

Field Notes

ANN K. FINKBEINER

Getting Through the Sleep Gate

Make a better sleeping pill and the world will beat a path to your door. So why hasn't it been done?

HAVE TROUBLE FALLING ASLEEP AND always have, and so I take advice from the experts. The best is Robert Burton, the seventeenth-century English scholar whose 1,000-page book, *Anatomy of Melancholy*, has a cure for everything: "To procure this sweet moistening sleep, it's best to take away the occasions (if it be possible) that hinder it," he writes, because "a hot and dry brain never sleeps well." As the mind cools, he continues, "'tis good to lie on the right side first, because at that site the liver doth rest under the stomach, not molesting any way, but heating him as a fire doth a kettle, that is put to it."

I've tried all this, and it doesn't work. I remember being a child, lying in bed looking out at the black sky and the blacker apple tree, waiting forever to fall asleep. I'm in good company, though. The onset of sleep is called—here scientific jargon coincides with poetry—the sleep gate. Getting through the sleep gate is a universal, sometimes serious problem. Around the world, one person in four has occasional bouts of insomnia, and in the United States, one person in three. People whose insomnia is chronic—in this country, one person in ten—are more depressed and anxious than average, and have more alcohol problems. Sleepy drivers cause 100,000 automobile accidents every year, according to the National Highway Traffic Safety Administration, and more than 1,500 deaths. Without sleep, the insomniac's motor skills get worse, cognitive skills get worse yet, and mood hits the bottom of the chart. Rats deprived of sleep eat more than usual but waste away; their body temperature goes out of whack and they die in two and a half weeks, and no one knows why. Clearly, we need help.

Today's equivalent of the liver heating the stomach is a sleeping pill. Last year Americans spent some \$14 billion on sleep problems. The sleep drugs sold over the counter are usually the same antihistamines people take for allergies. But antihistamines do not always work, and whether they do or not, the body does not clear them out by morning, and so they make people feel fuzzy and hung-over. The most common prescription

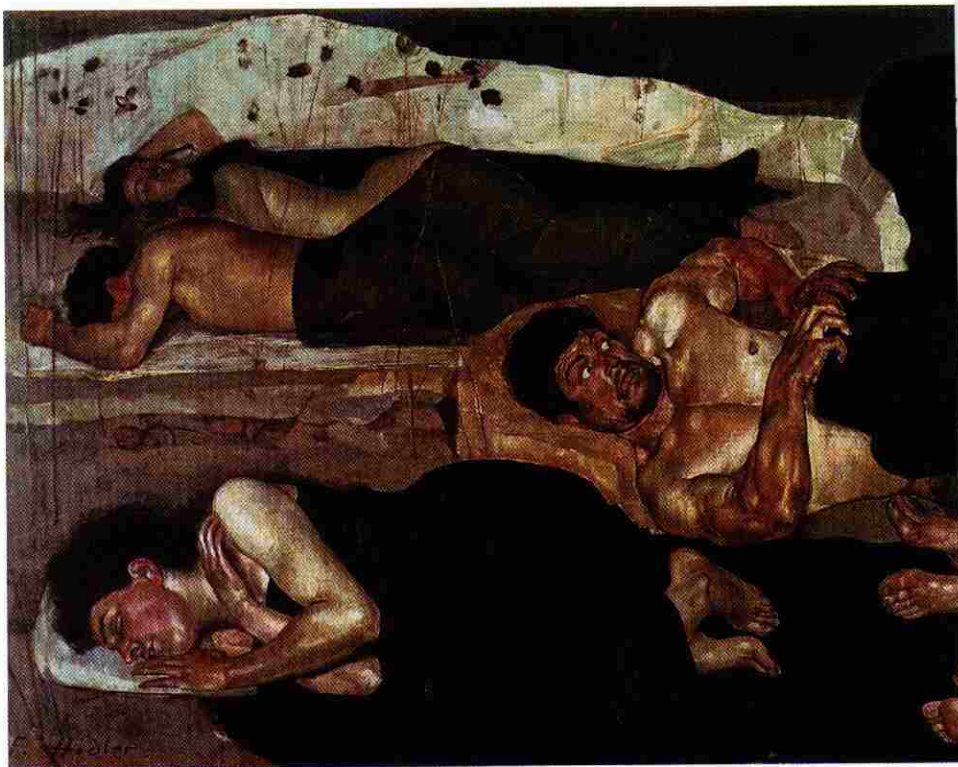
drugs for insomnia are the benzodiazepines, which are also taken to reduce anxiety. "Benzodiazepines work," says the sleep investigator Thomas Roth of the Henry Ford Hospital in Detroit, Michigan, "and in the right doses, they're safe." But people can become dependent on benzodiazepines; low doses often become ineffective and cause people to raise the dosage; and the sleep they induce does not run through the normal stages.

