



THE SANDMAN'S VISITS HAVE A LOT TO DO

WITH OUR MENTAL HEALTH | BY DAVID R. ELTZ

MORE THAN A
GOOD
SNOOZE

Plato believed that vapors, rising from the stomach during digestion, gathered at the base of the brain, blocked its pores, and cut the brain off from the body to induce sleep. The process is a little more complicated than what Plato described 2,400 years ago, but, in some ways, he wasn't all that wrong.

The onset of the sleep process indeed seems to be the gathering of *something*—perhaps a substance like the neurochemical adenosine building up in our basal forebrain during the day while our body's natural, 24-hour clock cycles toward sleep. The two processes may or may not combine to flip an elusive “sleep switch” in our hypothalamus; no one can quite say for sure—yet. What is known: Sleep is crucial for our physiological and

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mental restoration and for strong memory. It keeps emotional outbursts in check, our immune systems humming, our motivation replenished.

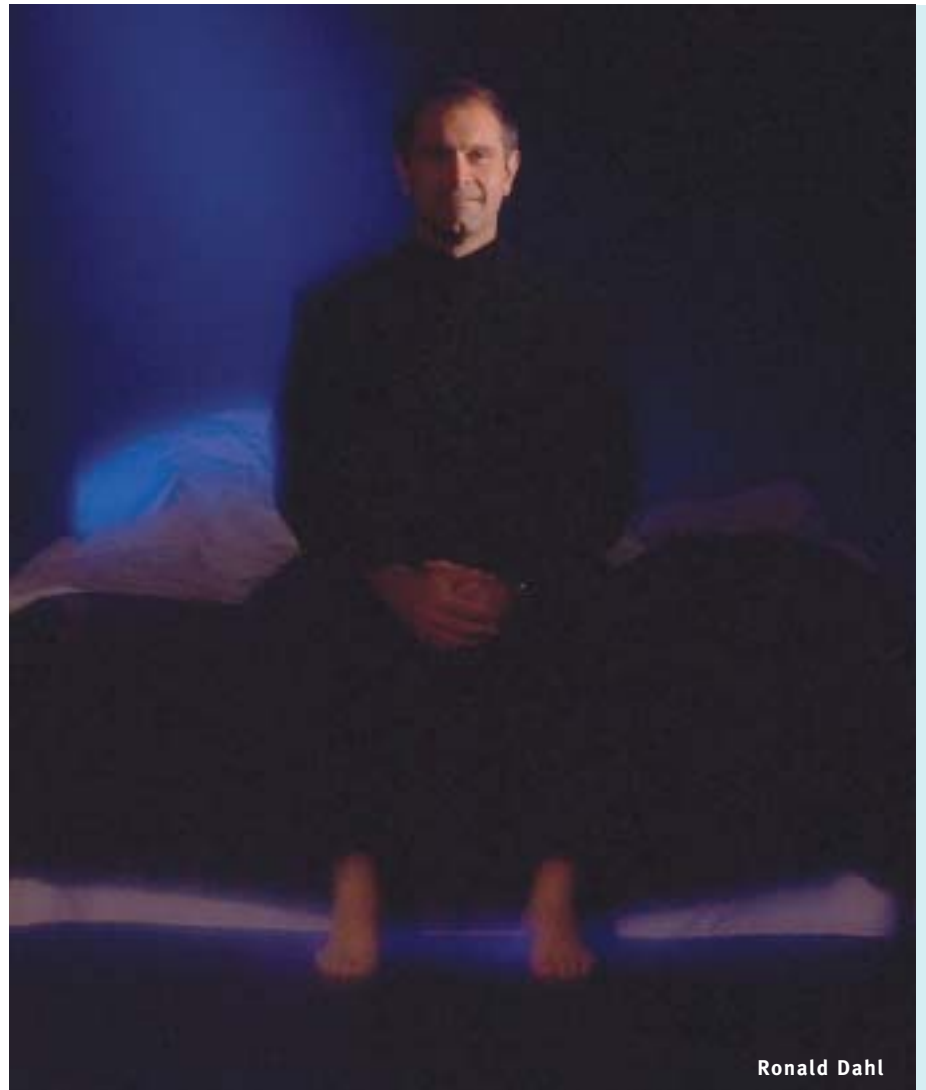
Human beings maintain a curious relationship with sleep, an intimacy beyond physiological necessity. When we sleep well, we are more likely to accomplish, to thrive. Yet sometimes we cheat sleep, pushing the limits of endurance to carve more from life; a drug named modafinil can keep one awake for nearly two days without bringing on physiological mutiny. When our courtship with sleep goes unrequited, pharmaceutical interferences aside, we complain of sluggishness, we lack focus. To recover, we might even visit the Web's sleep chat rooms, sleep services, sleep seminars, and sleep malls. We take power naps and sleep in on weekends.

