MEDICAL DISPATCH

EYES WIDE OPEN

Can science make regular sleep unnecessary?

BY JEROME GROOPMAN

The United States Army Aeromedical Research Laboratory is housed in a low orange brick building in Fort Rucker, Alabama, an isolated rural area covered with pine forest. Fort Rucker is the largest training base for helicopter pilots in the United States. It is also where, for more than a decade, the sleep researchers John and Lynn Caldwell have been conducting pioneering work on sleep deprivation. Their laboratory contains an elaborate flight simulator, in which a replica of a helicopter cockpit is mounted on a hydraulic base that reproduces the complex movements of flight: the downward pitch of takeoff, the torque of yawing left or right. Wraparound projected images mimic the visual experience of flight. "It's not like sitting at a video monitor or a computer screen,"John Caldwell said recently. "It's as close to the real thing as you can get." Not long ago, six helicopter pilots, in green Army flight suits and combat boots,were kept awake continuously for two forty-hour periods,separated by one night of recovery sleep. Detailed performance evaluations were conducted at regular intervals. The pilots were ordered to execute precision maneuvers:"Straight level for two minutes"; "One-hundred-eighty-degree turn at one hundred twenty knots"; "Now! Left standard-rate turn." The Caldwells were thus able to assesshow sleep deprivation affected the pilots'performance.

The military has a practical interest in such matters. Last month, for example, the first American bombing missions over Afghanistan required the two-man crew of a B-2 stealth plane to fly there from Missouri without stopping—a trip halfway around the world. In ordinary circumstances, as the Caldwells' research confirmed, sleep-deprived pilots make more errors and respond more slowly. Yet some of the pilots in the Caldwells' study were little affected by the loss of sleep. These were pilots who had been given the compound 2-(diphenylmethyl)-sulfinylacetamide, also known as modafinil. "Drugs are a tactical necessity for sleep deprivation," John Caldwell says.

Modafinil, which was approved not long ago by the Food and Drug Administration for the treatment of narcolepsy, is not a conventional stimulant, and has almost no detectable effect on people who are already fully alert. Yet the drug is at the center of a burgeoning new area of research into the neurochemistry of sleep and wakefulness, which promises to transform the treatment of sleep disorders. At the same time, scientists are exploring the prospect that people may be able to sustain a state of poised and productive alertness for days on end. Some have even raised the question of whether advances in biopharmacology will ultimately make regular sleep unnecessary.

Three years ago, scientists in Texas identified a new family of neurotransmitters called orexins. These are proteins produced by a remarkably small number of nerve cells—a few thousand, at most—in a single area of the hypothalamus. To find out what orexin did, scientists created "knockout" mice, which lacked the gene for that particular protein. The genetically engineered mice seemed normal in all respects but one: they had trouble staying awake. The scientists got in touch with Dr. Thomas Scammell, a sleep expert at Beth Israel Deaconess Medical Center, in Boston, and Dr. Clifford Saper, a professor of neurology at Harvard, who together confirmed that orexin regulated the sleep-wake cycle.

"If you think about a normal day, ninety-eight per cent of the time is spent either awake or asleep," Saper says. "There is a very short transition period between the two. The brain seems to have a flip-flop switch that changes the state from wakefulness to sleep, and orexin acts like the thumb that keeps this switch in the 'on' position." A deficiency of orexin causes narcolepsy.

Not long ago, Scammell and his research team dissected the hypothalamus of a narcoleptic. The hypothalamus appeared normal: it was the size of a plum, and had the color and consistency of tofu. A technician mounted it on a microtome, a precision instrument with a sharp blade, and cut the tissue into slices that were forty microns thick, or a little more than a thousandth of an inch. Each slice fell into a petri dish filled with a preservative solution, and floated like gossamer. Because tweezers might rip the delicate tissue, Scammell used a fine-haired paintbrush to lift and inspect the slices. He traced the part of the hypothalamus that normally contains the orexin neurons, a thin ivory-white band the width of a pencil lead, not far from the optic nerve, which runs from the retina to the base of the brain. Then a special reagent was used to test the tissue for the presence of orexin. On a normal hypothalamus, a swath of black dots would appear over the ivory-white band, indicating the presence of the protein. On the narcoleptic's hypothalamus, however, no black dots appeared.

