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WHY WE SLEEP:

The reasons that we sleep are gradually becoming less enigmatic

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Birds do it, bees do it, and, in a departure from the Cole Porter song lyrics, even fruit flies appear to do it. Humans certainly do it. The subject is not love, but sleep. Shakespeare's Macbeth said it "knits up the raveled sleeve of care" and was the "balm of hurt minds, great nature's second course, chief nourisher in life's feast." Cervantes's Sancho Panza sang its praises as "the food that cures all hunger, the water that quenches all thirst, the fire that warms the cold, the cold that cools the heart ... the balancing weight that levels the shepherd with the king, and the simple with the wise."

The simple and the wise have long contemplated two related questions: What is sleep, and why do we need it? An obvious answer to the latter is that adequate sleep is necessary to stay alert and awake. That response, however, dodges the issue and is the equivalent of saying that you eat to keep from being hungry or breathe to ward off feelings of suffocation. The real function of eating is to supply nutrients, and the function of breathing is to take in oxygen and expel carbon dioxide. But we have no comparably straightforward explanation for sleep. That said, sleep research—less than a century old as a focused field of scientific inquiry—has generated enough insights for investigators to at least make reasonable proposals about the function of the somnolent state that consumes one third of our lives.

What Is Sleep?

U.S. SUPREME COURT JUSTICE Potter Stewart's famous quote about obscenity—"I know it when I see it"—is a useful, if incomplete, guideline about sleep. Despite the difficulty in strictly defining sleep, an observer can usually tell when a subject is sleeping: the sleeper ordinarily exhibits relative inattention to the environment and is usually immobile. (Dolphins and other

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marine mammals swim while sleeping, however, and some birds may sleep through long migrations.)

In 1953 sleep research pioneer Nathaniel Kleitman and his student Eugene Aserinsky of the University of Chicago decisively overthrew the commonly held belief that sleep was simply a cessation of most brain activity. They discovered that sleep was marked by periods of rapid eye movement, commonly known now as REM sleep. And its existence implied that something active occurred during sleep. All terrestrial mammals that have been examined exhibit REM sleep, which alternates with non-REM sleep, also called quiet sleep, in a regular cycle.

More recently, the field has made its greatest progress in characterizing the nature of sleep at the level of nerve cells (neurons) in the brain. In the past 20 years, scientists have mastered techniques for guiding fine microwires (only 32 microns wide, comparable to the thinnest of human hair) into various brain regions. Such wires produce no pain once implanted and have been used in humans as well as in a wide range of laboratory animals while they went about their normal activities, including sleep. These studies showed, as might be expected, that most brain neurons are at or near their maximum levels of activity while the subject is awake. But neuronal doings during sleep are surprisingly variable. Despite the similar posture and inattention to the environment that a sleeper shows during both REM and non-REM sleep, the brain behaves completely differently in the two states.

During non-REM sleep, cells in different brain regions do very different things. Most neurons in the brain stem, immediately above the spinal cord, reduce or stop firing, whereas most neurons in the cerebral cortex and adjacent forebrain regions reduce their activity by only a small amount. What changes most dramatically is their overall pattern of activity. During the awake state, a neuron more or less goes about its own individual business. During non-REM sleep, in contrast, adjacent cortical neurons fire synchronously, with a relatively low frequency rhythm. (Seemingly paradoxically, this synchronous electrical activity generates higher-voltage brain waves than waking does. Yet just as in an idling automobile, less energy is consumed when the brain “idles” in this way.) Breathing and heart rate tend to be quite regular during non-REM sleep, and reports of vivid dreams during this state are rare.

A very small group of brain cells (perhaps totaling just 100,000 in humans) at the base of the forebrain is maximally active only during non-REM sleep. These cells have been called sleep-on neurons and appear to be responsible for inducing sleep. The precise signals that activate the sleep-on neurons are not yet completely understood, but increased body heat while an individual is awake clearly activates some of these cells, which may explain the drowsiness that so often accompanies a hot bath or a summer day at the beach.

On the other hand, brain activity during REM sleep resembles that during waking. Brain waves remain at low voltage because neurons are behaving individually. And most brain cells in both the forebrain and brain stem regions are quite active, signaling other nerve cells at rates as high as—or higher than—rates seen in the waking state. The brain’s overall consumption of energy during REM sleep is also as high as while awake. The greatest

neuronal activity accompanies the familiar twitches and eye motion that give REM sleep its name. Specialized cells located in the brain stem, called REM sleep-on cells, become especially active during REM sleep and, in fact, appear to be responsible for generating this state.