THE OBVIOUS ALTERNATIVE TO RELYING on the usual sleep drugs is to figure out what chemical the body uses to induce sleep. But finding that chemical isn't so easy. A lot of substances cause sleep, but the sleep isn't necessarily normal. Normal sleep has five stages. People who take benzodiazepines, for instance, tend to miss the deepest stage of sleep. Furthermore, even though a chemical induces sleep and the body has receptors for that chemical,

the chemical may not be the one the body uses to induce sleep. In fact, nobody knows just how the body induces sleep.

Nevertheless, the need is great, so a number of new sleep inducers have been developed in recent years. One such chemical, an analogue of pregnanolone, is in clinical trials and on its way to the market. Pregnanolone is a steroid, found in the urine of pregnant women, that quiets neural communication throughout the body and thus induces sleep. In rats, the sleep induced by the pregnanolone analogue has stages similar to those of normal sleep; low doses don't seem to become ineffective; and its side effects are not severe. Still, pregnanolone is only a variation on an old favorite: it attaches to the same receptor complex in the brain as the benzodiazepines do.

Another candidate is melatonin, a substance secreted by the pineal gland that helps regulate the circadian system—the



body's internal clock. In adults, levels of melatonin are low during the day and higher at night. When the neuroscientists Irina V. Zhdanova, Richard J. Wurtman and their colleagues at the Massachusetts Institute of Technology raised people's daytime melatonin levels to nighttime levels, people got sleepy. Moreover, when they slept, their sleep was normal. Melatonin can be sold over the counter because it isn't classified as a sleep drug; it's classified as a food supplement. As a result, says Roth, its dosage and purity are regulated "the way they regulate Kool-Aid."

Judging from the drug's astonishing popularity—in 1995 alone there were 20 million new melatonin users in the United States—Roth and Wurtman say the American public is running a vast, uncontrolled trial of the safety and side effects of melatonin. The typical melatonin pill is sold in what is called a pharmacological dose—an amount not usually found in the body—of around three milligrams. The physiological dose—the amount by which daytime levels rise to reach nighttime levels—is less than a tenth that amount: between 0.1 and 0.3 milligram. "The problem with pharmacological doses is, we just don't know their long-term effects," Zhdanova says. "Melatonin's a hormone. It may be involved in reproductive-system functioning or thermoreg-

ulation." A low-dose version, targeted at middle-aged and elderly people whose bodies produce little melatonin, and who therefore have trouble sleeping, is now available and seems to have no side effects.

THAT LEAVES ANOTHER NATURAL SLEEP inducer, and a particularly intriguing one: adenosine. Adenosine is the A in ATP, adenosine triphosphate; ATP fuels every living cell in all known organisms. For nearly twenty years investigators have known that adenosine inhibits neural communication. In the mid-1980s, the pharmacologist Miodrag Radulovacki of the Univer-

ONE IN THREE AMERICANS OCCASIONALLY suffers from insomnia, and sleepy drivers cause 100,000 automobile accidents every year. Clearly, we need help.

sity of Illinois at Chicago found that adenosine also triggers sleep. When adenosine is injected into the brain of a rat, the rat falls asleep; when the brain's receptors for adenosine are blocked, the rat stays awake. And the clincher: adenosine receptors in the brain can be blocked by caffeine.

