Clockwork Genes: Discoveries in Biological Time
Lecture One—Biology in Four Dimensions
Joseph S. Takahashi, Ph.D.

1. Start of Lecture One (00:15)

From the Howard Hughes Medical Institute, the 2000 Holiday Lectures on Science…This year's lectures, "Clockwork Genes: Discoveries in Biological Time," will be given by Dr. Michael Rosbash, Howard Hughes Medical Institute investigator at Brandeis University and Dr. Joseph S. Takahashi, Howard Hughes Medical Institute investigator at Northwestern University. The first lecture is titled "Biology in Four Dimensions." And now to introduce our program, the President of the Howard Hughes Medical Institute Dr. Thomas Cech.

2. Introduction by HHMI President Dr. Thomas Cech (01:05)

Welcome to the year 2000 Holiday Lectures on Science. As you can see our auditorium is filled this morning with students from high schools here in the Washington, D.C. area. Good morning, everyone. We're also joined on the air by groups of high school students who are gathered at the University of Miami, at the Fox Chase Cancer Center in Philadelphia, and at East Lyme High School in Connecticut. Good morning to all of you and to everyone who's joining us across the country or watching on the Internet. Let me say a special hello to a group who's joining us from Moscow, Russia. Instead of saying good morning to you, I need to say good evening -- "dobre vechher." Now, if any of you here in the auditorium were to fly around the world to join our friends in Moscow, you would find that when you arrived there you'd probably be jet-lagged. That's because you have a biological clock that controls your patterns of sleeping and waking. Today and tomorrow, you're going to hear from two scientists who have done groundbreaking research on what biological clocks really are and how they work. Joseph S. Takahashi and Michael Rosbash will help you understand why you may have trouble getting up in the morning when it's time to go to school. Both are outstanding scientists and wonderful speakers. I don't think you'll sleep through their lectures. The Howard Hughes Medical Institute organizes these Holiday Lectures every December so that students like you can hear from leading medical researchers. I had the honor of presenting these talks myself in 1995, and like most of the lecturers and like I was at that time, Joe Takahashi and Michael Rosbash are investigators of the Howard Hughes Medical Institute. They carry out research at our Hughes Laboratories that are located at universities and medical schools across the United States. You can learn more about them and about all of our scientists at HHMI's web site. Our main job here at the Institute is to carry out biomedical research, but we're also trying to help young people like you to learn about the incredible advances that are taking place in modern biology. We award more than one hundred million dollars every year in grants, mainly for science education programs, and we encourage our scientists to interact with students as Joe and Michael are going to be doing here over the next couple of days. We have four lectures, two today and two tomorrow. Joe Takahashi will speak first. He's an HHMI investigator and also a professor of neurobiology and physiology at Northwestern University in Evanston, Illinois. He's gained worldwide recognition for his efforts to sort out the genes and proteins that make up biological clocks in mammals, such as ourselves. Joe's going to speak for 40 minutes. He'll take questions halfway through his talk and then again at the end. Those of you who are watching from our remote sites will also be able to ask questions, so get them ready. After the first lecture, we'll take a short break and then we'll hear from Michael Rosbash. So, with the introductions out of the way, let's get started. We'll show a brief video to introduce Joe Takahashi. Then we'll all synchronize our biological clocks and, Joe, you can take it away.

3. Introductory interview with Dr. Joseph S. Takahashi (04:27)

I became interested in science in general when I was a kid because I love animals and nature. But it, in fact, never occurred to me you could have a career in science. In my lab, we do almost everything. That's one of the reasons I love science is that it's not only intellectually challenging but it's also technically very interesting. We have to build equipment, think of new ways of measuring things, and also to figure out the answers to unknown questions. We are trying to understand how, in a general sense, how genes control behavior. And it turns out that 24-hour clocks that animals have are a beautiful example of control of behavior by genes and the nervous system. One of the important discoveries we made was to show that individual cells had clocks. And then I think more recently perhaps the most significant piece of work for us was the discovery of the clock mutant mouse. When we undertook this kind of genetic screen in a mouse everyone thought we were crazy. But it turned out that very rapidly we actually found a very interesting variant mouse that had a slow clock. And that variant was inherited as a single gene, which is called the clock gene, and we hope that some of our work on circadian clocks will lead to a better understanding of why people have insomnia or problems in the timing of sleep. As far as my goal for the Holiday Lectures, I really would like to not only tell the students about how genes might control behavior but also give them a feeling for how interesting science really is...and to emphasize that we're in an incredible period of human history where we're essentially days away from the publication of a complete human genome sequence. So, this is really a revolutionary period in biology.