What had happened to the orexin neurons? Unlike the knockout mice, the majority of human narcoleptics have normal genes for producing orexin proteins and receptors. Researchers believe that the orexin neurons are destroyed as part of an autoimmune reaction.

Until recently, the only "countermeasures" to sleepiness have been conventional stimulants, most notably amphetamines like Dexedrine. Dexedrine has been the standard treatment for narcolepsy, and it has had military applications as well: the United States Air Force supplied it to most air crews during the Persian Gulf War. More than sixty per cent of the pilots who used the drug said it was "essential" to accomplishing their mission. Unfortunately, amphetamines, in addition to a high potential for addiction, cause jitteriness, hypertension, rapid and irregular heartbeat, overconfidence, and a negative "rebound" effect—nonrestorative sleep—when they wear off. What scientists have sought instead is something that would boost wakefulness by replicating the brain chemistry of healthy, well-rested people.

JULES FEIFFER

Like many drugs, modafinil was discovered before its mode of action was understood. In the early nineteen-eighties, a French pharmaceutical company, Laboratoire Lafon, was exploring new treatments for somnolence by injecting hundreds of compounds into lab animals and observing the results. In rats and then in humans, modafinil was found to be awake," Matthew Miller, a pharmacologist at Cephalon, says. Miller believes that through evolution we have developed two different systems in the brain which previously were lumped together under the broad term of wakefulness. The first system is associated with vigilance, where one is tensely alert to potential threats in the environment.

A wakefulness drug appeals to "our relentless desire to control time," a researcher says.

cause wakefulness, yet, unlike stimulants, it did not give rise to hyperactivity. In clinical trials conducted by Cephalon, a Pennsylvania-based company that licensed the drug, modafinil was demonstrated to be a safe and effective treatment for narcolepsy. Somehow, it made up for the missing orexin.

"Modafinil is a key to understanding biologically what it means for us to

The physiology of vigilance seems to involve the dopamine, norepinephrine, and serotonin pathways: stimulating these pathways results in hyperactivity and a reduction of reaction time. The second system is the "calm" type of wakefulness, where one is attentive and engaged in so-called "executive functions"—able to focus on cognitive tasks. Such wakefulness may involve the histamine pathways. In Miller's view, the trouble with conventional stimulants—caffeine and cocaine, as well as amphetamines—is that they indiscriminately activate all the wakefulness-promoting neurons throughout the brain. Modafinil, by contrast, promotes the more selective firing of neuronal circuits in the cerebrum, particularly in the prefrontal cortex, where many of the higher executive functions of cognition and emotion seem to lie.

For narcoleptics, the results can be dramatic. The condition was recently diagnosed in a graduate student I'll call Joan LeBlanc, and modafinil was prescribed. She says she experiences neither a "rush" nor a "kick" as it takes effect, and there is no "crash" when it wears off. Dexedrine interferes with normal sleep, leaving its users feeling hung over when they awaken. This so-called sleep inertia often prompts the user to take more pills, and a vicious cycle ensues. Modafinil preserves normal "sleep architecture." "I have no problem going to sleep, and I wake up feeling refreshed," she says. "I'm not desperate for an afternoon nap, but I can take one when I want one." Unlike stimulants, modafinil seems to have no potential for addiction; nor have users been known to develop tolerance. Indeed, because of modafinil's effectiveness and safety, many physicians are experimenting with it for patients with other disorders; modafinil has been shown, for instance, to alleviate drowsiness and fatigue associated with multiple sclerosis, Parkinson's, and depression.

Of course, one of the reasons so many Americans have trouble staying awake is that they have trouble falling asleep. Dr. David White, a sleep expert at Boston's Brigham and Women's Hospital, estimates that nearly thirty per cent of the population has significant insomnia on occasion; for ten to fifteen per cent, it is a regular condition. Some researchers believe that the orexin pathway may point toward a new-generation sleeping pill that would not have the disadvantages of conventional sleeping pills, which almost always degrade the quality of the sleep they induce. A drug that blocked orexin might replicate the sort of rapid transition to sleep that narcoleptics experience. "But there is still a lot we don't know about the kind of sleep that might result," Thomas Scammell, the Boston sleep researcher, warns. "If it meant prolonging REM sleep, you might have eight hours of intense dreams with an erection." Paradoxically, some investigators speculate that modafinil itself could be helpful for insomniacs, since they report low energy during the day. A more alert, fruitful day could usher in a night of restorative sleep.

