

# THE STATES OF SLEEP

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Light and deep sleep differ physiologically, deep sleep having much in common with being awake. Studies with cats now suggest that the two states of sleep are induced by different biochemical secretions

by Michel Jouvet

Early philosophers recognized that there are two distinctly different levels of sleep. An ancient Hindu tale described three states of mind in man: (1) wakefulness (*vaiswanara*), in which a person "is conscious only of external objects [and] is the enjoyer of the pleasures of sense"; (2) dreaming sleep (*tajasa*), in which one "is conscious only of his dreams [and] is the enjoyer of the subtle impressions in the mind of the deeds he has done in the past," and (3) dreamless sleep (*prajna*), a "blissful" state in which "the veil of unconsciousness envelops his thought and knowledge, and the subtle impressions of his mind apparently vanish."

States 2 and 3 obviously are rather difficult to investigate objectively, and until very recently the phases of sleep remained a subject of vague speculation. Within the past few years, however,

studies with the aid of the electroencephalograph have begun to lift the veil. By recording brain waves, eye movements and other activities of the nervous system during the different sleep states neurophysiologists are beginning to identify the specific nervous-system structures involved, and we are now in a position to analyze some of the mechanisms responsible.

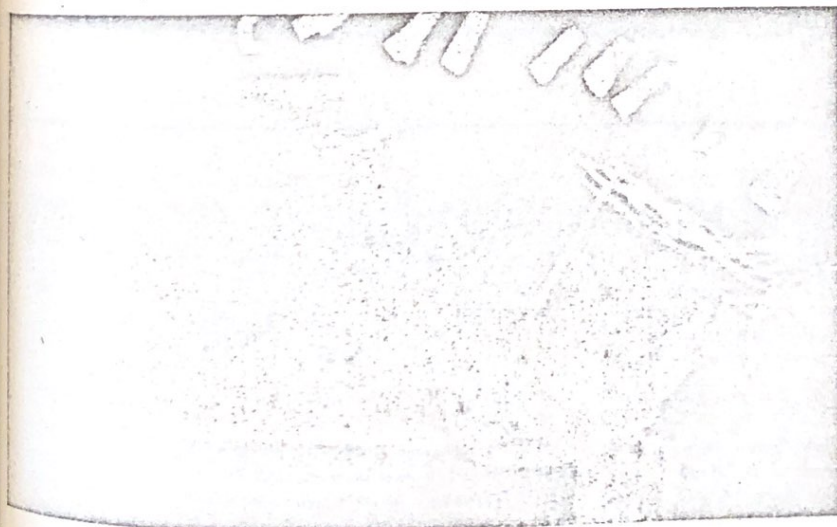
## Brain Activities in Sleep

Lucretius, that remarkably inquisitive and shrewd observer of nature, surmised that the fidgetings of animals during sleep were linked to dreaming. Some 30 years ago a German investigator, R. Klaue, made a significant discovery with the electroencephalograph. He found that sleep progressed in a characteristic sequence: a period of light sleep, during

which the brain cortex produced slow brain waves, followed by a period of deep sleep, in which the cortical activity speeded up. Klaue's report was completely overlooked at the time. In the 1950's, however, Nathaniel Kleitman and his students at the University of Chicago took up this line of investigation. Kleitman and Eugene Aserinsky found (in studies of infants) that periods of "active" sleep, alternating with quiescent periods, were marked by rapid eye movements under the closed lids. Later Kleitman and William C. Dement, in studies of adults, correlated the eye movements with certain brain-wave patterns and definitely linked these activities and patterns to periods of dreaming [see "Patterns of Dreaming," by Nathaniel Kleitman; *SCIENTIFIC AMERICAN*, November, 1960]. In 1958 Dement showed that cats may have periods of sleep similarly marked by rapid eye movement and fast cortical activity. He called such periods "activated sleep."

Meanwhile at the University of Lyons, François Michel and I had been conducting a series of experiments with cats. In the cat, which spends about two-thirds of its time sleeping, the process of falling asleep follows a characteristic course, signaled by easily observable external signs. Typically the animal curls up in a ball with its neck bent. The flexing of the nape of its neck is a clear sign that the muscles there retain some tonus, that is, they are not completely relaxed. In this position the cat lapses into a light sleep from which it is easily awakened.