4. What is circadian rhythm and what organisms have it? (07:14)

Good morning. It's a real pleasure for me to be here since I grew up in the Washington, D.C. area and actually went to Richard Montgomery High School in Rockville. So I'm a Montgomery County high school student alumnus myself. In today's lecture, what I'd like to do is to give you an introduction to the field of circadian rhythms and also to tell you what we know about the physiological control of rhythms in mammals. So, it's a great honor to be here. Let's get started. As all of you probably realize, we live in an environment that is cyclic. The earth's rotation around its axis generates a 24-hour cycle of light and darkness. And throughout evolution, over the past four billion years, many different living systems have evolved cellular clock systems that predict the rotation of the sun around its axis. This biological clock actually creates what we call a day within the cell to control metabolism, biochemistry, and many other functions inside our bodies. Now, this next slide, which is taken from a colleague of mine, Jay Dunlap. Jay has shown in this tree of life all the organisms in which circadian rhythms have been documented in either yellow or blue. And this spans the eubacteria, a cyanobacterium here, all the way through plants, animals, and fungi, and including single-cell eukaryotic organisms as well.

5. Video: Time-lapse video of reconstructing a dinosaur fossil (09:07)

If I could have the next time lapse, we illustrate another obvious rhythm for us and that is human activity in this time lapse that we are able to obtain from the field museum showing the construction of the well-known dinosaur, Sue. As all of us know, we have very pronounced activity-rest cycles but this is really just an external manifestation of many physiological rhythms that are actually going on in our body. For example, our metabolism, our heart rates, numbers of endocrine hormones are all fluctuating.

6. Human-isolation experiment: Properties of circadian rhythm (09:59)

Now, in the 1970s, the first really controlled experiments were done on human subjects. And this is a record taken from a young German medical student who volunteered for an experiment to go into temporal isolation at the Max-Planck Institute in Germany an institute run by Jurgen Ashoff. And what the student is doing is he's living in an apartment with the door open for the first week. And this bar, the blue bar, shows when he's awake and the yellow bar shows when he's sleeping. And so, for the first seven days -- time is just in days vertically -- he's waking up about 8:00 a.m. in the morning and going to sleep around midnight. Now, in this experiment, the apartment door was closed at this time. He went -- it's actually underground, and we call this apartment the bunker. All TV, clocks, radios, were turned off, and what you see is a very interesting feature and that is he continues to show a sleep-wake cycle. It persists in the absence of time cues. But he tends to wake up a little later each day. He drifts in time so that, for example, down here he's actually waking up about midnight. And so this rhythm which persists in the absence of time cues, environmental cues, is really the essence of circadian rhythms -- that's how we define them -- and argues very strongly that they are controlled or generated by a clock inside our bodies, and we know that the clock is in our brain. Now, at the bottom here, the apartment door was opened again and he continued to live here another couple of weeks. And you see a second very important feature of rhythms and that is he goes back to a pretty regular schedule of waking up about 8:00 a.m. and going to sleep at midnight. And so, what this illustrates is that the environment has a very important role and that is to synchronize our biological clocks to exactly 24 hours. And more importantly, to control the phase of our rhythms. That is, so that we are diurnal and wake up in the morning. You can see this happening here. So, circadian rhythms have these two fundamental properties: they persist in constant conditions, yet they are entrained or synchronized by the environment, and finally, they are also resistant to changes in temperature.

7. Activity-measurement experiment on a graduate student and Dr. Cech (12:34)

Now, this next slide, taken from a more recent study in which we've measured the activity of a young graduate student who is actually in my lab, we can see that activity is clearly rhythmic in human subjects. And, in this case, this is a young male, apparently normal. Except if you look very carefully at what time he wakes up, he wakes up about noon every day and goes to sleep about 5:30 in the morning. So he's clearly a night owl. This is just one of three such night owls in my lab the so-called night shift. There are certain advantages: I'm not around very much, they get to use all the equipment in the lab...So, they kind of like this. Now, more recently, Dennis Liu convinced Dr. Cech to wear one of these actiwatches. And it turned out that we caught him in one of his jet-setting trips when he went between Chevy Chase and Colorado. So at the beginning he's in Chevy Chase and at the end, in the yellow here, he's in Colorado. And then back here at the end, he came back to Chevy Chase. And you actually can see he has a very regular wake-up time, and he woke up about an hour later in Colorado as compared to Chevy Chase. Now, it turns out it's very easy to measure activity rhythms with a very simple device that I have shown here on my wrist that measures movement. And with this device, we actually did a very interesting experiment with a set of volunteers who are actually in the audience.