We organize around sleep. Governments place sleep requirements on airline pilots and truckers (yet, interestingly, not on doctors and politicians). In November, the National Science Foundation hosted a Drowsy Driving Summit in Washington, DC, for good reason: The National Highway Traffic Safety Administration estimates that driver fatigue causes 100,000 crashes annually, translating into 1,550 deaths and 71,000 injuries.

In 1910, Americans averaged nine hours of sleep a night; today, we're lucky if we get seven. The National Institutes of Health (NIH) reports that 70 million Americans suffer from sleep problems, 60 percent of them from chronic disorders, adding \$15.9 billion annually to the cost of health care. The NIH believes sleeplessness is so pervasive, the agency is attempting to educate children about the importance of adequate sleep, enlisting the cartoon tomcat Garfield on a "Star Sleeper" mission online.

At the University of Pittsburgh, for the better part of 30 years, scientists at Western Psychiatric Institute and Clinic (WPIC) have disassembled

and reassembled the workings of sleep, offering insight into adolescent mood swings, circadian rhythms, and then some. Their hallmark, though, has been giving wake-up calls on sleep's relationship to depression. What they've found gives credence to the Welsh proverb, "Disease and sleep keep far apart."



Ronald Dahl

EMOTIONAL RESCUE

Alum Ronald E. Dahl (MD '84) began his research in the early 1980s during medical school under, among others, David J. Kupfer, chair of psychiatry. (By then, Kupfer had put WPIC on the sleep-research map with discoveries like the finding that depressed people slip into REM sleep about 20 minutes sooner than those who aren't depressed.)

But Dahl was interested in the circadian rhythms of beta-endorphin, an opiate-like peptide that increases pain thresholds. He found sleep to be "this messy thing on this beautiful side of the

rhythms of hormones.” Yet Dahl had a notion that this messiness played a role in the development of regulatory systems, including the regulation of emotions. Soon he was asking, *What is this sleep stuff?*

“We had *no idea* what the purpose of sleep was,” Dahl says, holding out both his palms with typical dramatic emphasis.

After heading to Duke University for his pediatric residency, Dahl returned to Pitt in 1987. He spent the next 10 years looking at sleep in relation to depression, à la Kupfer. Dahl’s research, which focuses on children and adolescents, has shown that, in youth, sleep problems are strongly linked to emotional and behavioral problems. His questions focused increasingly on changes to sleep and emotions that are tied to puberty.

From his early work, Dahl, today the director of the child and adolescent sleep laboratory at WPIC, knew that people who slept fewer hours than they needed had difficulty regulating their emotions. “This system that controls the level of arousal for emotions and the system that controls the level of arousal related to sleep regulation share some of the same machinery in the brain,” Dahl says.

Hints about what’s happening in that machinery and how to understand depression, in particular, appear during adolescence. Teenagers’ bodies are flooded with hormones. Their biological tendency is to stay awake later and rise later. Social pressures also mount. They stay up to chat with friends on the Internet but still need to be up at, perhaps, 5 a.m. for school. They require some nine

hours of sleep a night but are running on six. They become sleep deprived. Their moods, already in flux, arc wildly. Sleep deprivation impairs their ability to curb behavior to meet social situations, to focus on music and other interests. They are tired and touchy.

