TECHNOLOGY TRANSFER

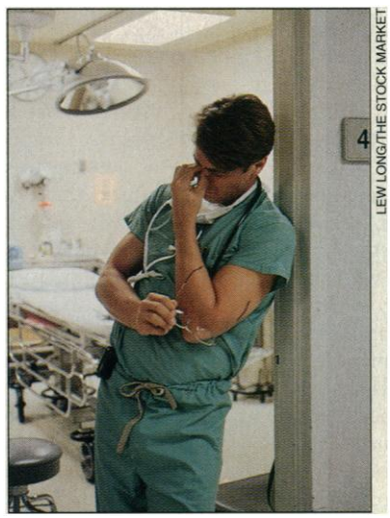
Chronobiologists Out of Sync Over Light Therapy Patents

Last December, Scott Campbell, a sleep researcher at Cornell Medical School, got a letter from Harvard's Brigham and Women's Hospital offering him a startling deal: He could use their patented technology in his research free of charge if he promised not to commercialize his findings and to provide Brigham and Women's—within 10 days of any request—written reports describing his research. That letter sparked an outcry that is still reverberating around the field.

For many in the community, it was the first indication that Brigham and Women's Hospital had won a slew of U.S. patents for light therapy—the use of bright artificial light to combat the insomnia and drowsiness that plagues shift workers, people with jet lag, and others who suffer from sleep disorders in which the body's clock fails to keep time with the external environment. A few sleep researchers were shocked to learn that the therapeutic use of light could be patented at all. Most were angry that Brigham and Women's had acquired a broad patent on a technique that they claim had been developed piecemeal by a whole generation of scientists—not just the three Harvard researchers, Charles Czeisler, Richard Kronauer, and James Allan, named on the patents.

The patents have so incensed chronobiologists—experts on how the body keeps in sync with the environment—that the Society for Light Treatment and Biological Rhythms (SLTBR) has drafted a statement, which it plans to send to its members this month, protesting the award. It reads in part: "Many scientists in several countries have reported on research carried out over the last 20 years concerning the use of light as a [tool for resetting body rhythms] and therapeutic agent in humans. In our view, this broad knowledge base is in the public domain. That which is in the public domain cannot be protected by patent claims." In a written statement to *Science*, SLTBR president Michael Terman of the New York State Psychiatric Institute explained that the society took this step because "many of our members...were confused and alarmed upon reading these patents. The Board of Directors of SLTBR considered it their responsibility to the membership to assist in clarifying and interpreting the situation."

For its part, the Harvard team hotly denies that they have done anything wrong. Indeed, Czeisler says that although he was "mortified" when he discovered that the patent awards so upset workers in the field, he doesn't regret that Brigham and Women's applied for them. "I was interested in [light therapy] being used in society," he says. "And no one would invest the necessary resources to make the transition from the laboratory to the workplace," without patent protection. The criticism, says Todd Keiller, vice president of the venture department at Brigham and Women's that helped win the patents, is motivated by jealousy. "What they get upset [about] is 'Boy. I should have cashed in on [light therapy],'" he says.



LEW LONG/THE STOCK MARKET

Lightening the load. Light therapy may cure shift workers' blues.

The rationale behind light therapy, although it took decades to unravel, is simplicity itself. Under normal conditions, the body's internal clock is set by natural sunlight, which is much brighter than indoor lighting. The clock in turn sets the cadence for every other 24-hour body rhythm—determining when a person is sleepy or fully awake, for example, as well as regulating less noticeable body rhythms such as cycles in temperature and levels of blood chemicals. Sometimes, however, things go awry.

Many of the 20 million shift workers in the United States cannot keep in tempo with their ever-changing work schedules, making it difficult for them to stay alert at work and to sleep during their off periods. That's not just bad for the workers' health and productivity, it also has dire consequences for industrial safety. For example, the strain of shift work is thought to have contributed to both the Three Mile Island nuclear power plant accident, and the grounding of the *Exxon Valdez*.

Exposing shift workers to bright lights at specific times can help reset the clock, markedly ameliorating the sleepiness associated with such work. Light therapy could also stave off the miseries of jet lag, and in the homes of the elderly it could be used to prevent the chronic insomnia that often occurs as the body clock ages.