8. Video: Interview with Dr. Seymour Benzer (14:30)

Before we go to the actual records, I wanted to play you a clip from an interview we did with a very famous scientist -- his name is Seymour Benzer -- who made a very apt comment about larks and night owls.

One reason I was interested in the project when Ron took it up was my own curiosity about people's behavior with respect to time, because I'm a night person. My wife is a morning person. There was nothing we could do about it. She was a lark, and I was an owl. And we'd see each other in between. But -- in observing other people, I could see that they often fell into one category or the other. Most people synchronize by having to show up for work at a particular time, but if you remove the synchronization, they drift.

9. Activity measurements from participating students (15:33)

So, in this experiment, about 20 of the audience -- students in the audience -- actually volunteered to wear one of these actiwatches. And what I've done is to pick out a couple records to show you and illustrate some of the points. In addition to the students in the room who wore them, we also had some of the HHMI staff wear these in the summer. So, I'll show you some of the staff records also. Now, in this first record here, we have an example of a student who we would call an early bird. He's clearly a night owl: 10:30 a.m. and here, very late, 2:00 to 3:00 p.m. actually. I don't know if I should reveal you now who he is but -- and in the next slide here: student 215, we have what I would call a much more typical example of a high school student. If you look carefully during the weekdays, Tuesday through Friday, he wakes up very early and very regularly -- say 6:30 in the morning because he has to go to school. But on the weekends, he's clearly a night owl, 10:30 a.m. And here very late, 2:00 to 3:00 p.m., actually. I don't know if I should reveal you now, Ian, but for the night owl, a T-shirt for you, too.

10. Activity-measurement study reveals students' sleep patterns (17:10)

So, the next slide shows a summary of all the data we just collected at the HHMI for the staff, comparing weekdays and weekends. And what you see is the staff are pretty regular also. They tend to wake up around 6:00 to 7:00 a.m. in the weekday and to sleep in about one hour later on the weekends. And they're getting about seven to eight hours of sleep on average during the weekdays and about eight hours of sleep on the weekends. But you'll see there is a range. Some people get only five or six hours, and some people perhaps are getting 10 hours of sleep among the staff. In the students, we see an even more dramatic difference between weekdays and weekends. So, here, the weekend wake-up time is very sharp between 6:00 and 7:00 a.m. for everyone. But on weekends, you see a large dispersion in times that goes from 5:00 a.m. all the way out to noon, kind of like my graduate students. And interestingly, if you look at sleep amount during the week, they're only getting about seven hours of sleep every night. But on weekends, some individuals are really making up for that sleep, and they're getting up to 12 hours. So, it's kind of interesting.

11. Self-assessment survey as a predictor of wake-up time on weekends (18:31)

Now, a second component of this experiment was to also have the volunteers fill out a survey that self-assesses your preference for wake-up time. And this survey is called a Horne-Ostberg questionnaire. And so, what I've done here in this plot is to see is there a correspondence between your self-assessment and the measured wake-up time that we use with the actiwatch. And so, on weekdays, there isn't a great correspondence. That is, the data tends to be rather flat, as if there is not much relationship between our self-assessment and wake time. There is a slope, and it is significant, but it's negative. On weekends this is more dramatic. There is a lot of scatter here, but there is a clear negative trend. So that if you call yourself a morning type, you tend to wake up early in the morning, 6:00 a.m. And if you call yourself an evening type, then you tend to wake up late.

12. Audience poll on preferred wake-up time (19:35)

Now, only a subset of you actually got to wear the actiwatch and fill out the questionnaire. So I thought it would be fun if we did our own little Horne-Ostberg survey in the audience. So, what I'd like to do is for you to think about being on vacation where you're completely unconstrained, and you don't have to go to any particular function or activity, when would you like to wake up if you had your choice? So if you wanted to wake up before 9:00 a.m. -- that would be your natural wake-up time, before 9:00 -- could you raise your hands? Let's see. Only those? OK. What about 8:00 a.m.? You can keep your hands up. Would you wake up before 8:00 a.m.? We have Tara here. Anybody else? Wow. That really -- that was a surprise to me. OK. So, who was the last one? Was it you, up there? I'm going to give you a T-shirt for being that rare early bird. So, let's do it on the other side. Raise your hand if you would prefer to wake up after 9:00 a.m. That should be the whole -- oh, wow. Now what about after 10:00 a.m.? Keep your hand up. After 11:00 a.m.? Keep your hand up. After 12:00 noon? Wow. Look at this. After 1:00

p.m.? Still have about three or four left. 2:00 p.m.? Is there anyone for 2:00? Ah! OK, great. Wow, that is great. You get a T-shirt for that. That was wonderful. Thank you.

