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Mind Over Time

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Now that we've finally figured out where our biological clocks are located, can we learn to control them?

by Mark Caldwell

Suppose you could reset the inner clocks that run your life--programming yourself, for example, to wake up fresh and alert at 5:30 a.m. if you had to make a crucial breakfast meeting, or shutting off the hunger that drives you to scarf a bag of tortilla chips every afternoon.

If the prospect of controlling your body's chronometers seems a pleasing luxury, consider the case of Jason K., a New Jersey attorney. Jason suffers from a debilitating malfunction of his biological clock called seasonal affective disorder, or sad. It may seem a remote or even a fanciful ailment,especially during the summer, when its effects ebb, but it can throw the entire year, not to mention a whole life, into terrible turmoil.

"It came up on me gradually, over time," Jason says. As the days got darker and darker going into fall and then winter, "My mood got darker. By winter I'd feel an overall sluggishness that made the work difficult; it took dramatically more effort to get anything done. Sleep wasn't restful; I found myself waking up 15 times every night just to see what time it was. And I developed an excessive craving for sweets."

Jason's experience is not uncommon. In a recent New York City survey, more than one-third of responding adults reported at least mild winter malaise; 6 out of 100 reported severe depression. Michael Terman, a clinical psychologist at Columbia Presbyterian Medical Center's New York State Psychiatric Institute in New York City, and a leading SAD researcher, notes that the degree of suffering goes well beyond typical holiday blues.

"When it hits," Terman says, "it's not just a matter of mood. It can be truly disabling for five months of the year, and it can cause an active social withdrawal--mothers who can't mother, a loss of interest in work, a total loss of libido." Although the pall usually lifts during the spring, he says, SAD can throw life permanently off course: "It's no small thing if you can't maintain a nine-to-five work schedule in winter." Some SAD sufferers, he says, simply gravitate toward a lifestyle that accommodates the disease. "They tend to drift into work subcultures. They become freelancers, theater people, perennial graduate students--and many end up feeling their early goals in life are unachievable." [See "Are You SAD?" below.]

Yet the syndrome is only one among a constellation of sleep disorders and related ills caused by biological clocks run amok. Indeed, inner clocks can sometimes cause trouble even when they're ticking away smoothly. The bleary-eyed miseries of jet lag are a familiar example of what can happen when you're hurled across time zones and your personal clock jolts out of sync with the pace of the rest of the world. These are only the obvious disorders. Susceptibility to pain, for example, tends to crest in the morning and ebb as the day wears on. Heart attacks are most likely to strike in midmorning. And biological rhythms can stretch across months as well as days and weeks: many animal species migrate and mate only according to strict seasonal timetables.

Folklore and common sense have been telling us for centuries that we depend on inner clocks, but what and where they are and how they work has long remained a mystery. Now, thanks to a series of recent laboratory coups, the once-baffling components of our biological clocks have become clearer. For the first time, scientists have a diagram, remarkable in both elegance and simplicity, that shows where in our brains the chronometer is, how it uses the machinery in our cells as clockwork, and how--like the clacking and jangling Baby Bens that once regulated the pace of American days--it can be slowed down, speeded up, or reset. Most recently researchers have divined how the brain's clock, uncannily like the built-in timer that automatically turns on your coffeemaker every morning, can switch on and turn off pieces of biological machinery, suggesting that we may ultimately be able to regulate these processes at our pleasure, instead of submitting crankily to their regulating us.

In the brain, a recently discovered cluster of nerve cells called the suprachiasmatic nucleus, or SCN, appears to be at the heart of timekeeping. In mammals, the organ is remarkably reliable: even if it's removed from an experimental animal and placed in a dish, it can continue to keep time on its own for at least a day. The SCN is actually a pair of structures, like most parts of the brain. One half sits in the left hemisphere and one in the right, just behind and a bit below the eyes. "Each is made up of about 10,000 densely packed neurons," explains Steven Reppert, the Harvard neurobiologist whose laboratory has been a key player in recent discoveries. "The SCNs are located just above where your optic nerves come together at the base of the brain." This is no accident: the SCN depends on light for what circadian-clock mavens call entrainment--synchronizing the inner clock with the cycles of light and darkness in the world outside. Some of the latest research, on mice, suggests that mammals have a set of special photoreceptors in their eyes, which pick up light signals and carry them directly to the SCN. These photoreceptors are different from the rods and cones used to perceive light hitting the retina.