Adenosine seems to have all the earmarks of a good sleep drug. And yet, of all the candidates mentioned so far, adenosine is the furthest from the mar-

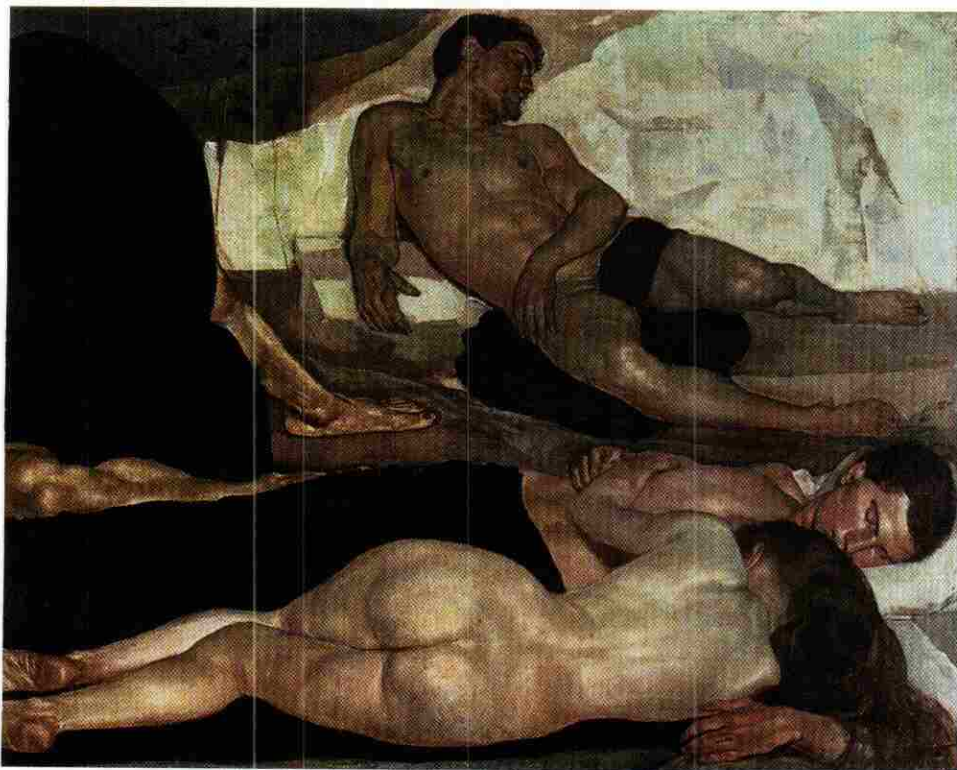
ket. Its principal investigator, the physiologist H. Craig Heller of Stanford University, thinks adenosine might work. But the company that has funded him in the past, and another that he has talked to about future support, have declined to pursue the drug, perhaps because of its potential side effects. With tens of millions of Americans lying awake, causing car accidents and spending billions on sleep drugs, why hasn't such a drug been refined and developed? Why isn't there a pill that puts people to sleep the way the body does? The answer is a case study in drug design, in the fretful economics of the sleep industry, and in the complex biology of sleep itself.

IT PROBABLY WENT wrong from the start. Drug companies pursue what Heller calls a shotgun approach: they develop a simple test for a certain effect, run thou-

sands of chemicals from the company's library through the test, and see which chemical causes the effect. Heller prefers the functional approach. "I want to understand how this system works," he says, "and by understanding how it works, I'll know how to design a drug to modify it." The functional approach sounds safer, much more rational and infinitely less efficient; you can hear the drug companies' capitalistic jaws drop as Heller speaks.

