior was completely unresolved at the time, and I saw that *Drosophila's* clock and the *period* gene would be in many ways an ideal starting point to study that relationship. I saw that a periodic, quantifiable behavior like the circadian wake-sleep cycle would be a great starting point to begin digging into the genetic mechanisms that make a behavior work.

As I was finishing my graduate work in 1975 and thinking about where to do my postdoc, I learned from Burke that David Hogness at Stanford was going to use *Drosophila* to isolate pieces of cloned DNA and study single genes from all over the genome, in detail, at the molecular level. I realized that if I ever wanted to come back to the circadian problem, the translocation I had found would be a very powerful entry point to find the *period* gene within cloned DNA. But no matter what my questions were going to be, I knew I was going to have unsatisfying answers without the ability to isolate a gene and map mutations along that gene. With that, you could define everything: phenotype and genotype, chromosomes and DNA. This was only going on at Stanford and only in Dave's lab. The big questions, as far as I was concerned, could only be answered by going there. Dave was a little bit like Benzer in the sense that he wanted to ask new questions and set off on a new frontier that presented risks, but also opportunities for some real excitement. I thought his taste in problems was fantastic.

Laurel was ready for graduate school at the same time that I was ready to begin my postdoc. She had been accepted into a Ph.D. program at Stanford and was looking forward to studying with Len Herzenberg in the Genetics Department. This meant I would be right around the corner from her in the Biochemistry Department. We packed up her car and a U-Haul truck and drove to California. We remember coming into San Francisco at night and all of a sudden seeing these lights up on the hills. We both thought it is like going to Mars or something. It was so different from anyplace we'd been before.

The big breakthrough that had happened at Stanford was the development of a method for cloning DNA – what we call recombinant DNA – in order to isolate large amounts of a single gene, or even a single segment of a gene. They had protocols for assembling these DNAs, for propagating them in bacteria or viruses, and for making maps of these isolated DNAs once they were present. And all of these things were very new at the time. Dave's project was really the first genome project, although it wasn't called that. It was an attempt to use *Drosophila* to fully define what the flies' chromosomes carried. There was a chromosome map outside Dave's office with tacks pressed into place everywhere a cloned piece of DNA had been located. Eventually these landmark DNAs would begin connecting with their neighbors. We all were enchanted by the tools and by the possibilities they represented. My first project was to isolate breaks in the DNA, using a method that I'd come up with at Texas, so I would have the complete picture of what a gene was doing and what phenotypes it was affecting.

I never lost my love for the outdoors and got pretty deeply invested in technical rock-climbing with a group of biologists at Stanford. We used to set up our experiments on a Friday night, knowing that they would have to incubate through the weekend, and we'd then take off for Yosemite with ropes and pitons and carabiners and all this equipment to climb rocks. We'd talk about work when we were out together, things that we wanted to find out, but there also was this excitement and terror of being on a big rock face. While I don't climb rocks anymore, I remember those times as great fun that rounded out our experience in California.

When it came time to look for a faculty position, Laurel and I realized that I had to go to a metropolitan area with more than one academic institution, so she would not be limited when looking for post-doctoral positions once she finished her Ph.D. We settled pretty quickly on Rockefeller. It had tremendous advantages and was just very different from all the other institutions I had considered. I remember my first visit and talking with Norton Zinder. He was in Smith Hall – where I would soon have my first lab next to his. It was a dusty, dark, cavernous building, but there was a charm to the classical laboratories because of the deep history they held.

When I came to Rockefeller in 1978, I had a series of things I thought I could accomplish in five or six years. I was still asking, what's odd or interesting and new about a gene from a multicellular animal? My thought was to isolate one or more genes from a genetically well-defined region and to see if we could hammer at them at the genetic and the physical levels to bring the functional and physical maps together and produce a complete picture of a piece of a chromosome. We had the new technology, recombinant DNA. We had libraries of cloned DNAs. That should mean that every gene in the fly was somewhere in that library; it was just a matter of fishing the right ones out.

And pretty quickly, we isolated two genes – *period* and *Notch*, a developmental gene – that we worked on in parallel for several years.

With *period*, the goal was to try to understand why or how it was making a contribution to behavior, to the flies' sleep-wake rhythm. Laboratories had been studying circadian biology for decades, but they were really just guessing, hypothesizing, about what the underlying mechanisms might be.