13. Q&A: Can we compensate for lack of sleep? (21:40)

So, what I'd like to do now is actually take a break here for questions. And if there's a question in the auditorium, I'd be happy to answer it at this time. Yes, in the back of the room there.

Before, when you mentioned something when we were looking at the graphs, is sleep something that can be compensated for if it's deprived or is it just on a continuous cycle where a certain amount is the ideal amount to have optimal metabolic functions in your body?

Right, so the question is can we compensate for sleep if we lose it? And so, that's a very good question, and the answer is yes. Our sleep -- our brain, which controls sleep, actually does compensate. So, if we lose a night of sleep, and you look at sleep on the following night, we see a rebound, a compensation. You tend to sleep more to try to make up for that sleep debt. In fact, I think that's what's going on on weekends in these records that we looked at already.

14. Q&A: How can you set your circadian clock? (22:50)

So, we're going to take a question from East Lyme, Connecticut. Go ahead, East Lyme.

Hi, my name's Ruchi. I'm a junior at East Lyme High School. And, I wanted to know can you set your own circadian clock in ways other than environment or habit?

So, yes, that's a very good question. Can you set your own biological clock in other ways besides environment or habit? And the answer is really that the environment is the dominant way to set your clock. Light is really the best agent. In other animals, temperature can also work. And in humans, some social cues help, too. So if we can see a watch, actually somehow that information gets to our brain and resets our clock. There are some other treatments like melatonin which can also shift your clock, but I would say that they are much weaker than the natural environmental cues.

15. Q&A: How do people on a night shift deal with the schedule? (23:50)

So, we're going to take another question from the house. Over there in the red.

How do you explain people who can work at nighttime, like police officers that have to work night shifts, how do their clocks work then if they have to work at nighttime when there's no light?

Right. So, many of us in fact, 20% of the United States work force works a nonstandard schedule and has to work either evening or night shift. And it turns out that this is a difficult schedule to adjust to. I'm going to talk about one of the consequences of jet lag in the second half of today's lecture. But basically, you have to have control of your environment. If you want to sleep during the daytime, you have to have shades and things like that and keep it quiet. The important thing is it takes time. It takes about a week or so for us to actually shift our rhythms over six to eight hours.

16. Q&A: What would happen if you couldn’t control your circadian clock? (24:47)

Now, we're going to take another question from East Lyme, Connecticut. Go ahead, East Lyme

Hi, my name is Vanessa Christensen, and I'm a senior at East Lyme. I was wondering what would happen if an organism wouldn't be able to control their circadian clock?

So, if you couldn't control your clock that is, say you couldn't synchronize to the day-night cycle, then you would free-run. You might be like that German medical student volunteer I showed you, who was in the bunker. And, in fact, in a subset of human patients who are completely blind, about half of those individuals actually cannot synchronize to the 24-hour schedule. And they have great difficulty. Some of those people actually are free-running in the real world, and it's very difficult to synchronize them.

17. Q&A: Would irregular sleep patterns alter the circadian clock permanently? (25:43)

Now we're going to take a question from right here.

If you have an irregular sleep pattern for an extended period of time, can it affect your circadian rhythm permanently?

We don't think that there's permanent effects on your circadian rhythm. Your circadian rhythm is really quite robust and, as you'll see, is really genetically controlled and pretty hard-wired. So I don't think that you're going to cause any damage to your clock. Thanks.

18. Q&A: Do all living things have a biological clock? (26:17)

We're going to take another question from Fox Chase. Go ahead, Fox Chase.

I'm Scott Williams from Wilson Middle School, grade six. Do all living things have a biological clock?

That is a great question. It turns out so far we've found biological clocks in all animals and all living systems that have a cell and a nucleus -- those are eukaryotes. We only have a few examples of bacteria that have clocks. And in the case of another class of very ancient bacteria, archaebacteria, there are no examples of circadian rhythms yet, and also in viruses and other forms that are lower than single cells there are no cases of rhythms. So not every living organism has a biological clock, but most.

19. Q&A: If your schedule is out of sync with your clock, would it affect you? (27:14)

Ah, we have a question from Moscow next. Go ahead, Moscow.

Yes, if you are a lark and you have to work according to the owl cycle, how does it affect your work ability?

Right. That's a very good question. If you have to work a schedule that's sort of out of sync with your natural -- your cycle, you will have to, you basically shift your cycle and your schedule, and it's going to be just a little more difficult for you to adapt. I think that, as in the case with my graduate student, you find that it's easier if you find a profession where you can just be a night owl. I think we're out of time now. And I'm going to go back to the second part of my lecture.