After about 10 to 20 minutes there comes a constellation of changes that mark passage over the brink into deep sleep. The cat's neck and back relax their curvature, showing that the muscles have completely lost tonus; they are now altogether slack. At the same time there



X RAY OF CAT'S HEAD shows a cluster of electrodes with which the author obtained a record of the electrical signals from various parts of the cat's brain. The cat's mouth is at the left; one electrode at far right measures the changes in the animal's neck-muscle tension.



CAT'S BRAIN, seen in front-to-back section, has a number of segments. Some of the principal ones are identified in the illustration

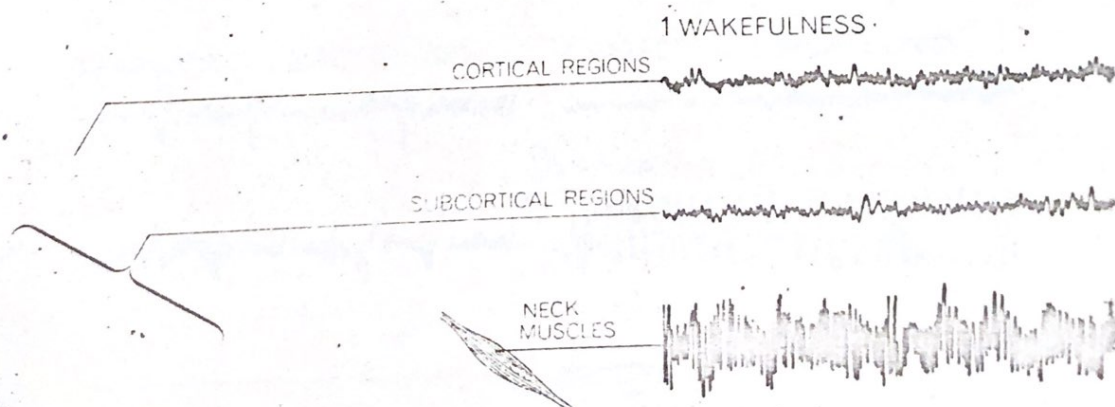
at the top of the opposite page. Many segments of the cat's brain, such as the cerebellum (top right), have no role to play in sleep.

are bursts of rapid eye movements (eight to 30 movements in each burst) in either the side-to-side or the up-and-down direction, like the movements in visual use of the eyes. Occasionally these eyeball movements behind the closed eyelids are accompanied by a sudden dilation of the pupils, which in the main are tightly constricted during sleep. Along with the eye movements go events involving many other parts of the body: small tremors of muscles at the ends of the extremities, causing rapid flexing of the digits and now and then small scratching motions; very rapid movements of the ears, the whiskers, the tail and the tongue, and an episode of fast and irregular breathing.

It is somewhat startling to realize that all this activity goes on during a period in which the animal's muscular system is totally atonic (lacking in tension). The activities are also the accompaniment of deep sleep, as is indicated by the fact that it takes an unusually high level of sound or electrical stimulation to arouse the cat during this phase. The state of deep sleep lasts about six or seven minutes and alternates with periods of lighter sleep that last for an average of about 25 minutes.

To obtain more objective and specific information about events in the brain during sleep we implanted electrodes in the muscles of the neck and in the midbrain of cats. We used animals that

