PHYSIOLOGY

Setting the Human Clock: Technique Challenged

Skeptics fault a study showing that people's sleep-wake cycles can be altered by shining light on the backs of their knees

Imagine getting over jet lag simply by strapping a light to your leg and leaving it on while you sleep or read in your airline seat. This scenario was suggested by a report published in *Science* 4 years ago describing a new way to reset the human internal clock. The discovery captured the imagination of scientists and entrepreneurs as well as the public. But researchers at Harvard Medical School in Boston now have cast doubt on the finding—and on prospects for commercializing this patented form of light therapy.

In the original study, Scott Campbell and Patricia Murphy of Cornell University Medical College in New York state reported that by shining light on the backs of the knees of human subjects, they could shift the so-called circadian clock that governs sleep-wake cycles (*Science*, 16 January 1998, p. 396). The scientists chose the area behind the knees because it is laced with blood vessels close to the skin, and they believed it might be possible to transmit a timing signal through blood. But many researchers in the field were skeptical. Now circadian clock researchers Kenneth Wright and Charles Czeisler of Harvard Medical School report on page 571 that they have refuted the earlier study.

Many clock researchers praise the new work: "I am convinced that this shows that it is very difficult to replicate the [original] finding," says circadian physiologist Derk-Jan Dijk of the University of Surrey, U.K. "This paper will have a high impact," adds clock researcher Shin Yamazaki of the University of Virginia in Charlottesville. "The experiment ... is really well controlled." Campbell counters, however, that the original study was properly controlled and has been replicated in his lab.

Before 1998, researchers had known that exposing animals or humans to bright light during the night could reset, or "entrain," their biological clocks. But Campbell and Murphy's report was shocking, says clock researcher Russell Foster of the Imperial College of Science, Technology and Medicine in London, because it "completely contradicted" a large body of research showing that in all mammals tested, including humans, light can reach the clock only through the eyes. "There was absolutely no evidence that individuals without eyes can entrain to light," says Foster.

But iconoclastic findings have been right before, and if this one were, it might mean more than a cure for jet lag. Light shone on skin areas might replace the unpleasant regimen for seasonal affective disorder, a type of depression brought on by the short days of winter, that exposes people's eyes to bright light for hours each day. And shift workers might use the therapy to avoid drowsiness in dimly lit conditions. "It would have been terrific," says Foster, "because it was a way of selectively hitting the circadian system without overwhelming the visual system." The Cornell group patented the approach, but it has not been licensed.

Based on its promise, other researchers tried to build on the finding but did not get the expected results. For example, if light to the knees resets the clock, it should suppress the nighttime hormone melatonin, but several labs found that it did not.

Night-light. BiliBlanket pads like this one were used in the study, carried out in total darkness, to shine light on the backs of knees.

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Until recently, no one had duplicated the conditions Campbell and Murphy used, and that is what Wright and Czeisler decided to do. They used the same light source, a fiber-optic lamp called the BiliBlanket, designed for treating premature infants with light. Like Campbell and Murphy, they wrapped the blanket around the subjects' knees, shielded it so no light reached the eyes, and treated their subjects for 3 hours.

But Wright and Czeisler were dissatisfied with some aspects of Campbell and Murphy's experiment. Subjects in the earlier trial had been seated in a dimly lit room for treatment. Dim light was believed at the time not to affect the clock, but Wright and Czeisler have since shown that even lower light levels can do so, so they kept their subjects in total darkness before and during the treatment. What's more, changing position can alter physiological indicators of a subject's circadian phase such as body temperature or melatonin levels. So the Harvard subjects remained lying down.

Campbell and Murphy had used body temperature as the indicator of circadian phase for all their subjects. But Elizabeth Klerman of Harvard Medical School reported in 1999 that body temperature can be off by as much as 5 hours from circadian phase in subjects who are allowed to move around. So Wright and Czeisler used melatonin levels, thought to be a more precise measure. Unlike the New York team, they gave their subjects several days to adjust to the laboratory routine before beginning the experiment, and neither researchers nor subjects knew who got the treatment and who didn't.

The result: Light to the back of the knees did not shift the subjects' clocks.

"We still don't know for sure why there are these differences between the results," says Dijk. But Dijk and others suspect that Campbell and Murphy's study could have been influenced by a statistical phenomenon called regression to the mean. A person's clock can be either delayed or advanced, depending on the time of light treatment. The subjects presented in Campbell and Murphy's report who underwent a delay had clocks that ran earlier than average to begin with, and those who underwent an advance had clocks that ran later than average. Statistically, Dijk says it was likely that even without any treatment, these subjects' cycles would be closer to the mean on the next measurement.

"Regression to the mean is always a legitimate concern in any experiment," says Campbell, but he believes his original results are valid. "I totally understand why there has been skepticism" about the work, he adds, given that there is no known mechanism by which the signal could travel from knee to brain. His team is currently searching for the answer. "If we can show physiological changes in which mechanism can be inferred," he says, "it would add a lot of credibility to the study."

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