“Most adolescents get by,” Dahl says. “Particularly if they’re smart, have social support, or push themselves. But for some, the burden of sleep deprivation tips the balance the wrong way. Kids who have trouble regulating their emotions may be especially vulnerable.”

In one study (*NeuroReport*, January 5, 1998), Dahl and Mark Redfern, a Pitt professor of bioengineering, otolaryngology, and rehabilitation science, examined the effects of sleep deprivation on postural balance. The researchers asked sleepy teens to stand on a platform that measured how much they swayed back and forth, even when they thought they were standing still. When the teens performed a single task—i.e., reacting as quickly as possible to a light—no problem. But when they needed to do a more difficult task, one that required judgment, their balance became unstable. (When the teens had plenty of sleep, however, they were able to keep their balance during the difficult task.) The results parallel studies showing that sleep deprivation can interfere when people balance challenging mental and emotional tasks. In other words, the results mirror what’s going on in a teen’s life, according to Dahl. Teens cope with intensely competing social and emotional tasks every day. Throw in sleep loss, and, says Dahl, “you couldn’t design a more powerful way to destabilize the system.”



Eric Nofzinger

DREAM WEAVING

In many ways, Eric Nofzinger (Fel '93, Res '91) began his career as a dream chaser. As a psychology major in the early 1980s at Miami University of Ohio, Nofzinger made a connection one day: Delusions, of grandeur, of being chased—the typical manifestations of schizophrenia—are also the occasional narratives of dreams. That seemingly strange relationship set Nofzinger, an associate professor of psychiatry, on a journey to see what was happening inside the brain during sleep. About six years ago, he had his first look—one of the very first neurobiological elucidations of sleep.

Naturally, Nofzinger started with dreams. Previous studies combining patient observation with the electroencephalogram (EEG), until about a decade ago the only scientific measure of sleep activity, indicated that the sleep of depressed people was disturbed during REM sleep, when dreams typically occur. But in the early 1990s, Pitt invested in new types of imaging, particularly positron emission tomography (PET), a technique that illuminates brain function through the injection of radioactive nuclides. Nofzinger knew from animal studies that REM sleep activated the limbic system, the “emotional brain,” one of the places in the human brain thought to be affected by depression. He was able to develop a technique in which a tagged glucose nuclide revealed what happened in the limbic system as people slept.

By 1997, Nofzinger was making public one of the first reports indicating that, in healthy individuals, the limbic system was active during REM sleep, *but not in depressed people*. The sleep disturbances and lack of neurological activity in those who are depressed, Nofzinger concluded, are due to a change in function in the frontal cortex—the area of the brain from which we get our focus and

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motivation. The findings seemed to confirm what clinical observation had long led psychiatrists to believe: Depressed people lose motivation and can't regulate their emotions because their brains aren't functioning properly.

Nofzinger has since been thinking about not only identifying where brain abnormalities occur, but also targeting treatments. In

one study, he has shown that the drug sustained-release bupropion restores function to the limbic system of some depressed people [*Psychiatry Research: Neuroimaging*, 2001, 106 (2)].

"In future studies we want to look at, for instance, 'Does psychotherapy do the same thing, or is this simply a neurochemical imbalance?'" Nofzinger says, gazing out the window of his office in WPIC at the unfolding urban landscape of Oakland. "It's very intriguing to think that, just by talking with somebody, you can change the underlying structure and function of the brain."



Martica Hall

DORMEZ-VOUS?

It was early 1998, and Martica Hall was receiving attention from the press about her work. She'd published a study indicating that disrupted sleep weakened the immune systems of elderly widows and widowers. This was the first direct evidence associating sleep disruptions with the stress-immune relationship in humans. The new faculty member at WPIC was about to be interviewed for a Pittsburgh evening news show. The office joke that day was that, with Pope John Paul II making a historic visit to Cuba, something would happen to bury Hall's work. "Monica Lewinsky happened," Hall says, laughing.