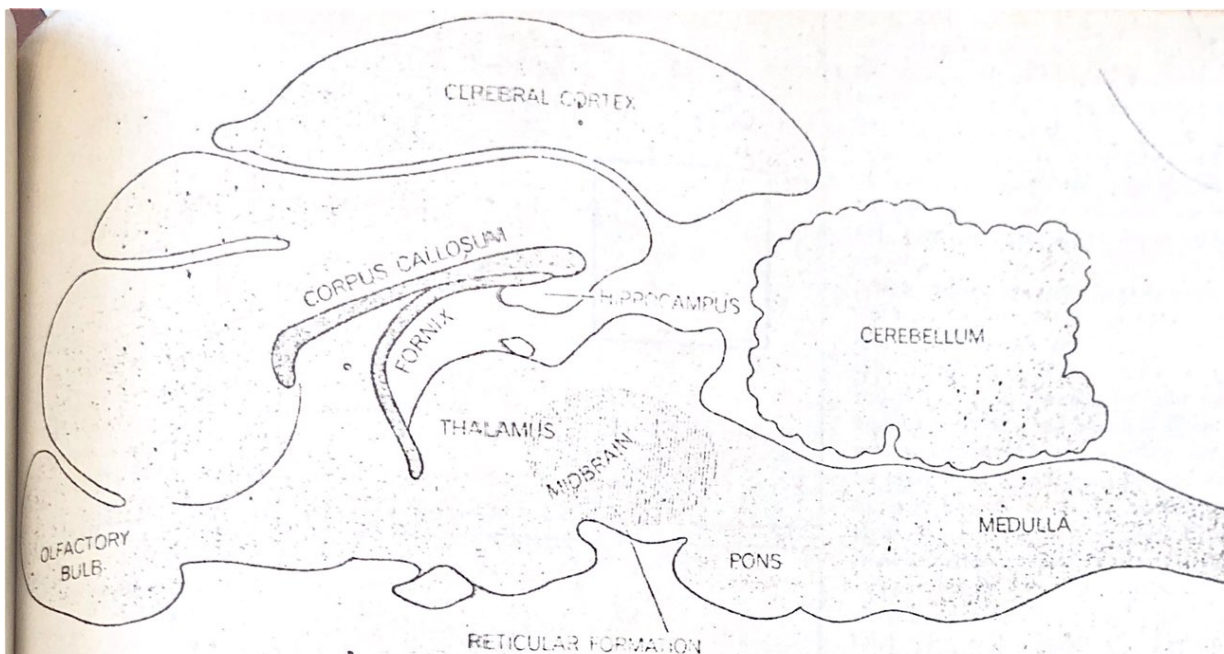
were deprived of the brain cortex, since we wished to study the subcortical activities. In the course of extended recordings of the electrical events we were surprised to find that the electrical activity of the neck muscles disappeared completely for regular periods (six minutes long), and the condition persisted when sharp spikes of high voltage showed up now and then in the pontine reticular formation, situated just behind the "arousal center" of the midbrain. These electrical signs were correlated with eye movements of the sleeping animal. Further, we noted that in cats with intact brains both the abolition of muscle tonus and the sharp high-voltage spikes were strikingly correlated with the rapid eye



VARYING RHYTHMS are identified with the various states of sleep. From left to right, a wakeful cat (1) shows high-speed alterations in electric potential in both cortical and subcortical regions

of the brain, as well as neck-muscle tension. In light sleep (2) the cat shows a slower rhythm in the traces from the cortical and subcortical regions, but neck-muscle tension continues. The phasic, or





BRAIN SEGMENTS associated with sleep include the reticular formation, which controls wakefulness. This region is under the con-

trol of an area in the lower brain. When the control is blocked by making a cut through the pons, a normal cat becomes insomniac.

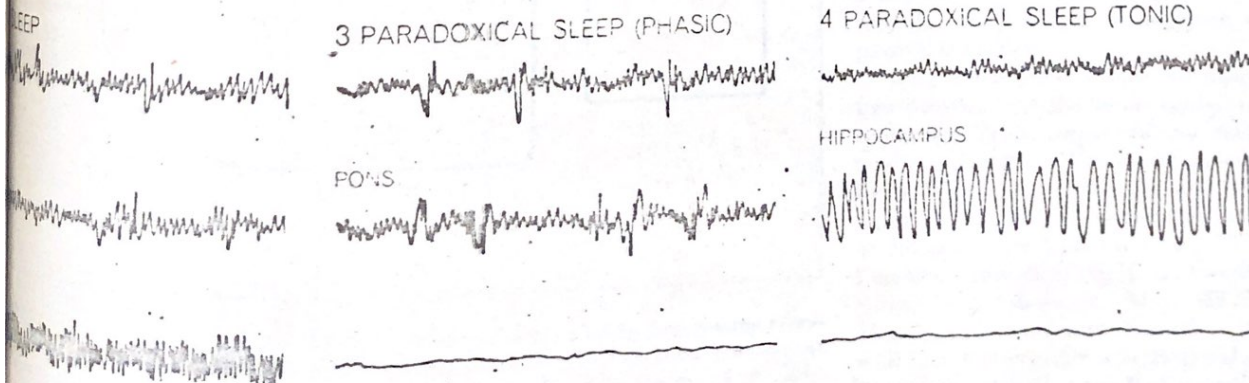
movement and fast cortical activity De-  
scribed had described. These findings pre-  
sented a paradox. It was surely strange  
to find fast cortical activity (generally a  
sign of wakefulness) coupled with com-  
plete muscular atony (invariably a sign  
of deep sleep)!