Our most vivid dreams occur during REM sleep, and dreaming is accompanied by frequent activation of the brain's motor systems, which otherwise operate only during waking movement. Fortunately, most movement during REM sleep is inhibited by two complementary biochemical actions involving neurotransmitters, the chemicals that physically carry signals from one neuron to another at the synapse (the contact point between two neurons). The brain stops releasing neurotransmitters that would otherwise activate motoneurons (the brain cells that control muscles), and it dispatches other neurotransmitters that actively shut down those motoneurons. These mechanisms, however, do not affect the motoneurons that control the muscles that move the eyes, allowing the rapid eye movements that give the REM sleep stage its name.

REM sleep also profoundly affects brain systems that control the body's internal organs. For example, heart rate and breathing become irregular during REM sleep, just as they are during active waking. Also, body temperature becomes less finely regulated and drifts, like that of a reptile, toward the environmental temperature. In addition, males often get erections and females experience clitoral enlargement, although most dream content is not sexual.

This brief description of sleep at the gross and neuronal levels is both accurate and as unsatisfying as being awakened before the completion of a good night's slumber. The tantalizing question persists: What is sleep for?

The Function of Sleep

AT A RECENT SLEEP conference, an attendee commented that the function of sleep remains a mystery. The chair of the session argued vehemently against that position—she did not, however, provide a concrete description of exactly *why* sleep's function was no longer mysterious. Clearly, no general agreement yet exists. But based on the currently available evidence, I can put forth what many of us feel are some reasonable hypotheses.

REM sleep is the proverbial riddle

wrapped in a MYSTERY inside an ENIGMA.

One approach to investigating the function of sleep is to see what physiological and behavioral changes result from a lack of it. More than a decade ago it was found that total sleep deprivation in rats leads to death. These animals show weight loss despite greatly increased food consumption, suggesting excessive heat loss. The animals die, for reasons yet to be explained, within 10 to 20 days, faster than if they were totally deprived of food but slept normally.

In humans, a very rare degenerative brain disease called fatal familial insomnia leads to death after several months. Whether the sleep loss itself is fatal or other aspects of the brain damage are to blame is not clear. Sleep deprivation studies in humans have found

that sleepiness increases with even small reductions in nightly sleep times. Being sleepy while driving or during other activities that require continuous vigilance is as dangerous as consuming alcohol prior to those tasks. But existing evidence indicates that “helping” people to increase sleep time with long-term use of sleeping pills produces no clear-cut health benefit and may actually shorten life span. (About seven reported hours of sleep a night correlates with longer life spans in humans.) So inexorable is the drive to sleep that achieving total sleep deprivation requires repeated and intense stimulation. Researchers employing sleep deprivation to study sleep function are therefore quickly confronted with the difficulty of distinguishing the effects of stress from those of sleep loss.

Researchers also study the natural sleep habits of a variety of organisms. An important clue about the function of sleep is the huge variation in the amount that different species need. For example, the opossum sleeps for 18 hours a day, whereas the elephant gets by with only three or four. Closely related species that have genetic, physiological and behavioral similarities might also be expected to have similar sleep habits. Yet studies of laboratory, zoo and wild animals have revealed that sleep times are unrelated to the animals’ taxonomic classification: the range of sleep times of different primates extensively overlaps that of rodents, which overlaps that of carnivores, and so on across many orders of mammals. If evolutionary relatedness does not determine sleep time, then what does?

The extraordinary answer is that size is the major determinant: bigger animals simply need less sleep. Elephants, giraffes and large primates (such as humans) require relatively little sleep; rats, cats, voles and other small animals spend most of their time sleeping. The reason is apparently related to the fact that small animals have higher metabolic rates and higher brain and body temperatures than large animals do. And metabolism is a messy business that generates free radicals—extremely reactive chemicals that damage and even kill cells. High metabolic rates thus lead to increased injury to cells and the nucleic acids, proteins and fats within them.