Brigham and Women's was well aware of this wealth of potential applications when it filed the first patent application on light therapy with the U.S. Patent and Trademark Office in 1987. The office ultimately awarded the hospital that patent in November 1992, and two further patents—adding up to over 100 claims in all—in the next 2 months. The patents cover the use of light to treat shift work and jet lag, as well as for certain types of insomnia. (The patents do not cover the use of light therapy for depression.) But most researchers in the field didn't become aware of the patents' existence for nearly a year—until Brigham and Women's venture department sent the letter to Campbell offering him the royalty-free research agreements. Campbell declined to sign his agreement, and the community reacted with outrage.

The critics' chief contention is that the key elements of light therapy were well established before the Harvard group filed its patent claims. "The effect of light on the circadian system [the body clock] was developed in the minds of many researchers who collaborated to develop the ideas, and suddenly one of our colleagues is taking out a patent on those ideas," says Serge Daan, a light researcher at the University of Groningen in the Netherlands. He claims Jürgen Aschoff, former director of the Max Planck Institute for Behavioral Physiology in Andechs, Germany, showed in 1979 that light entrains body rhythms. "These studies precede anything done at Harvard," says Daan.

Charmane Eastman, a sleep researcher at Rush-Presbyterian-St. Luke's Medical Center in Chicago, agrees. "Other people have used light to phase shift rhythms in humans including me and Al Lewy [a psychiatrist at Oregon Health Sciences University in Portland]." Still other researchers cite a presentation by Josephine Arendt of the University of Surrey, England, at the March 1986 meeting of England's Physiological Society as the key paper demonstrating that light pulses shift body rhythms in humans.

But Czeisler's having none of it. "The generation of chronobiologists that I grew up with said that light had no impact on the [human body clock]," he says. "I spent 10 years trying to convince people that light was the synchronizing agent." Although he says many of his colleagues had come around to that view by the late 1980s, Czeisler maintains that the first study to show beyond all doubt that light could reset the body clock was conducted by his team, which presented the results at meetings in 1987 and published them in *Science* in 1989. That study, which

underpins the patents, also showed for the first time that very bright light acts as a "strong" synchronizer of the body clock, shifting it to a new schedule in as little as 2 or 3 days, Czeisler says. This result, Kronauer maintains, "made the use of light practical in circumstances such as shift work."

Even that finding is controversial, however: In an upcoming issue of the *Journal of Biological Rhythms*, Daan and Domien Beersma, who also works at Groningen, will argue that the Czeisler team has not proven that "strong" resetting occurs in humans.

Not that the Czeisler team is without supporters. Robert Moore, director of the University of Pittsburgh's Center for Neuroscience and president of the Society for Research on Biological Rhythms, says he's not worried because the patents have passed muster at the patent office. Moreover, he says, "Dr. Czeisler has explicitly stated that they will not use the patents to interfere with research."

But not everyone is so sanguine about the implications of the patents. As Eve Van Cauter, a sleep researcher at the University of Chicago Medical School, who also received a licensing agreement from Brigham and Women's asks: Will researchers be able to continue consulting to companies on how to use light therapy protocols that they themselves developed? And, once light therapy is accepted by the American Sleep Disorders Association as a mainstream medical practice—a move that is expected by the fall—will clinical researchers be able to offer light therapy to their patients without violating Harvard's patents? Such questions can probably only be answered in court, predicts patent lawyer David Parker of Arnold, White, and Durkee, of Austin, Texas, who has studied the patents.

Brigham and Women's, meanwhile, has licensed the patents to Shiftwork Systems Inc. of Cambridge, Massachusetts, a company founded last June. The three inventors stand to gain 25% of all royalties with the rest going to Harvard University and Brigham and Women's Hospital. So far, the company, to which Czeisler and Kronauer are scientific advisers, has sold rhythm-resetting systems, for between $150,000 and $300,000, to at least five companies and government agencies—including the National Aeronautics and Space Administration and the Nuclear Regulatory Commission. The systems include high-intensity lights, and the computer equipment needed to change the lights in a manner that will most rapidly adjust the workers to their changing shifts. "We've demonstrated very exciting improvements in alertness, performance, and off-shift sleep quality," says Shiftwork president Theodore Baker. "The application of this technology to benefit shift workers is long overdue."