Even as sleep disorders increase, firms are pushing their employees to disrupt their normal sleep patterns in order to provide services around the clock. A fitness center that is open twenty-four hours a day, or a restaurant that can deliver in the early morning, or a brand manufacturer that can take orders and ship clothes and shoes and backpacks and watches whatever the hour may enjoy a significant advantage over its competitors. As *USA Today* recently reported, there are two hundred and thirty-seven Home Depots and nearly thirteen hundred Wal-Marts that never close. A health-club chain called 24 Hour Fitness has more than four hundred and thirty facilities; the chain spends an extra five million dollars a year to stay open all the time, and the extended hours generate an estimated fifty million dollars in additional revenue. In the corporate world, of course, to be able to get by on five hours of sleep or less is a badge of honor, a mark of the Olympian executive who can straddle time zones, bridging the Nasdaq and the Nikkei.

In fact, researchers have coined a term, "shift-worker syndrome," to describe people who, in moving between day and night schedules, develop persistent drowsiness when they are supposed to be active and insomnia when they are trying to sleep. Dr. Charles Czeisler, a professor at Harvard, and Dr. David Dinges, a researcher on sleep deprivation at the University of Pennsylvania, recently conducted a study in which sixteen healthy subjects were placed in shift-work conditions in a laboratory. (The work was funded by the Air Force Office of Scientific Research and by Cephalon.) Some were given modafinil, others a placebo. They underwent one twenty-eight-hour period of sleep deprivation to replicate the habits of real-life shift workers. Then they began a four-day period of being awake at night and sleeping from 11 A.M. to 7 P.M. Despite these radical changes in their sleep cycles, the volunteers found that modafinil sustained their alertness and the capacity to perform well in a variety of cognitive tests. In one such test, volunteers were asked to memorize symbols that represented different numbers. When a particular symbol was shown to the volunteer, he had to type the designated number for that symbol on a computer. The error rate among those who were on a placebo was significantly greater than it was for those taking modafinil.

Meanwhile, the military's sleep research is going far beyond shift-worker experiments and flight-simulator studies. This summer, the Department of Defense Advanced Research Projects Agency, or DARPA, solicited "innovative research and development proposals in the prevention of degradation of cognitive performance due to sleep deprivation." DARPA will provide more than a hundred million dollars in research grants, and sets forth its rationale as follows:

> The capability to resist the mental and physiological effects of sleep deprivation will fundamentally change current military concepts of "operational tempo" and contemporary orders of battle for the military services. In short, the capability to operate effectively, without sleep, is no less than a 21st Century revolution in military affairs. . . . As combat systems become more and more sophisticated and reliable, the major limiting factor for operational dominance in a conflict is the warfighter. Eliminating the need for sleep while maintaining the high level of both cognitive and physical performance of the individual will create a fundamental change in warfighting and force employment.

Several studies have already been launched. One, based at Sea World in San Diego, focusses on dolphins,which never go fully to sleep. "If these dolphins fell asleep, they could die in the water," John Carney, a neuropharmacologist who oversees the DARPA program, says. "As mammals, they have to surface regularly for oxygen, so they've had to adapt." In dolphins, only one cerebral hemisphere sleeps at a time: when the left hemisphere is asleep, the right one is awake, and vice versa. Carney believes that working out how the dolphin hemispheres shift between wakefulness and sleep while the animal maintains a basic level of alertness may lead to methods by which cognitive performance might be sustained in human beings.