Free-radical damage in many body tissues can be dealt with by replacing compromised cells with new ones, produced by cell division; however, most brain regions do not produce significant numbers of new brain cells after birth. (The hippocampus, involved in learning and memory, is an important exception.) The lower metabolic rate and brain temperature occurring during non-REM sleep seem to provide an opportunity to deal with the damage done during waking. For example, enzymes may more efficiently repair cells during periods of inactivity. Or old enzymes, themselves altered by free radicals, may be replaced by newly synthesized ones that are structurally sound.

Last year my group at the University of California at Los Angeles observed what we believe to be the first evidence for brain cell damage, in rats, occurring as a direct result of sleep deprivation. This finding supports the idea that non-REM sleep wards off metabolic harm.

REM sleep, however, is the proverbial riddle wrapped in a mystery inside an enigma. The cell-repair hypothesis could explain non-REM sleep, but it fails to account for REM sleep. After all, downtime repair cannot be taking place in most brain cells during REM sleep,

when these cells are at least as active as during waking. But a specific group of brain cells that goes against this trend is of special interest in the search for a purpose of REM sleep.

Recall that the release of some neurotransmitters ceases during REM sleep, thereby disabling body movement and reducing awareness of the environment. The key neurotransmitters affected—norepinephrine, serotonin and histamine—are termed monoamines, because they each contain a chemical entity called an amine group. Brain cells that make these monoamines are maximally and continuously active in waking. But Dennis McGinty and Ronald Harper of U.C.L.A. discovered in 1973 that these cells stop discharging completely during REM sleep.

In 1988 Michael Rogawski of the National Institutes of Health and I hypothesized that the cessation of neuro-transmitter release is vital for the proper function of these neurons and of their receptors (the molecules on recipient cells that relay neurotransmitters' signals into that cell). Various studies indicate that a constant release of monoamines can desensitize the neurotransmitters' receptors. The interruption of monoamine release during REM sleep thus may allow the receptor systems to "rest" and regain full sensitivity. And this restored sensitivity may be crucial during waking for mood regulation, which depends on the efficient collaboration of neurotransmitters and their receptors. (The familiar antidepressants Prozac, Paxil, Zoloft and other so-called selective serotonin reuptake inhibitors—SSRIs—work by causing a net increase in the amount of serotonin available to recipient cells.)

The monoamines also play a role in rewiring the brain in response to new experiences. Turning them off during REM sleep then may be a way to prevent changes in brain connections that might otherwise be inadvertently created as a result of other brain cells' intense activity during REM.

Interestingly, in 2000 Paul J. Shaw and his colleagues at the Neurosciences Institute in La Jolla, Calif., noted a connection in fruit flies between monoamine levels and sleeplike periods, during which the insects are relatively inactive. They found that disrupting the flies' downtime led to increased levels of monoamines, as is the case in humans. This discovery suggests that restoration of neurotransmitter function, eventually to become an attribute of what we now know as sleep, came into being well before mammals even evolved on the earth.

Other Possibilities

WHAT ELSE MIGHT REM sleep do? Researchers such as Frederick Snyder and Thomas Wehr of the National Institutes of Health and Robert Vertes of Florida Atlantic University have proposed that the elevated activity during REM sleep of brain cells that are not involved in monoamine production enables mammals to be more prepared than reptiles to cope with dangerous surroundings. When waking in a cold environment, reptiles are sluggish and require an external heat source to become active and responsive. But even though mammals do not thermoregulate during REM sleep, the intense neuronal activity during this phase can raise brain metabolic rate, helping mammals to monitor and react more quickly to a given

situation on waking. The observation that humans are much more alert when awakened during REM sleep than during non-REM periods supports this idea.

Sleep deprivation studies indicate, however, that REM sleep must do more than prime the brain for waking experience. These studies show that animals made to go without REM sleep will undergo more than the usual amount when they are finally given the opportunity. They apparently seek to make up the “debt”—yet another clue that REM sleep is important. Of course, if brain arousal were the only function of REM sleep, being awake should also pay back the debt, because the waking brain is also warm and active. But wakefulness clearly does not accomplish this task. Perhaps REM sleep debt results from the need to rest monoamine systems or other systems that are “off” in REM sleep.

