Sleep Researchers Awake to Possibilities

Advances in sleep disorders medicine have brought more clinicians into sleep research, but there are many basic research questions about sleep that are just beginning to be resolved

SLEEP RESEARCHERS are popular at cocktail parties for a simple reason: nearly everyone either has, or knows someone who has, a problem sleeping and would like a little free advice. While research in the last decade has brought a more confident tone to that free advice, when big, simple questions such as why do we sleep and why do we dream get asked—and they inevitably do—sleep scientists start to hope that some guest will choke on a canapé.

The fact is that despite amassing an impressive amount of information about the physiological changes during sleep, there is still precious little known about the function of sleep, or why highly evolved mammals need it at all. That much was all too clear at last month's meeting of the Association of Professional Sleep Societies (APSS) in Washington, D.C.

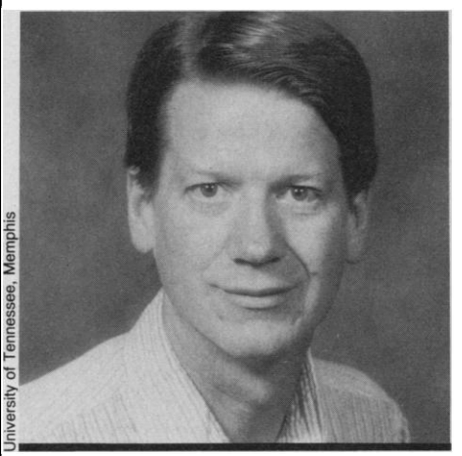
But there were encouraging signs as well, suggesting a vitality at the core of sleep research. The most obvious advances in the field have come in the treatment of clinical sleep disorders. But the conference papers also reflected painstaking work in neurophysiology and neuroanatomy, which is yielding a clearer picture of the brain structures crucial for sleep. And new biochemical analyses of sleep factors in the brain hint at the chemical orchestration of different states of arousal.

Even in the relatively short history of sleep research—the field didn't really get going until the 1950s—sleep disorders medicine is very new. William C. Dement got it under way in 1970 when he established the first sleep disorder clinic in the United States at Stanford University. Dement's example stimulated others to follow suit, and today there are 150 sleep disorders centers accredited by the American Sleep Disorders Association, and some 50 more are either awaiting accreditation or simply offering therapeutic services on their own.

Their popularity is understandable. Although the centers had little to offer beyond diagnosis at first, today there are reasonably successful therapies for treating several disorders.

Take sleep apnea—a cessation of breathing during sleep that causes a brief awakening before the breathing restarts. The Association of Professional Sleep Societies estimates that as many as 20 million people suffer from this condition. These unwanted arousals can occur up to hundreds of times per night, but a typical sufferer—men are much more commonly afflicted than women—will have no recollection of them. His only clue that something is amiss is the tremendous trouble he'll experience staying awake during the day.

At first, apnea was classified in two ways: obstructive apnea, involving some anatomical blockage of the upper airway; and central apnea, where autonomic breathing control from the brainstem ceases to function properly. Now, says Joan Hendricks of the University of Pennsylvania, even the obstructive form is thought to have a central component. "The mechanism in both cases is a decrease in drive of the muscles of respiration," she says



University of Tennessee, Memphis

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—James Kreuger

In some cases, apnea can be prevented by weight loss, since the obstruction of the upper airway can result from excess fat. Surgical methods to remove fat or realign the trachea are also being pursued. But an effective, noninvasive approach that has recently become popular is CPAP, or continuous positive airway pressure. A pump next to the bed provides a steady stream of air to a mask worn over the nose. The continuous airflow prevents the upper airway from closing off completely.

The most common problem of sleep disorders—insomnia—which effects some 30 million people in the United States is also yielding to treatment. Clinicians used to think of insomnia as a single problem, but a wide variety of factors can interfere with falling and staying asleep. Medical and psychiatric illnesses, for example, can often disrupt sleep, and treating those conditions usually relieves the sleep problems. For the more "garden variety" insomnias, clinics offer a range of approaches. Teaching good sleep hygiene—skipping caffeine in the evening, getting out of bed when you can't sleep, maintaining a regular sleep schedule—helps in many cases. Sleep restriction, simply going to bed later and getting up at the usual time, can help some people get to sleep. And hypnotic drugs can bring short-term relief, although long-term drug use creates more problems than it solves.