20. Animation: Neuroanatomy of suprachiasmatic nucleus (SCN) (28:07)

If we could begin the next time lapse -- or not the time lapse, the next animation, that would be good. So, what I'd like to do in the second half of this lecture is to really tell you about what we know about the control of rhythms in mammals. In humans we synchronize to light, and that light is received by our eyes and the retina, and this information travels down the optic nerve into the base of the brain in a region called the hypothalamus. And within the hypothalamus sit two very small, winglike structures shown here in yellow that are composed of a few thousand neurons. And we know now from animal experiments that I'm going to tell you about in a few minutes that these structures actually contain our biological clock. The suprachiasmatic nucleus, or the SCN as we call it, acts as a biological clock system for us in our brain. Now, if we look inside the SCN, we find that it's really made up of a network of nerve cells, many thousands of them, and interestingly these nerve cells fire with a circadian rhythm, and I'm going to show you an example of that at the end of my lecture. This kind of experiment has led to the idea that the clocks in this suprachiasmatic nucleus are actually cellular clocks. And so, it is within the individual cell that the clock mechanism really emerges fundamentally.

21. Anatomy of SCN in rodents; cage for measuring mouse activity (29:58)

Now, in animals, the suprachiasmatic nucleus looks a little bit different -- it's more oval shaped. This is a cross-section through a rat brain just to illustrate where it's located. But it's in the same position right above the optic chiasm at the base of the brain in the hypothalamus. And these nuclei in animal experiments have been shown to be necessary for the control of rhythms and to be sufficient for the control of rhythms. And so, I'm going to give you a couple of examples of experiments in animals since it's difficult to do these kinds of manipulations in humans. Now, before I begin, I wanted to just demonstrate for you the kind of very simple apparatus we use to measure rhythms. This is a mouse cage. A mouse is one of our favorite experimental animals. And what we do is give the mouse a running wheel. Anybody who has had a pet mouse or hamster knows they like to run on the wheel at night. And when the animal runs on the wheel, we can just record with a switch, and the switch is hooked up to a computer, and the computer runs 24 hours a day, 7 days week, 365 days a year.

22. Video: Time-lapse video of mouse activity in the cage (31:17)

And so, in the next time lapse video sequence we can just see an example of the mouse in one of these wheel cages over about 3 days. And what you see is at night, it really runs on the wheel a lot. In the daytime, it's still a little active but it doesn't run on the wheel so much. And it turns out if you were to quantitate this amount of activity, there is a striking difference. Almost all the activity is in the night. Interestingly, these rodents are all long-distance runners. They run about 5 to 6 miles a night on that wheel, every night.

23. Mouse-activity chart for normal and SCN-lesioned mice (32:00)

Now, if you plot this rhythm... This is an activity chart of a mouse. First, on this light cycle, it runs at night. Then the lights are turned out, which we call D.D. here, and the mouse then exhibits its own free-running period which is a little shorter than 24 hours. So it drifts to the left because it wakes up a little earlier each day. This is what a normal mouse record looks like. If you surgically lesion the suprachiasmatic nucleus which looks like this in a mouse so that you have a lesion here, what happens is the mouse completely loses its biological rhythm. So here's the record of a mouse with its SCN lesioned. Even on a light-dark cycle, it just shows a little bit of rhythmic activity which appears to be driven by the light primarily. But in constant darkness, there is no evidence of a 24-hour rhythm at all. So lesioning the SCN abolishes essentially all rhythms in rodents.

24. SCN transplant experiment in SCN-lesioned hamsters (33:09)

Now, in the mid to late eighties, a number of different laboratories were able to use brain transplants to restore rhythms in rodents. And so, what they did was to lesion an animal -- in this case a hamster, which causes the rhythms to go away -- but then to take a transplanted -- a transplant from another animal and put it back into the brain of this lesioned hamster. This restored the rhythm. And this suggests that the SCN can control the rhythm in the recipient. Now, more recently, in 1990, a more sophisticated experiment was done by Martin Ralph and Mike Menaker using a mutant hamster that has a 20-hour clock. It wakes up four hours earlier each day, so its activity pattern streaks across the page here as compared to a normal hamster. And what Martin Ralph did in this experiment was to take either wild-type or mutant lesioned recipients and to transplant the SCN But to now crisscross, he put a tau mutant SCN into a wild-type hamster, or vice versa -- a wild-type SCN into a mutant hamster -- and then assess what was the period of the restored rhythm. And amazingly, what happened is if you put a mutant SCN into a wild-type hamster, it has a 20-hour rhythm. Conversely, if you put a normal SCN into a mutant hamster, it will have a normal rhythm. So this kind of experiment argues definitively that the SCN controls the period of our rhythms.