Old ideas that REM sleep deprivation led to insanity have been convincingly disproved (although studies show that depriving someone of sleep, for example by prodding him or her awake repeatedly, can definitely cause irritability). In fact, REM sleep deprivation can actually alleviate clinical depression. The mechanism for this phenomenon is unclear, but one suggestion is that the deprivation mimics the effects of SSRI antidepressants: because the normal decrease in monoamines during REM does not occur, the synaptic concentration of neurotransmitters that are depleted in depressed individuals increases.

Some researchers are pursuing the idea that REM sleep might have a role in memory consolidation, but as I examined in detail in a 2001 article in *Science* [see “More to Explore” on opposite page], the evidence for that function is weak and contradictory. The findings that argue against memory consolidation include the demonstration that people who have brain damage that prevents REM sleep, or who have a drug-induced blockade of REM sleep, have normal—or even improved—memory. And although sleep deprivation before a task disturbs concentration and performance—sleepy students do not learn or think well—REM deprivation after a period of alert learning does not appear to interfere with retaining the new information. In addition, dolphins experience little or no REM sleep yet exhibit impressive reasoning and learning ability.

In fact, learning ability across species does not appear to be related to total REM sleep duration. Humans do not have particularly long REM sleep times—90 to 120 minutes each night—compared with other mammals. (And humans with higher IQs or school performance do not have more, or less, REM sleep than those with lower IQs.) The amount of time spent in REM does change over an individual’s life, however. In all animals studied, the portion of each day devoted to REM sleep is highest early in the subject’s life and falls gradually to a steady, lower level in adulthood. An additional, fascinating fact emerges from comparing numerous species: the best predictor of the amount of REM sleep time for an adult in a given species is how immature the offspring of that species are at birth.

In 1999 Jack Pettigrew and Paul Manger of the University of Queensland in Australia and I were able to study an unusual research subject, the platypus. This evolutionarily earliest of extant mammals surprised us by revealing itself to be the champion REM sleeper: about *eight hours* a day. The platypus is born completely defenseless and blind, cannot thermoregulate or find food on its own, and stays attached to its mother for weeks after birth.

At the other extreme, the new-born dolphin can and must thermoregulate, swim, follow its mother and avoid predators. And adult dolphins, as previously noted, do almost no REM sleeping.

Time spent in REM sleep is highest early
in LIFE and falls GRADUALLY.

Michel Jouvet, the pioneering sleep researcher who discovered four decades ago that the brain stem generates REM sleep, has a provocative suggestion for the large amounts of REM in immature animals. REM sleep's intense neuronal activity and energy expenditure, Jouvet believes, have a role early in life in establishing the genetically programmed neuronal connections that make so-called instinctive behavior possible. Before birth, or in animals that have delayed sensory development, REM sleep may act as a substitute for the external stimulation that prompts neuronal development in creatures that are mature at birth. Work by Howard Roffwarg, director of the Sleep Disorders Center at the University of Mississippi Medical Center, and his colleagues support this idea. Roffwarg found that preventing REM sleep in cats during this early period can lead to abnormalities in the development of the visual system.

Animals that engage in a lot of REM sleep shortly after birth continue to experience relatively large amounts when mature. What is it about immaturity at birth that causes REM sleep duration to be high later in life? In simple evolutionary terms, animals that have low REM time should need less fuel and leave more descendants than animals that experience long periods of high energy consumption. From that perspective, it is most likely that animals that still have high REM times must have evolved a use for REM sleep that is not found in precocial animals. But that function remains to be identified. Sleep researchers are confident that progress in identifying the brain regions that control REM and non-REM sleep will soon lead to a more comprehensive and satisfying understanding of sleep and its functions. As we further study the mechanisms and evolution of sleep, we will probably gain insights into exactly what is repaired and rested, why these processes are best done in sleep, and why knitting up Shakespeare's raveled sleeve of care ultimately helps us to stay awake.

Overview/*Uncovering Sleep*

- Researchers are still debating the function of REM and non-REM sleep and why we need both, but new findings suggest several reasonable hypotheses.
- One is that reduced activity during non-REM sleep may give many brain cells a chance to repair themselves.
- Another is that interrupted release of neurotransmitters called monoamines during REM sleep may allow the brain's receptors for those chemicals to recover and regain full sensitivity, which helps with regulation of mood and learning.
- The intense neuronal activity of REM sleep in early life may allow the brain to develop properly.