A flood of light striking the right photoreceptors at the right time does just what the knobs on the back of that vintage Baby Ben do: reset the hands of the clock. A burst of light in the morning sets the clock ahead; a burst in the evening puts it backward. If, like Jason, you're a northerner, your inner clock may run slow in winter, falling behind without early-morning light that would normally nudge it forward. "When I talk with patients here in New York," Terman explains, "I tell them that, biologically speaking, they're living in Chicago." When the bedside alarm goes off, New York wakes up, slipping into high gear. But their inner timers lag an hour or more behind, at Chicago or even California time, insisting that their brains and bodies should still be sound asleep.

Not everyone has the problem. Most people aren't as vulnerable to a lack of morning light, which helps keep the inner clock in tune with the external environment. Every morning, the light of dawn makes its way to the SCN and advances the inner clock, allowing it to catch up with local time, rousing and easing us into daytime activity in blissful synchrony with local time. And because the nerve pathway from the eyes into the SCN bypasses those parts of the brain that register conscious sight, the inner clock can react to ambient light even when we're sound asleep. The light of dawn penetrates the eyelids, registers on the retina, and relays a silent signal into the SCN. If the internal clock has a tendency to run slow, morning light automatically shifts it ahead, putting it back in step with the world outside. It's beautifully simple--unless you live far enough above the equator so that in winter you're up, breakfasted, and at work before dawn. In fact, SAD seems to be more common in northern latitudes. When natural light is scarce, the best way to reset the inner clock is with a burst of artificial light.

The vital importance of the SCN as a biological time setter is a recent discovery, though not a new one. While its roots go back to the early 1900s (See "Father of Circadian Clocks," below) it wasn't characterized until the early 1970s. What's really new is an understanding of the SCN's internal mechanism. Neuroscientists have begun to pry off the clock's cover to get a look at the workings. Research at a number of laboratories--Brandeis, Dartmouth, Harvard, Northwestern, Rockefeller, and Scripps--has revealed the workhorse of the biological clock to be an ingenious and ingeniously simple device in the individual cells that make up the SCN (and perhaps other time-sensitive organs as well). Such cells seem to run the whole system from the bottom up. "We're now pretty certain," Reppert says, "that the SCN is made up of numerous autonomous clocks in individual cells--and all the molecular machinery you need seems to reside in a single neuron." Underneath it all is one clock, the clock in the cell.

But how? Let's take a simple model: Drosophila melanogaster, the common fruit fly. In principle its cellular clock works much like those found in mammals. The cycle begins with two of the fly's genes. Like most active genes in living DNA, they form templates for the construction of proteins, in this case called dCLOCK and dBMAL1. As these proteins build up in the cell nucleus--a process that takes time--they join and glide downstream. There they bind to and switch on two more clock genes, called per and tim. These additional genes begin producing proteins of their own, which form in the cytoplasm surrounding the cell nucleus, where they join and accumulate as the day wears on.
That, in essence, is the tick of the clock. The truly ingenious part is the tock. Once they reach a critical mass, per and tim proteins move back into the cell nucleus, where they appear to block the operation of the genes that make dCLOCK and dBMAL1, shutting down the production of per and tim proteins--just as the swing of its pendulum brings the motion of a mechanical clock to an ever-so-brief halt. In the cell, this halt lasts until the per and tim proteins dissipate. Once they're gone, the dCLOCK and dBMAL1 proteins reappear, starting the whole process again. The cycle takes about a day.