Nevertheless, in the late 1980s the Upjohn Company (now Pharmacia & Upjohn, Inc., in Bridgewater, New Jersey) agreed to fund Heller's approach. Heller, whose specialty is the physiology of sleep and circadian rhythms, began by studying sleep as a homeostatic system—that is, a system in which a certain need (for, say, food or warmth) grows, and then is satisfied. In the case of sleep, that need builds up during wakefulness and is restored during sleep. One clue to the homeostasis between waking life and sleep is that the longer people are awake, the more deeply they sleep. More precisely, the longer people are awake, the deeper is their deepest phase of sleep, in which electroencephalograms show long, slow, regular waves—"like Gregorian chants," Heller says. "Slow waves are really pretty."

Like any homeostatic system, the sleep system must be controlled: the level of some governor must rise during wakefulness, trigger and maintain slow-wave sleep, then fall. Heller and his graduate student Joel H. Benington thought that finding the governor of slow-wave sleep might help them understand the function of sleep in general—and, along the way, identify a new sleep-drug candidate. Among the



Ferdinand Hodler, *The Night*, 1889–90



Holly Lane, *The Toil of Sleep*, 1997

most likely governors was adenosine. Its central role in energy metabolism suggested a fitting and lovely function for sleep: it restores energy—in Burton's words, it "moistens and fattens the body."

So Heller and Benington began to study why cells—brain cells in particular—release adenosine. The short answer was, they do so to signal energy starvation. "The way you fuel your muscle contractions, your biosynthesis, everything you do, is by using the energy in ATP," Heller says. The energy in ATP is stored within the chemical bonds attaching adenosine to its three phosphate groups; breaking off individual groups releases the energy. In the process, ATP first becomes ADP (adenosine diphosphate), then AMP (adenosine monophosphate) and finally just A. Adenosine then gets released by the cell and is recycled back into ATP. The faster adenosine is released, Heller says, the more energy-deprived the cell is.

If starved cells release adenosine, and if, as Radulovacki showed, adenosine triggers sleep, how does sleep replenish starved cells? And why do they take so long—eight hours, on average—to replenish? In the period when he was thinking about those questions, Heller was lecturing on exer-

cise metabolism, a process in which the body takes many hours to restore strings of glucose molecules, called glycogen, to the muscle cells, thereby reviving spent muscles. Maybe, he thought, the brain works the same way.

GLUCOSE IN THE BLOOD IS THE BRAIN'S main energy supply. When glucose enters brain cells and is metabolized there, it gives rise to ATP. But off and on during the day, and here and there in the brain, the glucose supply doesn't meet the demand. The brain's only backup is the glycogen stored in multipurpose cells called glia. During wakefulness, when the energy demand is high, enzymes chop the glycogen into glucose, releasing ATP, which degrades to adenosine. "Eventually," Heller hypothesizes, "you get to the point where you have depleted your glycogen and then further demand causes adenosine release."

Adenosine quiets the neurons and sends people into slow-wave sleep. Heller and Benington think that the glia take advantage of the quiet to string glucose from the blood back together into glycogen. The process of making glycogen requires ATP,

which, throughout the night, degrades to adenosine. "So our very simple hypothesis is, the function of slow-wave sleep is to replenish brain energy reserves," Heller says. "And the signal that controls that process is adenosine." Sleep does not restore the body, he concludes, "it restores the brain."

If that hypothesis is right, it implies that adenosine should act specifically to trigger slow-wave sleep. And it does: when adenosine is given to rats that have already had what passes for a good night's sleep in a rat, they return to slow-wave sleep. Another implication is that glycogen levels in the glia should rise and fall with cycles of slow-wave sleep and wakefulness. But that implication remains untested. Laboratory animals have to be killed before their glycogen levels can be measured; and since dying neurons use glycogen, the levels would have to be measured in the instant after death. "That's very difficult to do," Heller says. "Death is really a slow process."