### The Two Sleep States

We named this strange state "para-  
doxical sleep." It is also called deep  
sleep, fast-wave sleep, rapid-eye-move-  
ment (REM) sleep and dreaming sleep.  
Whereas the lighter sleep that precedes  
is often called slow-wave sleep. We  
consider paradoxical sleep a qualitative-  
distinct state, not simply a deepened

version of the first stage of sleep. Very  
schematically (for the cat) we can de-  
scribe the three states—wakefulness,  
light sleep and paradoxical sleep—in the  
following physiological terms. Wakeful-  
ness is accompanied by fast, low-voltage  
electrical activity in the cortex and the  
subcortical structures of the brain and by  
a significant amount of tonus in the mus-  
cular system. The first stage of sleep, or  
light sleep, is characterized by a slacken-  
ing of electrical activity in the cortex and  
subcortical structures, by the occurrence  
of "spindles," or groups of sharp jumps,  
in the brain waves and by retention of  
the muscular tension. Paradoxical sleep  
presents a more complex picture that we  
must consider in some detail.

We can classify the phenomena in  
paradoxical sleep under two heads: tonic  
(those having to do with continuous phe-  
nomena) and phasic (those of a periodic  
character). The principal tonic phenom-  
ena observed in the cat are fast electrical  
waves (almost like those of wakefulness)  
in the cortex and subcortical structures,  
very regular "theta" waves at the level of  
the hippocampus (a structure running  
from the front to the rear of the brain)  
and total disappearance of electrical ac-  
tivity in the muscles of the neck. The  
principal phasic phenomena are high-  
voltage spikes, isolated or grouped in  
volleys that appear at the level of the  
pons and the rear part of the cortex  
(which is associated with the visual sys-



phasic aspects of paradoxical sleep (3) are marked by isolated  
discharges from the rear of the cortex and the pons, as well as  
rapid eye movement and limb movements. Loss of neck-muscle

tension is a tonic (4) rather than a phasic phenomenon. Other  
tonic, or continuous, aspects of paradoxical sleep are high-speed  
cortical rhythms and regular "theta" waves from hippocampus.



cent of the time. Our results were closely related to those of Moruzzi's. His operation dividing the brainstem cut through the raphe system. We found that when we destroyed only the raphe cells on one side or the other of the site of his cut, our animals were reduced to the same amount of sleep (20 percent) as those on which he had performed his experiment. This gives us further reason to believe the raphe system may indeed be the main center responsible for bringing on sleep in cats.

These new developments bring serotonin into a prominent place in the research picture and offer an avenue for biochemical attack on the mysteries of sleep. The fact that the raphe cells are chiefly notable for their production of serotonin seems to nominate this substance for an important role in producing the onset of sleep. We have recently been able to demonstrate a significant correlation between the extent of the lesion of the raphe system, the decrease

in sleep and the decrease in the amount of serotonin in the brain as measured by means of spectrofluorescent techniques.

In physiological terms we can begin to see the outlines of the system of brain structures involved in initiating the onset of sleep and maintaining the first stage of light slumber. At the level of the brainstem, probably within the raphe system, there are structures that apparently counteract the RAS and by their braking action cause the animal to fall asleep. Associated with these structures there presumably are nearby structures that account for the modulations of electrical activity (notably the slow brain waves) that have been observed to accompany light sleep. This slow activity seems to depend primarily, however, on the higher brain structures, particularly the cortex and the thalamus; in a decorticated animal the pattern characteristic of light sleep does not make its appearance. We must therefore conclude that the set of mechanisms brought into

play during the process of falling asleep is a complicated one and that a number of steps in the process still remain to be discovered.