25. Isolated SCN tissue oscillates with a circadian rhythm for more than 30 days (35:06)

Now, in the next slide, what I'd like to do is to sort of give you a feeling for what we think the SCN is really doing. Now, in mammals, I told you that there is a clock in the SCN in the brain, but it turns out that if you look in the body, recent experiments that come from gene cloning -- which we're going to be talking about in the next three lectures -- that has led to the discovery that many tissues in our body actually express oscillations. And so, in this experiment done by Shin Yamazaki, Sakaki, Tei, and Menaker, an international Japanese- American collaboration, they created a rat that allowed them to look at the expression of a gene that Dr. Rosbash will be talking about later this afternoon in many tissues throughout the rat. And so, this rhythm here is the rhythm that they were able to record of this gene expression from a piece of suprachiasmatic nucleus tissue that was isolated in culture. And so, you isolate the SCN in culture, it shows a beautiful circadian rhythm of gene expression which goes for 32 days. So this is like the energizer bunny; it keeps ticking forever.

26. Cells isolated from other parts of the body have circadian oscillations lasting several days (36:40)

In the next slide here, this shows you -- however, it's not only the SCN that oscillates many tissues that you look at, the lung, the liver skeletal muscle, all have circadian oscillations. There is a difference, however, which is hard to see, and that is that the SCN oscillates for 30 days. All these other tissues damp out in two to seven days and do not persist for as long. So the peripheral oscillators in mammals presumably are damped oscillators, OK?

27. Simulated jet lag: How fast do the body's clocks adjust? (37:18)

Now, what Yamazaki did next was to ask: What happens to all these body clocks when we go into a situation where we have to shift our clocks, either advancing them, as if we're going to Europe or to Paris, or delaying them by six hours, as if we're going to Hawaii. And so, this is the activity record of the rats in this experiment, they're first on this light cycle, then they are shifted six hours earlier, as if they're going to Paris, France on this day. And then the rhythms were assessed where the orange arrowheads are shown, and this is also done for a delay, as if they're going to Hawaii. OK. And so, the question is, that was addressed here is, "How fast does your biological clock reset? And how fast do your body clocks reset?"

28. Summary of simulated jet-lag experiment (38:17)

And so, here's sort of a general summary of the advance situation as if we sent the rats to Paris. What happens is on the very first day after the shift, within one day, the suprachiasmatic nucleus is fully shifted six hours. But, interestingly, all our body clocks lung, liver, and skeletal muscle take at least six days to reset. They lag behind. And, in fact, advances are harder to achieve It takes these tissues a few days to actually get across, to shift fully when we advance the rhythm. So there is clearly a desynchrony between our SCN clock and our body clock. Now, what about the delay situation, if we went to Honolulu, for example? Again what happens is your SCN can actually set in one day -- this six-hour shift. It takes your lungs and skeletal muscle about six days. And, interestingly, your liver doesn't shift for more than nine days. In fact, it took 16 days or longer for your liver to shift. And during this interval, the liver actually lost its rhythm in many cases. And so, what's happening is that jet lag is really causing what we would call a temporal disorganization or desynchrony in our body. This six-hour shift is one that's hard for our body to adapt to. Our SCN clock can shift very rapidly, but it takes many days for our peripheral clocks to shift over. One of the reasons for this is perhaps the way that our clocks are organized in mammals. That is, we have a hierarchical organization: the SCN is a master clock that is self-sustained, and it somehow then drives damped circadian oscillators in our body. Of course, through evolution, organisms didn't have to undergo jet lag. And so, they never had to face this situation. And it's clear that this is a more modern malady for humans, and evolution really did not anticipate having to shift our biological clocks quickly. Without shifting, of course, everything would function fine. It wouldn't matter if your clock could shift faster or slower.

29. Properties of individual neurons of SCN (40:56)

OK. So, what I'd like to now do is to go back to the SCN If I can have the next slide... and remind you that the SCN itself is really composed of a network of neurons. In rats, about 16,000 or 20,000 neurons, very tightly packed in the nucleus, make up the SCN And, indeed, in the SCN we can look at the properties of these individual neurons. And so, this is an experiment that was done in collaboration with Eric Herzog and Gene Block at the University of Virginia using SCNs taken from mice, which are then dissociated -- separated -- and then maintained in culture, in cell culture on a special planar electrode array. So this is like an integrated circuit in which we grow the cells. And what happens is this then allows us to measure the electrical activity of individual cells in culture. And so, this is an example of one culture dish that has five individual SCN neurons. Each of them are showing a beautiful rhythm of spontaneous firing activity in culture, about 24 hours. And the majority of the cells that fire exhibit this rhythm. Now, if you look more carefully at this record, what you'll actually see is that each cell is firing at its own intrinsic rhythm. So, for example, they show peaks at different times when you look at these various cells. And if you were to measure the periods of each cell, you would see that each cell has its own period that is different from the other ones. And so, this very interesting feature allows us to conclude that each cell must then have its own clock. The circadian rhythm is really intrinsic to the SCN neuron.