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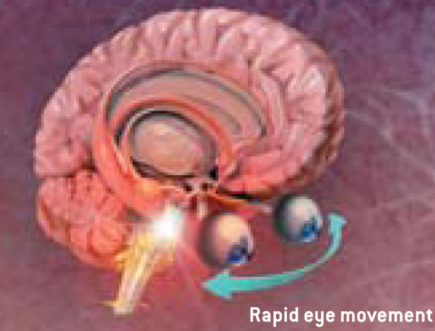
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Sleeping, Dreaming, Waking

REM AND NON-REM SLEEP differ in several ways, some of which are illustrated below, along with one of the proposed functions of each type of sleep.

REM SLEEP

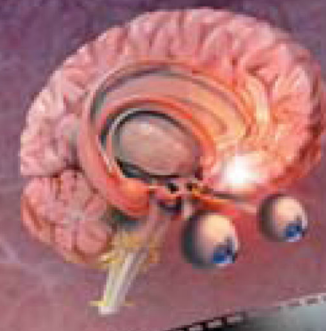
Brain stem REM-sleep-on neurons fire



Vivid dreams occur

NON-REM SLEEP

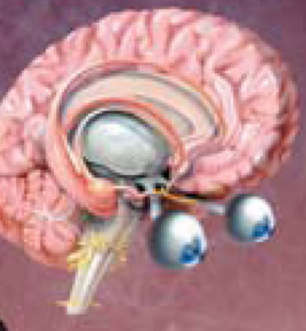
Forebrain sleep-on neurons fire



Absence of vivid dreams

AWAKE

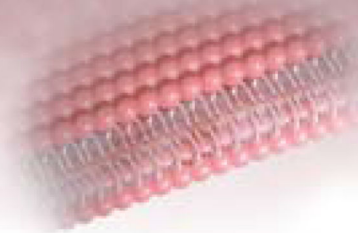
Sleep-on neurons are inactive



Wakeful state



Certain receptors are inactive during REM sleep, which may be necessary for their proper functioning during the awake state



Non-REM sleep may allow cells to repair membranes damaged by free radicals



Free radicals damage cell membranes when neurons are active, as when we are awake

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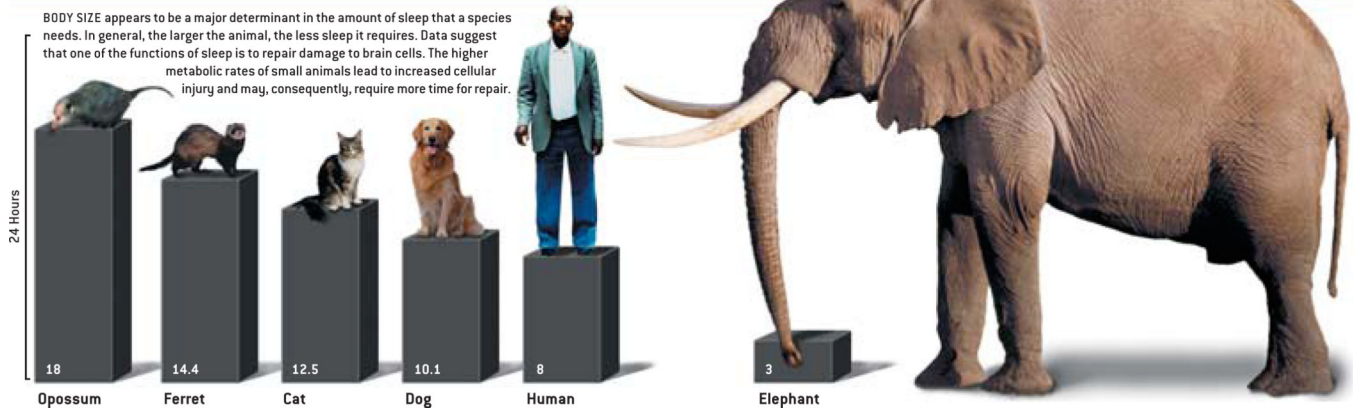
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Counting Sleep

BODY SIZE appears to be a major determinant in the amount of sleep that a species needs. In general, the larger the animal, the less sleep it requires. Data suggest that one of the functions of sleep is to repair damage to brain cells. The higher metabolic rates of small animals lead to increased cellular injury and may, consequently, require more time for repair.



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