Adenosine levels, too, should rise and fall with cycles of wakefulness and slow-wave sleep, and in some animals, at least, they seem to do so. Last year the psychiatrists Robert W. McCarley, Tarja Porkka-Heiskanen and Robert W. Greene of Harvard Medical School measured adenosine levels in the parts of cats' brains that keep the animals awake. When the cats were deprived of sleep for six hours—"we actually played with the cats for six hours," McCarley says—the levels of adenosine were double what they had been six hours earlier. When the cats went into slow-wave sleep, the adenosine levels slowly fell back down. And to nail the issue: cats given a drug that increases adenosine in the wake-up areas of the brain slept the same way as they did after being awake for six hours. McCarley doesn't believe or disbelieve the glycogen-repletion part of Heller and Benington's hypothesis: "We haven't tested it," he says. But he does agree that adenosine is the governor of sleep: "We think adenosine controls sleep and builds up with wakefulness."

THE ENERGY-RESTORATION HYPOTHESIS goes wider and deeper than I've described so far. It extends to the molecular level and includes a homeostasis not only between wakefulness and slow-wave sleep, but also between slow-wave sleep and REM, or rapid eye movement, sleep. The long form of the hypothesis, according to one of the field's leaders, the pharmacologist Alexander A. Borbély of the University of Zurich, is "a shining example of an innovative, integrative and testable hypothesis."

But whether drug companies care is doubtful. What they, and we insomniacs, want to know is whether adenosine would make a good sleeping pill. Ten years ago,

in the hope of developing a new generation of hypnotics, Upjohn began funding a center for the neurobiology of sleep at Stanford University. The center studied circadian rhythms, the homeostasis of sleep and the extreme form of sleep known as hibernation, on levels ranging from the molecular to the behavioral. Heller and the eminent sleep specialist William C. Dement were the principal investigators.

Let Heller—now graying ten years afterward, sitting in an office with light but no room—tell the rest of the story: “At the end of five years, we had these really important leads about the function of sleep and the control of sleep and rhythms. We started negotiations for another five years, and Upjohn gave us a sixth year while we negotiated. And then in this period, the main players at the top changed, and the company decided they weren’t going to do any more work in hypnotics. So that sort of left us dead in the water.”

Heller’s group did what every research group does in such circumstances: it applied elsewhere, specifically to the National Institutes of Health. Meanwhile, he says, Glaxo Wellcome, in Research Triangle Park, North Carolina, expressed some interest in his work. Heller contin-

ues: “We went through a couple years of sharing information and coming up with plans. And once again, the main players at the top kept changing and then they also decided no, they weren’t interested in going into hypnotics. So. I have not really approached other companies since then, and I should. There’s a huge need, and we can do it, I know we can. I just haven’t had time to go out and hunt.”

HELLER’S STORY MIGHT CLARIFY THE relation between basic science and commercial drug development, but the question still remains: Why can’t you buy a drug that puts you to sleep the way the body does? It’s no use asking Upjohn and Glaxo. One of the investigators with Upjohn who worked with Heller was Philip F. Von Voigtlander, now the company’s director of neurobiology. “We never had a serious effort in adenosine,” he told me, choosing his words carefully. “Pharmaceutical companies look into lots of mechanisms. We have no current program, nothing to talk about.”

Von Voigtlander does hint at a possible reason for abandoning adenosine: “There were lots of cardiovascular effects,” he says. “That’s one of the unattractive things about

adenosine.” And in fact, adenosine has been developed as a drug in the past precisely because it affects the heart. Receptors for adenosine are scattered everywhere in the body, both throughout the brain and in what biomedical investigators call the periphery. (As Illinois south of Chicago is “downstate,” and New York north and west of New York City is “upstate,” so the body south of the brain is the periphery.) According to the pharmacologist Noel J. Cusack, chief scientific officer at Discovery Therapeutics, Inc., in Richmond, Virginia, adenosine causes the coronary blood vessels to dilate, and so it can function as a diagnostic tool. Moreover, it damps down electrical activity in the heart, so physicians use it to treat paroxysmal supraventricular tachycardia, the more-rapid-than-normal beating of the heart’s upper chambers. If adenosine were given as a sleep drug, Cusack says, “it might drop the bottom out of blood pressure or stop the heart.”