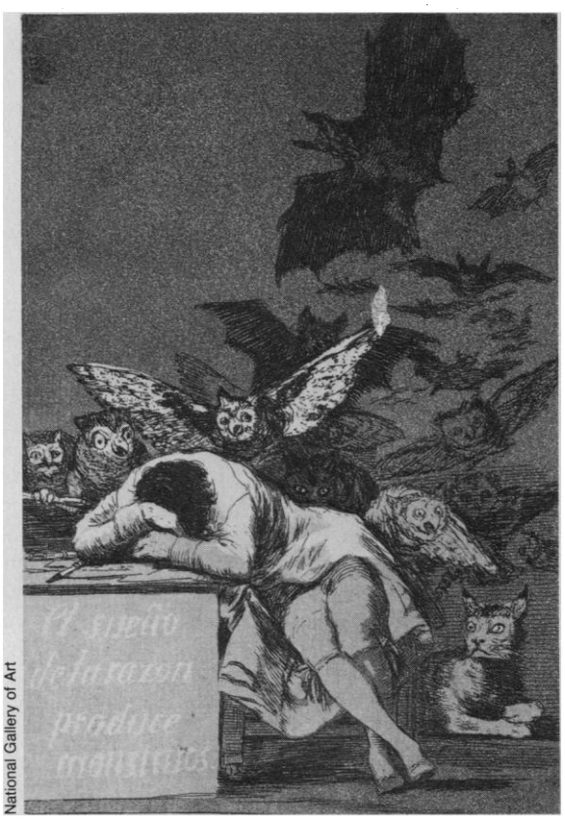
Sleep clinics have largely been responsible for swelling the rosters of professional sleep societies, as physicians enter the field in increasing numbers. The down side of this, some argue, is that basic sleep research has suffered. "A lot of sleep people are being gobbled up by the sleep disorders medicine," says James Horne of Loughborough University. "It's a nice area [for a physician] to get into because it makes a lot of money; you can't kill your patient in the diagnosis, so lawsuits are an unlikely hazard; it's a secure job for many years; and you don't have to spend half your life writing grant proposals."

Burgeoning numbers of clinical sleep researchers have boosted NIH funding for sleep research, up nearly 80% in the last 3 years at a figure of $17 million. About one third of that amount comes from grants from the National Heart, Lung, and Blood Institute for apnea-related research.

Last year, Congress passed legislation creating a National Commission on Sleep Disorders Research, and James O. Mason, As-

sistant Secretary for Health, has promised to name members to the commission shortly, but federal bureaucracy is slowing the process. Meanwhile, federal interest in sleep goes beyond funding for basic and clinical research, reaching into safety on the road and in the air. The Department of Transportation, for instance, is becoming more interested in how sleep habits may affect transportation safety. Stanford's Dement maintains that "sleepiness causes more accidents than alcohol." In a report to Congress earlier this year, Secretary of Transportation Samuel Skinner wrote that "the Department is examining changes in work rules, work shifts, and work environments for air traffic controllers, truckers, train crews, and others."

All this means more work—and funding—for sleep researchers. The Federal Aviation Administration, for example, recently relaxed its rules about napping in the cockpit to permit preliminary studies of "controlled napping" on Pacific routes notorious for causing pilot fatigue.



National Gallery of Art

Nocturnal mysteries. *Francisco de Goya's, "The Sleep of Reason Produces Monsters."*

Although progress on the clinical side of sleep research has recently attracted money and attention, there have been impressive gains on the basic research side.