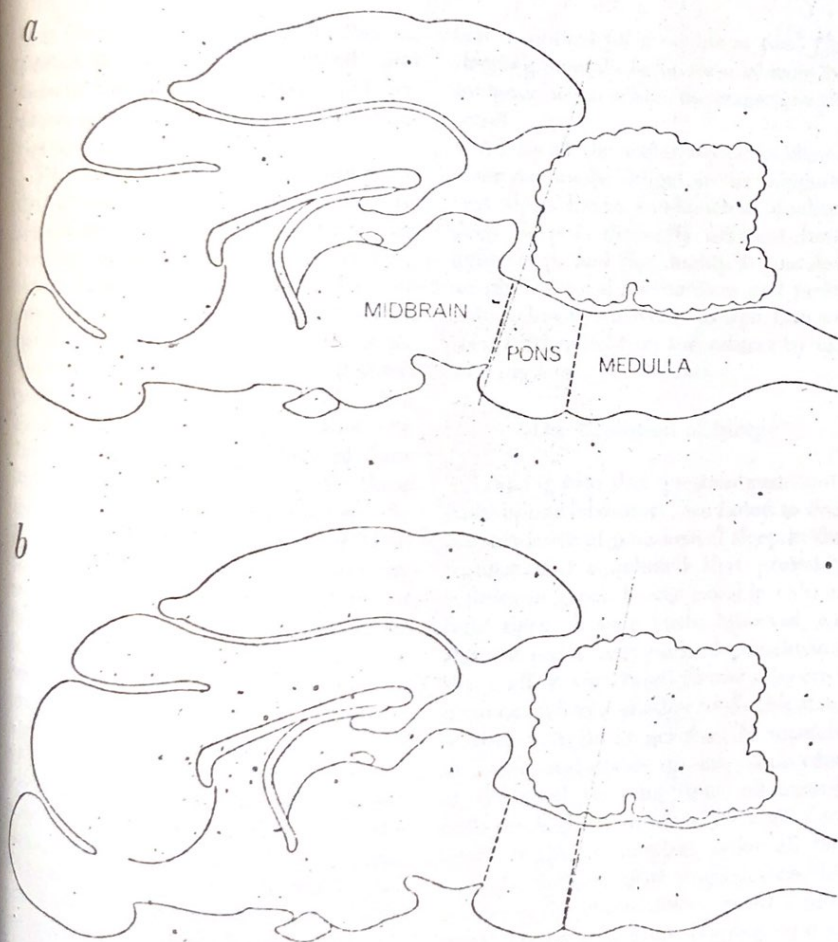
### Paradoxical Sleep

In searching for the structures involved in paradoxical, or deep, sleep we are in a somewhat better position. When an animal is in that state, we have as clues to guide us not only the electrical activities in the brain but also conclusive and readily observable signs such as the disappearance of tonus in the muscles of the neck. This is the single most reliable mark of paradoxical sleep. Furthermore, it enables us to study animals that have been subjected to drastic operations we cannot use in the study of light sleep because they obliterate the electrical activities that identify the falling-asleep stage.

A cat whose brainstem has been cut through at the level of the pons, so that essentially all the upper part of the brain has been removed, still exhibits the cycle of waking and deep sleep. Such an animal can be kept alive for several months, and with the regularity of a biological clock it oscillates between wakefulness and the state of paradoxical sleep, in which it spends only about 10 percent of the time. This state is signaled, as in normal animals, by the typical slackness of the neck muscles, by the electroencephalographic spikes denoting electrical activity in the pons structures and by lateral movements of the eyeballs.