But what *Drosophila* had were mutations in these genes, like those that Ron Konopka and Seymour Benzer had found, that suggested you didn't have to rely on hypotheses and you didn't have to guess about the basis for the biology. You could use the fly and find out answers. You could create mutants that have an interesting change in behavior and then ask what the underlying gene looked like. By exploring the genes that were critical to behavior, you could go in without the baggage of a model. You could simply let the fly and its genetics tell you what path to take. Before molecular approaches were in place, naming the *period* gene and having mutations that could be mapped by classical genetics to a given location on a chromosome provided no clear path for learning more about circadian biology.

So, we thought we had a great problem to work on and that we could attack it on our own. Initially, it was just a postdoc, Ted Bargiello, and I who started a "chromosomal walk" to get to the *period* gene. From my graduate school days in Texas, I had the translocation that broke the gene and told us where in this chromosomal walk it could be found. So, we were able to take a series of cloned DNAs to make a map, to put them together, and then to see where this break was. Then we asked which

parts of the chromosomal walk were transcribed to make an RNA. When we discovered an RNA that was broken by this translocation, we knew this must be the *period* gene.

It was an interesting and stressful time because we started this work in the early 1980s without knowing anyone else was interested enough to invest time and energy in it. Ron and Seymour's paper was not heavily cited. But as we were somewhere approaching this level of analysis, we learned that Jeff Hall and Michael Rosbash were on a similar mission to try to isolate the *period* gene and that they also had made some pretty good progress.

When we finished the first round of work, we had very good genetic and molecular evidence that we had found a single transcription unit that was *period*. We didn't know any more about it. We didn't have a gene sequence, but we could say that it was about 7,000 base pairs long. We published that in *PNAS* in April of 1984. It was the first publication to come out on the isolation of *period*, and the first molecular study to address circadian rhythms in any organism.

The next step, we realized, was to see if we could confirm that everything was limited to that one transcription unit. We needed a device that could record the sleep-wake activity of individual flies, so the in-house shop at Rockefeller made it for us. It was a combination of old microscope slide boxes, some sheet metal, and some primitive electronics. We generated DNA composed of just the wild type version of our transcription unit and we microinjected it back into embryos that were *period* null mutants, that is, they were arrhythmic. Then we put the flies in the machine, five flies at a time. The event recorder wiggled when a fly moved up or down. Ted, Rob Jackson (another postdoc who had joined the lab), and I camped out most of the time in the lab just to see what would happen. A few feet of chart paper would come out every day and after a few days, we could see that putting the transgene back into the null mutants had restored the flies' rhythms!

That was exciting because it confirmed that we had the gene. It also had another level of import because this was the first time anyone had transplanted a gene to generate behavior. We had a simple animal and an easily measured, ubiquitous behavior that was well-understood but only at the level of phenomenology. The fly went from having none of that behavior to having the full range of that behavior just because this one gene was put back into it.

We published the report, which confirmed that the gene was the only thing that was necessary to restore the behavior, in the 1984 year-end issue of *Nature*. Hall and Rosbash published in 1984, too, and we could all see that *period* was the gene to move in on. A couple of years later we reported the sequence of the gene and the changes associated with Konopka and Benzer's long-period, short-period and arrhythmic mutations. All three were single nucleotide changes, and the two that adjusted period length each changed a single amino acid.

Because we had competition, we thought carefully about how we might carry the project in a new direction, and give ourselves more room to operate independently. We wanted to avoid having two groups just doing the same things. And that's when we decided to initiate a big screening effort to find additional genes involved in the clock. We thought we could learn more about the sleep-wake rhythm by looking for other genes that affected it. Meanwhile, Hall and Rosbash continued to work exclusively on the molecular biology of *period*. And I think both plans worked well because it kept us from making duplicative discoveries.

Initially our genetic screen went on and on without giving us anything meaningful, until finally, in the early 1990s, after seven thousand assays, two postdocs in the lab, Amita Sehgal and Jeff Price, found a new mutation. We named the gene *timeless*, and it had many of the same behavioral properties as *period*. Most importantly, in 1995 we discovered it encoded a protein that was a physical partner for the Period protein.

What excited us most is that we'd taken an agnostic approach to how circadian rhythms worked. We weren't asking for genes that work with *period*. We weren't saying let's collect the things with which *period* interacts. We just said let's find another gene that affects circadian rhythms. Incredibly, that took us to another piece of the same molecular system that depended on *period*. This was our first hint that there would be a single mechanism for keeping time in the fly.