–Rachel Nowak

SCIENCE FUNDING

Program Gives Some States A Head Start in Bid for Grants

In 1977, Richard Atkinson, then director of the National Science Foundation (NSF), was caught off guard when a congressman from Arkansas tossed him a curve during a hearing: How much research did NSF fund in his state? Atkinson said he wasn't sure, but it probably wasn't very much. The congressman quickly followed up with a soft pitch. "I told him I didn't want a handout," recalls Ray Thornton (D–AR), but "I wanted NSF to realize discoveries could happen anywhere in the country. And to make discoveries, Arkansas scientists had to improve their ability to compete for grants."

Thornton's impromptu remarks set Atkinson thinking about how NSF could narrow the gap between Arkansas and powerhouses like California and Massachusetts in the competition for federal research dollars. Three years later, NSF awarded the first grants in the Experimental Program to Stimulate Competitive Research (EPSCoR), a novel program that makes small, competitive awards to assist academic researchers in "have-not" states. The money helps researchers take the first step on the road to obtaining other federal grants, and a requirement for matching funds forces states to play a more active role in supporting science.

The formula has recently proved to be a winner—at least in accumulating funds. State officials, who view EPSCoR as a valuable supplement to their plans for economic development, have been spectacularly successful in lobbying to expand the program. In the past 3 years, six other federal agencies have launched their own EPSCoR programs and the combined funding has grown 10-fold, to $70 million a year (see map). Congress likes these programs because they spread money around the country. They are also popular with NSF and the research community because they parcel out their funds on the basis of rigorous merit review, not a congressional earmark.

But EPSCoR's popularity is a double-edged sword: States are having an increasingly tough time meeting the requirement that they match whatever money the federal government puts in. Indeed, the program has now grown to the point where some states are beginning to wonder how much more of a good thing they can afford. "This is a case where prosperity could be [EPSCoR's] worst enemy," says Irwin Feller, an economics professor at Pennsylvania State University who has evaluated the program.

For researchers funded by EPSCoR, however, the program can be a godsend. At a recent meeting of EPSCoR's 19 state directors, for example, dozens of scientists, in what one observer described as a revival-like atmosphere, offered personal testimonials to the value of the program to their careers. Take the case of Jack Horner. In 1982, Horner, then a young paleontologist at Montana State University, wanted to lead a dig at "Egg Mountain," a site in the middle of Montana where he had done some preliminary digging a few years earlier. Horner stood little chance of getting a traditional federal grant, however: He lacked a college degree. So he submitted a proposal to the state's EPSCoR committee, which secured $15,000 for his dig. The rest, as they say, is history. Horner's work at Egg Mountain, coupled with observations from earlier digs, led him to posit that dinosaurs nurtured their young—a theory that is now widely accepted by paleontologists and has been popularized in the novel/movie *Jurassic Park*.

In its own way, NSF's approach to helping scientifically disadvantaged states has also become a classic. The feds and the states each invest anywhere from $50,000 to $1.5 million a year in peer-reviewed projects and programs judged most likely to succeed by a network of state scientific committees that NSF helped to set up in the 1980s. NSF reviews the projects to ensure they're scientifically sound and have potential to help states build up their research capacity; it also reviews the funding requests. This system "empowers institutions and states to think about their science and technology goals," says Richard Anderson, NSF's EPSCoR program director.

These modest attempts to improve the ability of scientists to compete for additional federal funds translates into a stronger research infrastructure, say NSF officials, which benefits the entire state. In particular, the program provides more opportunities for undergraduates to learn firsthand about research, gives budding scientists the chance to pursue their careers close to home, and increases the possibility of collaboration with industry, leading to new jobs and economic development. "Some states have traditionally been like Third World countries, simply exporting talent, natural resources, and people," says Joseph Danek, head of NSF's systemic reform program, which operates EPSCoR. "We've begun to change that."

NSF is currently funding a study of how