30. Higher level of organization of the clock in mammals (43:24)

And so, even in mammals, we believe that the fundamental unit for study, for understanding circadian rhythms, is really the individual cell. Now, of course, in the intact organism, the cells are not all free-running and desynchronized. What happens is if we were to, instead of look at a cell culture where the cells are dissociated, if we look at a slice of tissue in which the normal tissue organization is preserved, what we then find is that all the cells fire in synchrony. And that is what we believe is happening in the intact animal, is that they all fire together. So, indeed, there is a higher level of organization that's important at the tissue level and that is integration of these thousands of cellular clocks within the SCN to generate a coherent 24-hour rhythm in the organism. OK. So, let me really just conclude my talk by saying that our focus over the next three lectures is really going to be what is going on within the cell. Evidence from many different domains suggest that the cell is the fundamental unit for the generation of circadian oscillations and, as you're going to hear from Mike Rosbash in the next lecture, is really a set of genes within cells that lead to the generation of circadian timing signals. So, thank you very much. We're going to go on to questions now. And first, we're going to start with questions from the house.

31. Q&A: What effects would delayed shift of the body have? (45:17)

Yes, right there.

You said that the liver and lung and skeletal muscles did not shift as easily as the SCN And what effects, if any, would that have on the body

So, what happens is that when we have to shift -- say we go to Europe -- even if our biological clock can shift in a day or two, our entire body is not shifted, in particular, our liver, for example. Turns out your liver has really dramatic circadian rhythms in a number of enzymes. They're involved in metabolic pathways related to digestion. And so, what I would say is that we would think that your body systems are really just not physiologically tuned to our normal schedule of having three meals a day at a particular time. Under normal circumstances, our entire body is really synchronized to that. And so, figuratively and literally, we are different people in the middle of the night and in the middle of the day. Our entire body and our body systems really are operating in different ways at these two different times. So I think, you know, to answer your question the lag really is just going to cause sort of a loss of optimum function. OK?

32. Q&A: How would human performance be affected if SCN were missing? (46:56)

So, we're going to take our next question from Moscow. Go ahead, Moscow.

My name is Vladim. What would be the working ability, how will it be affected if the SCNs are lacking? How fatigue will be affected in a man, and how fast he will be getting tired, and how his work ability will be affected by the lack of SCN?

Very good question. It's actually hard to answer directly for humans. There are a few case studies in which humans have, by accident, received an injury to the hypothalamic region. And in those cases, there are one or two subjects that have lost rhythms, but in general it's hard to actually say something about what the effect would be on that particular person. If we look at animal models, however, we have lots of information. So, for example, if you look at an SCN-lesioned rodent, their activity is no longer consolidated. They sleep throughout the day in very short rest activity bouts. And were this to happen in a human, this would be very debilitating because you would have a tendency to fall asleep at any time during the day or night and would not show this very clear difference of very high cognitive function during the day and very consolidated deep sleep at night. You would have very fragmented activity. And so, we think that would be a bad idea.

33. Q&A: Do cancer cells exhibit circadian oscillations? (48:41)

The next question is from Fox Chase Cancer Center in Philadelphia. Go ahead, Fox Chase.

Hello, I'm Scott Weiss from Abingdon High School. I'm in eleventh grade. My question is, do cancer cells exhibit these oscillations in the cells in these clocks?

So that's a very interesting question. Some recent work done by a colleague of ours named Uli Schibler in Geneva has shown that cells in culture actually can express circadian rhythms. Cells that are derived from our skin, fibroblasts. And so, we believe that there could be a link between the control of cell growth and circadian clocks, but I think right now it's safe to say that that link is still tenuous. But it is an area of intense activity.

34. Q&A: Do some animals have 12-hour tidal rhythms? (49:39)

We're going to now take a question from the house. Let's see. Right there.

The animals that respond to the tides, for instance, do they have a 12-hour circadian clock as opposed to a 24-hour one?

Yes. Do tidal organisms have 12-hour tidal rhythms, and the answer is yes. In the few organisms that have been studied, there is evidence that organisms that live in the tidal zone can express tidal rhythms. These don't persist as well as the examples that we're showing you when they go into constant conditions, but there clearly are tidal rhythms.