The Pentagon wants soldiers who can be awake and high-functioning for up to a full week, even in circumstances where a single error can have disastrous consequences. And for civilian society, too, the prospect of gaining control over the cycles of sleep and wakefulness has great appeal; lost productivity caused by sleep disorders costs an estimated eighteen billion dollars every year. But will biology permit it? The widespread assumption that sleep is necessary was supported by early studies of sleep-deprived rats:they suffered deterioration not only in behavior but in body metabolism and immune defenses. As repeated experiments have verified, when rodents are prevented from sleeping they often die of sepsis, with some succumbing after

TO THE GRASS OF AUTUMN

You could never believe
it would come to this
one still morning
when before you noticed
the birds already
were all but gone

even though year upon year
the rehearsal of it
must have surprised
your speechless parents
and unknown antecedents
long ago gathered to dust
and though even the children
have been taught how to say
the word *withereth*

no you were known to be
cool and countless
the bright vision on all
the green hills
rippling in unmeasured waves
through the days in flower

now you are as the fog
that sifts among you
gray in the chill daybreak
the voles scratch the dry earth
around your roots
hoping to find something
before winter
and when the white air stirs
you whisper to yourselves
without expectation
or the need to know

—*W. S. Merwin*

only five days, the hardiest lasting a full month. Yet such effects have not been seen in human subjects. And, surprisingly, there is very little hard data showing that prolonged sleep deprivation truly has deleterious effects on us. The lore that it can cause psychosis dates to the Korean War, when Chinese Communists were said to torture prisoners by preventing them from sleeping; however, later researchers have concluded that the psychosis resulted from the kinds of stimuli and stresses applied by torturers under these gruesome conditions, rather than from the lack of sleep per se.

A record for documented continuous wakefulness was set in 1964, when a high-school student named Randy Gardner kept himself awake for almost twelve full days. Though his rate of thinking and response slowed, he experienced no dramatic physiological problems. More systematic work on the effects of prolonged wakefulness has recently been conducted by David Dinges, the researcher on sleep deprivation at the University of Pennsylvania. He kept twenty-eight people continuously awake for four days, and found that the major consequence was the expected decline in cognitive functioning.

Other studies of chronic sleep deprivation, where subjects are allowed to sleep for four hours and are kept awake for twenty, found temporary changes in glucose metabolism, with an increase in insulin resistance, a condition seen in early diabetes. Dinges says that some of his sleep-deprived subjects also have about a twenty-five-per-cent increase in the number of circulating white blood cells. Still, the clinical significance of such changes is unclear. Though many researchers, including Dinges, believe that sleep is necessary for the brain to replenish its energy stores, the hypothesis remains unproved. In the absence of such basic medical knowledge, sleep experts caution about the use of drugs like modafinil as a substitute for sleep. They worry that high-achieving types may be tempted to take them in order to stay awake two or three days a week throughout the year. And they worry about abuse among students cramming for exams. In fact, the medical consequences of such regular on-off sleep behavior are simply not known, and probably will not be known for a long time.

"Modafinil is the most tempting drug for our society to come along in decades," David Dinges says. "It promises to satisfy our relentless desire to control time." He traces a historical arc that begins with the industrial revolution, when technology increased demands on workers and simultaneously permitted them greater freedom in their leisure time. Paradoxically, people have become eager to maximize their periods of activity at will, prolonging the workday until one merges into the next. Dinges sees caffeine use as a mirror of society's craving, and its view of sleep as a dispensable commodity. "For years, coffee was taken in small doses, but the growth of Starbucks says it all," he says. "A venti"—twenty ounces of coffee—"is loaded with the drug. It's the beverage of choice in America. In middle school, it's Mountain Dew, which is also packed with caffeine." But research by Dinges and others has shown how limited caffeine's effects are. When his team studied people kept awake for eighty-eight hours, caffeine turned out to be effective for only some twenty hours. "Modafinil looks *much* better than caffeine," Dinges concludes. "Wakefulness becomes effortless." It's a prospect he finds both exciting and disturbing.

"I just returned from a meeting with people at the Boeing Corporation," Dinges recounts. "They are planning an airplane that can circumnavigate the globe, needing to land only once every twenty hours. How should the crew sleep, if at all? What are the rules that apply to sustain work on flights like that?" In the light of our rapidly advancing understanding of the neurochemistry of sleep, modafinil is "just the tip of the iceberg," as Dinges sees it. "Now is the time to have an open and frank discussion on how far we will go as a culture, what are our priorities, how regularly do we want to manipulate our brain chemistry," he says. "What are the limits?" ♦