In practice, of course, the clock is more complex, with some intriguing refinements. In fruit flies, light breaks down the tim protein, while in mammals, light activates per genes--which may explain how bursts of light can reset the cellular clock when it drifts out of alignment. Although the details vary from species to species, the basic principle seems to be universal, and it could possibly be the ultimate time source for everything that lives. The clocks are self-starting and remarkably reliable. Even when cut off from external light and temperature cues that reveal the time of day, they slip out of alignment only gradually. Ambient light doesn't control the clocks; it simply helps adjust them.
Although we're still uncertain how a malfunctioning biological clock affects behavior, or how it can lead to debilitating cycles of gloom and anguish, Reppert's team has just published a paper suggesting an answer. They established a

connection between the individual nerve cells whose microscopic inner machinery drives the SCN mechanism, and the manufacture of hormones. The same proteins that build up and break down over a 24-hour cycle to run the circadian clock directly cause a similar oscillation in the release of a hormone that can regulate how animals act. "Basically, we had a framework for the molecular gears of the circadian clock in mammals," Reppert says. "What we wanted to get was a link to actual behavior."

Reppert found that clock proteins switch on and off the gene that produces vasopressin. Outside the brain, vasopressin is important in controlling the salt and water balance in the body. In the brain, however, it's practically a different hormone, implicated in cycles of rest and activity in mammals. While vasopressin doesn't seem to influence the kinds of behavior involved in seasonal affective disorder, it does supply an exciting model for the a-to-z operation of biological clocks and for how a malfunction can cause abnormalities in mood or behavior. Now scientists can see a continuum from the cycling of light and dark in the atmosphere around us, the world clock, inward to the SCN personal clock, then still further inward to the microscopic nerve-cell clocks, and finally, to the production of a hormone.
That is only a beginning. Vasopressin is just one of a vast range of substances that regulate behavior. Cellular clocks haven't yet been directly linked to the cycling of familiar behavior- and mood-modulating substances like serotonin and melatonin (See "Melatonin: Miracle or Myth?" below). "It's going to take another decade to work out a connection between Reppert's work and therapeutics," Terman predicts. But it isn't hard to foresee how visionary circadian-clock therapies might work. As a matter of fact, a couple are already in place. Jet lag, for example, might respond favorably to melatonin, at least for some people (see "Can Jet Lag Be Avoided?" below). And there's also an effective treatment for SAD. In 1980, Alfred Lewy, at the Oregon Health Sciences University's Sleep and Mood Disorders Laboratory, successfully relieved a man who suffered from recurrent winter depression simply by exposing him to bright light over several days, from six to nine every morning and four to seven every evening. In later treatments Lewy worked the dosage down to two hours of exposure a day at an intensity of 2,500 lux, which approximates the strength of natural light just after the sun has fully risen. Today, standard therapy for SAD patients involves exposure to artificial light for 30 minutes each morning at an intensity of 10,000 lux (which approximates the strength of natural light about 40 minutes after sunrise).

Terman's group has been working on refining the treatment: a computerized light system for the bedroom, imitating the gradual, naturally intensifying light of dawn. Jason tried it, and it worked beautifully. "Over a couple of hours it simulates the sun coming up," he says. "Somehow you're aware of it even when you're asleep: the light coming through your eyelids is a luxurious feeling." Within days, Jason's depression dissipated, his sleep habits returned to normal, and the sweet tooth cravings became somewhat less pronounced.
The possibilities raised by the discoveries on the workings of the biological clock go beyond moodiness and depression. If heart attacks happen at the prompting of a time signal, for example, is there a way to turn that signal off? Is there a way to control weight by spacing out the timing of hunger pangs? Is it possible to predict, even control, not just the day, but the hour, a baby is born? For the first time, science knows where and how to look for the answers to these questions.

Are You SAD?
Experts on seasonal affective disorder are quick to warn that the field is ablaze with misinformation and rife with scams. If you search the World Wide Web at random for information, you may end up in the hands of commercial interests more bent on selling you a pricey light box than making a careful diagnosis. Michael Terman of Columbia Presbyterian Medical Center's New York State Psychiatric Institute has devised the following preliminary self-examination, but he cautions that "the diagnosis of SAD requires the assistance of a mental health professional." *Does work and family life become more difficult for you every winter? *Do you experience constant fatigue or waves of fatigue in winter but not in summer? *Do your eating habits change in winter, with more sweet or starch intake? *Does your general feeling of well-being tend to decline during the winter? *Do you usually feel fine in late spring and summer--or even energized and exuberant--without underlying depressed emotions?