The problem might be more tractable than it sounds. The receptors for adenosine come in four subtypes. The A2a subtype is known for its effects on the blood vessels. A1, the subtype Heller has studied, occurs throughout the body but also modulates slow-wave sleep. A1 receptors may be more

The Evolution of Sleep

ALL GOD’S CREATURES HAVE PERIODS WHEN THEY don’t do much. Protozoans, planarians, crabs, squid, houseflies and butterflies all, every day, rest. Fish have cycles of stillness during which their senses keep working. Amphibians and reptiles sleep: they close their eyes, relax their muscles and stop responding to stimuli. Among certain seagoing mammals—dolphins, pilot whales, porpoises and a sea cow—only one hemisphere of the brain sleeps at any given time, so that the animals can keep swimming to the surface and breathing. But all mammals sleep. Recordings of the electrical activity of their brains, called electroencephalograms (EEGs), taken during sleep, show the frequency of brain waves gradually slowing, bottoming out, then quickening. In the quickened state, the mammal’s eyes move beneath closed eyelids, muscles twitch, and for a time the EEG looks as lively as one depicting the waking brain; the quickened state is called rapid eye movement, or REM, sleep. During REM sleep in humans, the visual centers of the brain are active; people wake from REM sleep and say they’ve been dreaming.

Biologists connect the varying degrees of complexity in sleep with the evolving complexity of the brain: insects and fish rest; amphibians and reptiles sleep; birds and mammals have REM sleep. “One idea that constantly boils to the top,” says the neuroscientist Jerome M. Siegel of the Veterans Affairs Medical Center in Sepulveda, California, “is that complicated brains evolved REM sleep.”

THAT SIMPLE PICTURE HAS ONE ANOMALY: MONOTREMES, the most primitive mammals, may not have REM sleep. About twenty-five years ago the neurologist Truett Allison and his colleagues at Yale University recorded the EEGs of echidnas, which are monotremes that live in Australia, Tasmania and New

Guinea. While the echidnas slept, the EEGs of their cerebral cortexes showed slow-wave sleep and waking, but no REM sleep.

Such unparsimoniousness left sleep investigators in a quandary. Did REM sleep evolve twice, once in birds and again in the next mammals up from monotremes, the marsupial and placental mammals? In 1993 Siegel repeated Allison’s experiment, this time with measurements in the brain stem as well as in the cortex. Siegel first studied cats and dogs, then an echidna. In cats and dogs, he found, when the EEG showed slow-wave sleep, the brain-stem neurons were firing slowly and regularly; when the EEG showed REM sleep, the brain-stem neurons were firing in high-frequency bursts. In the echidna, however, he recorded something unexpected. When the animal’s EEG showed slow-wave sleep, Siegel says, the brain-stem neurons, most of the time, “were bursting.” Although the echidna’s cortex didn’t show REM sleep, its brain stem did.

Siegel isn’t sure what that means. But it suggests that the REM activity of the cortex hasn’t always been linked to the REM sleep triggered by the brain stem. “Maybe when REM sleep first appeared,” he speculates, “it was purely a brain-stem state that went on independently of the cortex.”

If REM sleep did evolve only once, in a reptilian ancestor common to mammals and birds, then it’s been around for roughly 250 million years. The brain stems of modern reptiles resemble those of mammals, and so Siegel has begun looking for high-frequency bursts from reptilian brain-stem neurons. Ultimately, Siegel, along with other students of sleep, would like to figure out why REM sleep evolved at all. “Non-REM sleep is for whatever resting is for,” he says. “But if the brain isn’t resting during REM sleep, what’s it for? It’s hard to imagine it’s not fundamental to the brain.”

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numerous in the brain, and A2a receptors may be more numerous in the periphery. So maybe an analogue of adenosine, engineered selectively to trigger A1 but not A2a receptors, could put people to sleep without stopping their hearts.

Investigators in both industry and academia are working to characterize all four subtypes. The clinical pharmacologist Nils O. Johannesson, vice president for research and development at Medco Research, Inc., in Research Triangle Park, said the company is looking into all the adenosine receptors and their potential applications. Would Medco consider developing a sleep drug? "It may very well be so," Johannesson says. "It depends on how the process of characterization goes." Cusack is slightly more optimistic. Would the hurdles to developing an analogue to adenosine as a sleep drug be prohibitively high? "Oh, no, not necessarily," he says. So there's no good reason why such an analogue couldn't be developed? "That's right."