She made the news for about three seconds that night, but has done much since then to spread the word to scientists about the relationship between stress and sleep loss. When Hall, an assistant professor of psychiatry, came to Pitt in 1995 to complete a PhD in biopsychology, sleep researchers rarely asked subjects what was happening in their lives and how they felt about it. Now it's routine to use stress measures in such studies at the University.

Hall prefers to study people in their natural environments—their homes. Sleep labs tend to be alien to a study participant's experience. There are no family distractions. Room temperature is constant. "It's actually like a vacation," Hall says. "We have a VCR. People read books. The lab is sterile. It is not reality."

As the principal investigator of the Pittsburgh portion of a four-center study funded by NIH, she is looking at the relationship between sleep and menopause. The study will measure sleep and stress in 430 black, white, and Chinese-American women at the onset of menopause. "We'll be able to look at their sleep across their cycles as they approach menopause," Hall says.

A separate and recent pilot study Hall conducted with caregivers of men with Alzheimer's disease showed the caregivers (who were women) took a half-hour longer than normal to fall asleep and were awake more often throughout the night. Hall gave the women speed-dial telephones with programmed support numbers, taught them muscle relaxation and visualization, and encouraged them to establish strict sleep schedules. The women, as a result, took less time falling asleep, slept longer, and doubled their amount of delta wave, or deep, sleep (the physiologically restorative part of snoozing). Hall now awaits funding for a larger study. The best news: The pilot study results tell her that stress-related sleep disturbances are likely treatable.

FASCINATING RHYTHMS

Daniel J. Buysse (Fel '89, Res '87) remembers a conversation that changed the course of his career. One day in the late '80s, when he was a senior psychiatry resident at WPIC, he was talking with David Jarrett, a former faculty member in the Department of Psychiatry. Jarrett was elucidating circadian rhythms—the machinery of the human biological clock.

“It was this entire aspect of human biology that was never discussed in medical school,” Buysse says. “To think that there was this time dimension to our biology in our mental processes was just cool.”

The past president of the American Academy of Sleep Medicine, Buysse has spent 15 years tracking biological rhythms in sleep, especially in older adults. His work has shown that young adults have a much stronger circadian drive to fall asleep at night than do older people. Yet older people typically go to bed earlier than their younger counterparts.

Using EEG, Buysse has been able to demonstrate that both adults who are younger (20- to 30-year-olds) and adults who are older (people who are 70 and up) experience the same rhythmic patterns in their brain throughout the night. Somewhere between 3 and 5 a.m., adults in both age groups fall asleep fastest. As we age though, the intensity of the circadian patterns during sleep decreases, probably because the function in the areas of the brain thought to be associated with that phantom sleep switch deteriorates from cell loss. Many older adults still arrive at what Buysse calls the “sweet spot” of sleep in the early morning hours, but their sleep until then is restless, interrupted.

They may be able to alleviate the problem. In his studies, Buysse has older adults turn in for the night later than they usually would. His results show the revised bedtime schedule produces more effective sleep.

To Buysse, the idea that people could improve their sleep efficiency seemed important also in combating insomnia. The disorder, loosely defined as difficulty falling or staying asleep, affects some 10 percent of Americans. Buysse has discovered that insomnia is one of the first symptoms of depression, particularly in people who suffer from recurring depression. The finding could have major public health ramifications.

“If it turns out that identifying insomnia and treating it prevents even a portion of the cases that might have gone into depression, you’ve really reduced human suffering, and you’ve reduced health care costs substantially,” says Buysse.

Soon, Buysse, who sometimes has study participants carry PDAs so they can keep sleep diaries, will begin visiting primary care offices throughout Pittsburgh as part of a new study. He’ll be asking elderly patients to stay awake longer before trying to fall asleep, and to record the results.

He also has begun PET studies to test his hypothesis

that insomnia is a disease of overarousal, in which brain activity refuses to decrease with the onset of sleep, an aberration in the rhythms of sleep.

If Plato only knew. ■



Daniel Buysse

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