While sleep was once viewed as a single, uniform state, the last few decades have shown that the brain can hardly be described as inactive during the night. In the initial hours of sleep, recordings of brain waves show a slow, regular pattern. But as the night progresses, there are more frequent occurrences of a brain wave pattern that closely resembles waking. Paradoxically, during this waking-like brain wave pattern muscles are more relaxed than at any other time during the night.

In addition to relaxed muscles, there is a wealth of other physiologic changes: the eyes dart back and forth beneath closed lids, breathing becomes irregular, and there are frequent small muscle twitches.

These changes characterize the onset of REM sleep, so-named for the rapid eye movements that occur. Understanding how REM and non-REM, or slow-wave sleep (SWS), differ from each other has been a dominant question for basic sleep researchers. REM sleep "is the neurophysiologist's delight," says Robert McCarley of Harvard University because of all the physiological changes that occur. McCarley believes that acetylcholine—a neurotransmitter—is critical for the control of REM sleep. McCarley likes to paraphrase Shakespeare: "Acetylcholine is the stuff of which dreams are made."

McCarley has injected drugs that mimic acetylcholine into the pons, a brainstem structure necessary for the onset of normal REM sleep, showing that he can induce a REM-like state. He has also shown that the pons both sends and receives fibers from the neighboring neurons that also contain acetylcholine, additional evidence for the role of that neurotransmitter in REM sleep. But critics like Adrian Morrison of the University of Pennsylvania point out that glutamate—a very different compound from acetylcholine—can also bring on a REM-like state when injected into the pons.

While REM continues to capture neurophysiologists' attention, "slow-wave sleep is probably more of a biochemist's delight," says McCarley. Biochemist James Krueger of the University of Tennessee agrees: "I think we're at a dead end in understanding [SWS] in terms of neurophysiology and anatomy," he says. "I really don't see where any real progress is going to be made until we [attempt to understand sleep] on a biochemical and molecular biology level. I think that's the avenue of the future."

Krueger believes control of sleep rests with the complex interplay of cytokines—intercellular messengers that are found in the brain—an idea new to most neurophysiologists. "Everybody's been looking for *the* sleep center in the brain, and I told them in terms of non-REM sleep that such a thing doesn't exist and they're wasting their time looking for it. Nobody jumped up and shot me," says Krueger.

He speaks instead of several "sleep factors" that have been identified. Krueger has concentrated on interleukin-1, one of several cytokines he believes are involved in regulating sleep. For instance, rabbits sleep 20% more than usual when given interleukin-1. In addition, the amount of interleukin-1 in the cerebrospinal fluid fluctuates in parallel with the normal sleep/wake cycle. Finally, interleukin-1 has been found in brain areas associated with the control of sleep, notably the anterior hypothalamus.

Krueger also believes he has found an interesting—and familiar—connection between sleep and illness. Cytokines not only appear to induce sleep, but they are also involved in the immune response to disease. The result: you sleep more when you are fighting an infection.

Another possible sleep controlling mechanism is a balance between two hormone-like substances called prostaglandins. For instance, Osamu Hayaishi of the Osaka Medical College in Japan concludes that prostaglandin D_2 can increase both SWS and REM sleep, and conversely prostaglandin E_2 increases wakefulness. In both cases Hayaishi injected the prostaglandins into the preoptic area of the hypothalamus, an area responsible for temperature regulation.

This link between sleep and temperature control may unite neurophysiological and biochemical studies of sleep. Body temperature goes down at night, regulated by a "thermostat" in the hypothalamus. Ralph Berger of the University of California at Santa Cruz believes this may explain why sleep evolved: turning down the thermostat saves energy for mammals that must work to maintain their high body temperature.

When will basic research be able to answer the fundamental questions about why we sleep? The discipline's wisemen are understandably tentative about when that day will come. Despite the fact that we spend approximately one third of our lives asleep, they like to say, sleep research has been peculiarly neglected.

But William Dement, an unflagging proselytizer for the field, thinks that may be changing. "America is finally getting in touch with the sleeping half of its life," says Dement. With any luck that popular interest will translate into renewed support, keeping scientists energized—and awake—when the secrets of sleep start to be revealed.

■ JOSEPH PALCA