So maybe someday adenosine will be sold as a sleeping pill, or maybe not. Surely part of the reason it's not sold already is that the biotechnology industry is a shark tank. According to the cardiologist Harlan Weisman, vice president for clinical research at Centocor, Inc., in Malvern, Pennsylvania, companies tend to work only on drugs that are provably useful and compellingly necessary. They need to focus narrowly: on molecules (such as adenosine) or on systems in the body (such as the cardiovascular system) they already understand thoroughly. "Lose focus," Weisman says, "and you won't get it accomplished." And whatever the focus, he says, "you want to be number one or number two. There are thousands of biotech companies and only a few survive." Those mandates would probably rule out Heller's rational but inefficient functional approach: understand how the system works, then design a drug to modify it.

IF ANYTHING IS TO BLAME FOR THE SORRY impasse in developing a sleep drug, it's neither cutthroat drug companies nor ivory-tower academics. It is sleep itself. Among the messy, complicated areas of human biology, the neurochemistry of sleep must be among the messiest—full of redundancy,

feedback loops and outright contradictions. To begin with, the brain doesn't just induce sleep; it first withdraws wakefulness, dropping the levels of three neurochemical stimulants. Not only do adenosine, pregabalin and melatonin induce sleep, but so do cytokines, prostaglandins and an agent

I hope not," Zhdanova says. "They're involved in so many other processes."

On top of everything else, the regulation of sleep and wakefulness is not only homeostatic, like a thermostat, seesawing between a need and its repletion, but also circadian, like a clock, cycling every twenty-four hours. So whereas the thermostat part of sleep uses adenosine as a governor, the clock part uses melatonin. You have to wonder who the engineer was.

THE ENGINEER WAS natural selection, of course, and it has been notoriously unparsimonious. The brain could easily have a hundred different reasons for sleep. Energy depletion, darkness, infection, digestion and pregnancy are all excellent reasons to sleep. And maybe each reason has its own neurochemistry. Heller thinks sleep is going to be logical when we know all the facts: "We just don't know all the facts." Zhdanova says it's like trying to understand the solar system without knowing about gravity: "We talk about the planets, and suspect there's a sun. For now, my small belief is we really don't understand sleep at all."

Burton's advice would be to stop thinking about it. In his *Anatomy of Melancholy* he quotes some worthy,

wondering "how Schoolmen could sleep quietly, and were not terrified in the night, or walk[ing] in the dark, they had such monstrous questions, and thought of such terrible matters all day long."

And people like me, who want to go to sleep as naturally as possible—what do we do, staring night after night at the black apple tree? For now, we rely on Burton. After lying on the right side, we ought to "hear sweet Musick," he writes, or to "read some pleasant Author . . . or to lie near that pleasant murmur, of water gliding by with gentle music, some flood-gates, arches, falls of water," and thus soothed, slip through the sleep gate. ●

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Remedios Varo, *Insomnia*, 1942–47

called vasoactive intestinal polypeptide, among other substances. A 1994 textbook lists thirty-six sleep inducers; James M. Krueger, a neurobiologist at Washington State University in Pullman, says he thinks that number will eventually rise to between fifty and a hundred.

Moreover, like adenosine, other known sleep inducers affect multiple systems in the body. Melatonin is central to the circadian system; pregabalin, to the endocrine system; the cytokines tumor necrosis factor and interleukin-1 (both of which Krueger studies) are messenger chemicals for the immune system, as is prostaglandin D₂; and vasoactive intestinal polypeptide is part of the digestive system. As a result, cytokines, for instance, are unlikely ever to be developed as sleep drugs. "You don't want to artificially stimulate people's immune systems," Krueger says. "I wouldn't say no, but it's going to be a hard sell." Nor are the prostaglandins or vasoactive intestinal polypeptide: "I don't think so and