35. Q&A: Where is the circadian clock located in other animals and plants? (50:23)

Next we're going to take a question from East Lyme, Connecticut. Go ahead, East Lyme

My name is Jeff. I'm a senior at East Lyme High School. You stated that the circadian clock is located in the hypothalamus region of the brain but only in mammals. Where is the circadian clock located in plants and other animals?

Obviously, if you're a plant, you don't have to have a brain to have a clock. And it turns out that we believe that many cells in the plant actually have circadian rhythms. And so, what we'll see in other types of animals -- well, not animals, but living organisms -- is that clocks can be distributed throughout the organism and not necessarily have such tight central control the way we see in mammals. Thank you.

36. Q&A: Would circadian rhythms be different at high latitudes? (51:16)

The next question is going to come from Miami. Go ahead, Miami.

Hello. My name is Leanna from Miami Northwest Senior High School. You mentioned that light plays a factor in synchronizing your biological clock. How would a person with a circadian rhythm in Alaska compare to someone in America?

So the question was how would circadian rhythms, for a person who lived, say, far north in Alaska compare to someone who's living in America. And the answer is, in say the Scandinavian countries there is actually a lot of interest in this. And they have trouble, in some cases, synchronizing to the 24-hour day very near the arctic circle in the summertime. And so, indeed, we do see evidence that living at extremes of the earth does cause problems in synchronization of our rhythms.

37. Q&A: Can you really reset your clock by shining a light behind the knee? (52:20)

So, we're going to take another question from the house. Right there.

On the television a few days ago, I saw a news report that said you could reset your biological clock if you're on a plane by having light shine under your knee. And I was wondering if there's any proof of something like that that you can reset your clock in order to help you in jet lag.

Ah, yes. So, this is a very famous experiment now that was conducted by some of our colleagues in which they shined light behind the knee and reported that rhythms could be reset in human subjects. I am actually one of the skeptics in looking at this experiment, so I'll give you a direct answer. I think that the design of the experiment was flawed and that there are other explanations for why the rhythm could have been shifted besides light. That's one answer. And the other is that in the time since that very famous experiment was published, a number of follow-up experiments have been attempted, some in animals and some in human subjects. All the animal subjects, which have readdressed this issue, have been negative, showing there's no evidence for photoreceptors in the body. And in the human subjects, there are about five studies that have attempted to repeat different aspects of this work. And unfortunately, all of them have reported negative results also. So we think that we have to call this particular conclusion into question.

38. Q&A: If you travel often, could your body adjust faster? (53:56)

The next question is going to come from Fox Chase in Philadelphia. Go ahead, Fox Chase.

Hi. My name is Drew Tannenbaum from Abingdon High School. I was wondering if you travel often, will your body clocks begin to adjust faster?

Ah, that's an interesting question. So, if you exercise your clock, can it adapt more rapidly? I guess we could ask... Michael and I could ask ourselves if that's true since we do a lot of travel back and forth. I think that we don't have any good evidence for the answer, but my guess would be that practice is not going to help in accelerating how fast our clocks shift, but we might be able to learn how to deal better with jet lag. So there are things that you can do to help you reset. So you can try to use bright sunlight which is the best agent for resetting to try to reset your clock and to sort of control your sleep. That's what we call having good sleep hygiene, not to deprive yourself, OK? So I think that you could learn in that sense. But I don't think your biological clock actually adapts any faster.

39. Q&A: Do isolated body clocks need the SCN for sync? (55:11)

Now we're going to take one last question from the house. A very quick one, please, in the back of the room there.

Yeah. I was wondering, you said that the tissues of the lungs and skeletal muscle and liver independently they still have their circadian rhythms... but you said that consistency decreased as the days went by. Would that be in relation to not being controlled by the SCN in the body, or have any relation to that, or is that just completely on its own?

Yes, so the body clocks all damp out. They lose their rhythms after about a week or so. But that's in isolation, when they're isolated in culture. When they're inside the body, all of those tissues have rhythms but that's because they're receiving a signal from the SCN presumably to maintain those rhythms. So in the animal, all those tissues are fine. So, thank you very much for listening. We're out of time. It's been a pleasure.

40. Closing remarks by HHMI President Dr. Thomas Cech

I would like to thank you, Joe, for a wonderful talk and thanks to the students both in the audience and around the world for some really great questions. When we return, Michael Rosbash is going to present the second lecture. More than 15 years ago, Michael and others used the new tools of molecular genetics to clone and sequence the first genes that were known to directly play a role in circadian rhythms. They did this research in the fruit fly, Drosophila melanogaster. In his talk, Michael's going to explain why scientists so often use fruit flies, not just to study circadian rhythms but other genetic phenomena such as biological processes that play a role in human diseases. We're going to take a break now for half an hour. We'll see you then.