To examine these issues in more depth, you may obtain the Personal Inventory for Depression and SAD Self-Assessment exam, which includes a clinical interpretation guide. The self-assessment exam is distributed by the Center for Environmental Therapeutics, in Georgetown, Colorado. The questionnaire can be easily downloaded from the World Wide Web at www.cet.org/cet2000. --M.C.

Father of Circadian Clocks

The history of biological clocks began, for all practical purposes, in 1911, with a classic experiment conducted by Karl von Frisch (1886-1982), an Austrian zoologist. He studied the European minnow, Phoxinus phoxinus, which turns dark in the presence of light and lightens whenever it gets dark. Von Frisch discovered that the minnows weren't responding to ambient light perceived through their eyes. Blind minnows, to his surprise, still reliably darkened in response to light. They continued to do so even when, in a series of increasingly grisly experiments, he anaesthetized them, removed their facial nerves, and kept paring away flesh until he reached their skulls.

Von Frisch inferred that something deep inside the brain itself could respond directly to light. He later traced this effect to the minnow's pineal gland, which we now know to be the source of melatonin. --M.C.

Melatonin: Miracle or Myth?

Mention biorhythms and most Americans think of one word: melatonin. Available as a so-called dietary supplement at most drugstores, melatonin is claimed to sometimes exceed the benefits of aspirin, penicillin, and premium Swiss chocolate combined. Doesn't it zap jet lag? Cure AIDS? Reverse Alzheimer's disease? Act as an antioxidant to help prevent cancer? Lengthen life? The short answers, according to the experts are: perhaps, no, no, maybe but don't count on it, and no.

So what good is it? The hormone is produced in the pineal gland near the base of the brain, peaking at night and ebbing during the day. The cycle isn't dependent on whether you're active or resting, and thus, says clinical psychologist Michael Terman, a careful measurement of melatonin levels can help determine whether your inner clock is misaligned with local time. In some mammals, melatonin seems to regulate changes in physical appearance and behavior that come with the onset of breeding season. When a fetus is developing in the womb, the mother's melatonin levels may reset the fetus's biological clock in the weeks or months before its retina has developed sufficiently to react to light.

Melatonin does help induce sleep, perhaps because as its levels peak at night, it tamps down the activity of nerve cells in the SCN, keeping the circadian clock in good running order. This may be why it helps jet lag. But the effects of taking melatonin are not well understood and little is known about dosage requirements. So most physicians are still wary of recommending it. --M.C.

Can Jet Lag Be Avoided?

Some people say it's worse when they're heading east, and their bodies think it's three or four hours earlier than local time. Others suffer more when it's 11:00 P.M. in Los Angeles but their bodies are still on New York time. Almost anyone who travels knows the feelings--fatigue, light-headedness, crankiness, upset stomach. And there's general agreement about the cause: a misalignment between one's inner clock and the day-night rhythms of the world outside. Remedies abound. Over the Internet you can buy a pricey portable battery-operated visor that fits over your head and bathes you with light. It comes with a slide rule that tells you when and for how long you're supposed to don it. Seven Hilton hotels offer rooms equipped with light boxes and a light-emitting alarm clock that expose you to light for half an hour before you're supposed to wake.

Then there's melatonin: the jury's still out, but some evidence suggests it's effective. Taken at twilight, melatonin seems to set your circadian clock back; in the morning, a dose pushes the timer forward. In 1997, Harvard neurobiologist Steven Reppert and his colleagues discovered another effect: during normal sleep, it may tamp down the operation of nerve cells in the suprachiasmatic nucleus (SCN), thus preventing it from being accidentally reset--an effect that may also help control jet lag.

Still, Reppert doesn't take it. It's known, for example, that melatonin affects reproductive behavior and body weight in other mammals. Is it worth potential health risks just to get over a day or two of irritability and grogginess? --M.C.