Isolating *timeless* and unpacking its relationship to *period* made us realize that following the genetics could perhaps take us to the heart of what was controlling circadian rhythms. It was a huge boost – and it convinced us that we should keep screening and get every mutation in every gene that we could to see if we could repeat our success. Would every new gene that we isolated point us back to the same system, to a single machine responsible for circadian biology? In fact, it did, and that was extremely gratifying.

When we found *timeless*, Jeff and Michael immediately saw the benefits of driving genetics of the fly forward – that is, searching for all genes relevant to the clock system – as rapidly as possible. Our labs began a joint screen for new mutants that was supported by the National Science Foundation. With any luck at all, we thought, there would be several new genes to work on and no one group could handle all of them. It would be more productive to have complementary assessments of different genes going on in our labs.

What we now understand is that all of the genes our labs ultimately found participate in the same mechanism: there are nine or ten key components that interact with one another to produce an oscillating molecular system that has a natural cycle time of about 24 hours. All of this was revealed by genetics. It wasn't by anyone coming up with ideas to test; it was by admitting that we didn't have the foggiest idea how the clock worked. We sought to collect all the mutations that are important to circadian rhythms and to understand them one by one, and then we looked at their relationships to each other. This is a story not of a single big discovery, but of the accumulation of smaller discoveries over many years that together enabled us to see the underlying biology of how cells track time.

We now know that the same clock system that applies to the fruit fly applies all the way to humans. We have also learned, by following gene expression, that flies and humans are a collection of clocks. We did not expect in the beginning that we would have cells outside the nervous system that use these clocks. And we didn't anticipate the degree to which cells in different organs find it useful to independently determine the time of day. In retrospect, it makes sense, for example, that liver cells are regulated with a 24-hour periodicity that is synchronized with feeding times, and that tissue-autonomous clocks are involved in that regulation. There is some coordination of what happens in different organs, but it is beginning to look like there is as much signaling among organs as there is between the brain and these systems. You can produce an animal that has its head set on New York time and its liver set on Tokyo time, thereby revealing a really surprising degree of autonomy between clock systems in the body.

I came to Rockefeller with a five-year plan and am still here after 40 years. I don't think there's any place in the world that would have provided me with the way forward on this adventure in the way that Rockefeller did. It's such an unusual community and the unwavering interest and encouragement from colleagues early on – particularly Norton Zinder, Jim Darnell, Torsten Wiesel, and Günter Blobel (who to my great sadness died as I was writing this) – made all the difference.

In 1998 Seymour Benzer wrote me – I have saved the letter in my copy of Jonathan Weiner's biography of him – to congratulate me on our progress. He was thrilled, he said, to see how the work on the clock was going. Seymour had pioneered the notion that you could study genetics connected to behavior, but he met with a lot of resistance. When he started his work, many people just didn't believe that working on single genes would reveal important things about behavior. And the work couldn't move very rapidly before the molecular tools became available. It has been incredibly gratifying to bring molecular biology to this field and to prove, with Michael and Jeff, that a gene-based approach could solve a deep problem about behavior and reveal this beautiful circadian mechanism.

For the past several years, research in my lab has focused on both *Drosophila* and humans. The *Drosophila* work now centers on the related problem of sleep: what controls its duration and how is that driven by genes? We know sleep is fundamentally important – when we collect mutants that get 60 percent of the sleep of a typical wild-type fly, their lifespan is cut in half – yet we still don't know what sleep is actually for, how it is regulated, or what it accomplishes. I think we can use *Drosophila* genetics to get at these questions in as meaningful a way as we did with the circadian work.

On the human side, we think that most clinically significant circadian disorders are probably represented in the very large genetic databases that are available now. The challenge is to figure out which genetic variations are important and why.

Figure 5. Hiking a desert canyon with Arissa, Laurel and Natalie in the mid-1990s.

Sleep, as I see it, has as much mystery to it as circadian biology once had – and deep progress is still ahead. And so we have a very fundamental set of questions on the *Drosophila* side and a more medically oriented set of questions now on the human side, and I think that's a nice mix at this point in the lab's history.

* * *

Life isn't all research, of course. Laurel, who is a biology professor at Hunter College, The City University of New York and I have been navigating family life and our careers together for a lucky, long time. We had two daughters in the 1980s: Natalie in 1986 and Arissa in 1989. Today, Natalie has a Ph.D. in sociology and Arissa is a medical resident. We built a house in New Mexico, where we retreat to hike, write papers, and explore the natural mysteries that have intrigued us from the beginning.

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Nobel Prizes and laureates

Nobel Prizes 2022