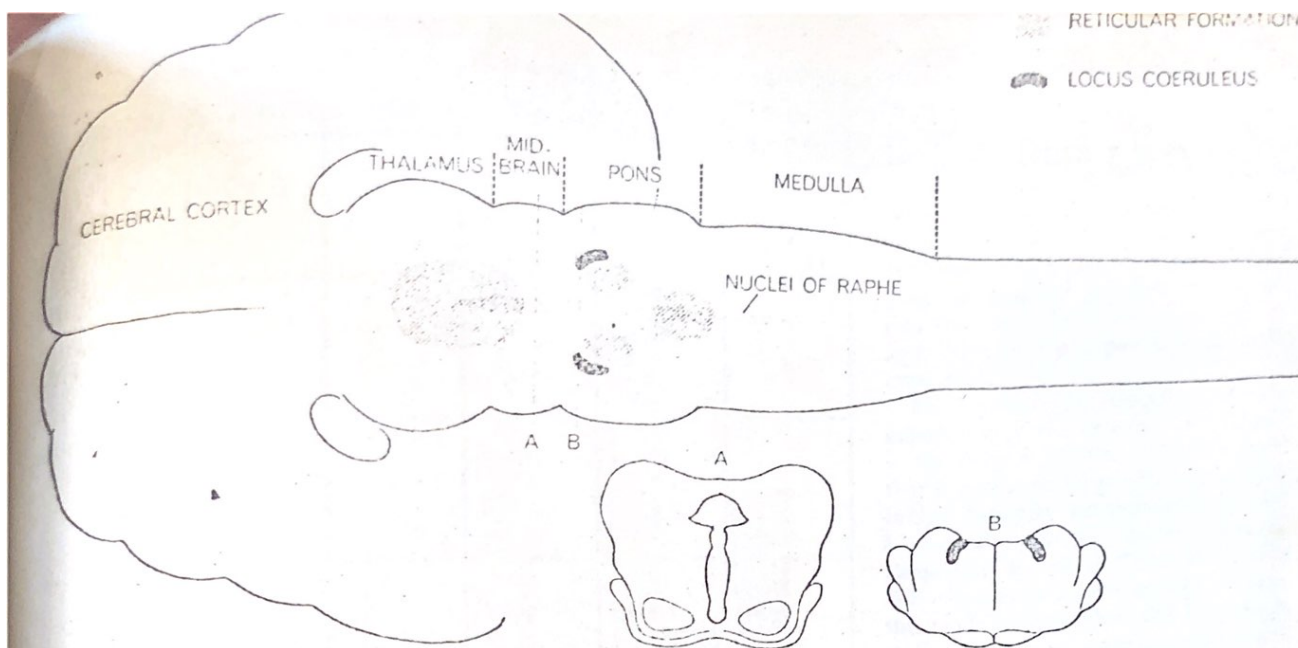
When, however, we sever the brainstem at a lower level, in the lower part of the pons just ahead of the medulla, the animal no longer falls into paradoxical sleep. The sign that marks this cyclical state—periodic loss of muscle tonus—disappears. It seems, therefore, that the onset of paradoxical sleep must be triggered by the action of structures somewhere in the middle portion of the pons. Further experiments have made it possible for us to locate these structures rather precisely. We have found that paradoxical sleep can be abolished by destroying certain nerve cells in a dorsal area of the pons known as the locus coeruleus. Dahlström and Fuxe have shown that these cells have a green fluorescence under ultraviolet light and that they contain noradrenalin. Hence it seems that noradrenalin may play a role in producing paradoxical sleep similar to the one serotonin apparently plays in bringing about light sleep.

What mechanism is responsible for the elimination of muscular tonus that accompanies paradoxical sleep? It seems



PARADOXICAL SLEEP STRUCTURES evidently lie far back along the brainstem. A cat deprived of all its higher brain function by means of a cut through the pons (a) will live for months, alternately awake and in paradoxical sleep. If a cut is made lower (b) along the brainstem, however, the cat will no longer fall into paradoxical sleep, because the cut destroys the brain cells in that region, which produce another monoamine, noradrenalin.





CATS BRAINSTEM is the site of the two groups of cells that produce the substances affecting light and paradoxical sleep. The nu-

clei of raphe (color) secrete serotonin; nerve cells lower down the pons, known as the locus coeruleus (gray), secrete noradrenalin.

most likely that the source of this inhibition lies in the spinal cord, and Moruzzi and his colleague Ottavio Pompeiano are making a detailed investigation of this hypothesis.

The objective information about paradoxical sleep developed so far gives us some suggestions about the mechanisms involved in dreaming. The controlling structures apparently are located in the dorsal part of the pons. They give rise to spontaneous excitations that travel mainly to the brain's visual tracts, and it seems possible that this excitation is related to the formation of the images that one "sees" in dreams. Regardless of how strongly the brain is stimulated by these spontaneous impulses (as Edward V. Evarts of the National Institute of Mental Health and others have shown by means of microelectrode recordings of the visual system), during sleep the body's motor system remains inactive because a potent braking mechanism blocks electrical excitation of the motor nerves. This inhibitory mechanism seems to be controlled by the hormone-secreting nerves of the locus coeruleus structure. If this structure is destroyed, the animal may periodically exhibit a spasm of active behavior, which looks very much as if it is generated by the hallucinations of a dream. In such episodes the cat, although it evinces the unmistakable signs of deep sleep and does not respond to external stimuli, will sometimes perform bodily movements of rage,

fear or pursuit for a minute or two. The sleeping animal's behavior may even be so fierce as to make the experimenter recoil.

All in all the experimental evidence from mammals obliges us to conclude that sleep has a fundamental duality; deep sleep is distinctly different from light sleep, and the duality is founded on physiological mechanisms and probably on biochemical ones as well. Can we shed further light on the subject by examining animal evolution?

### The Evolution of Sleep

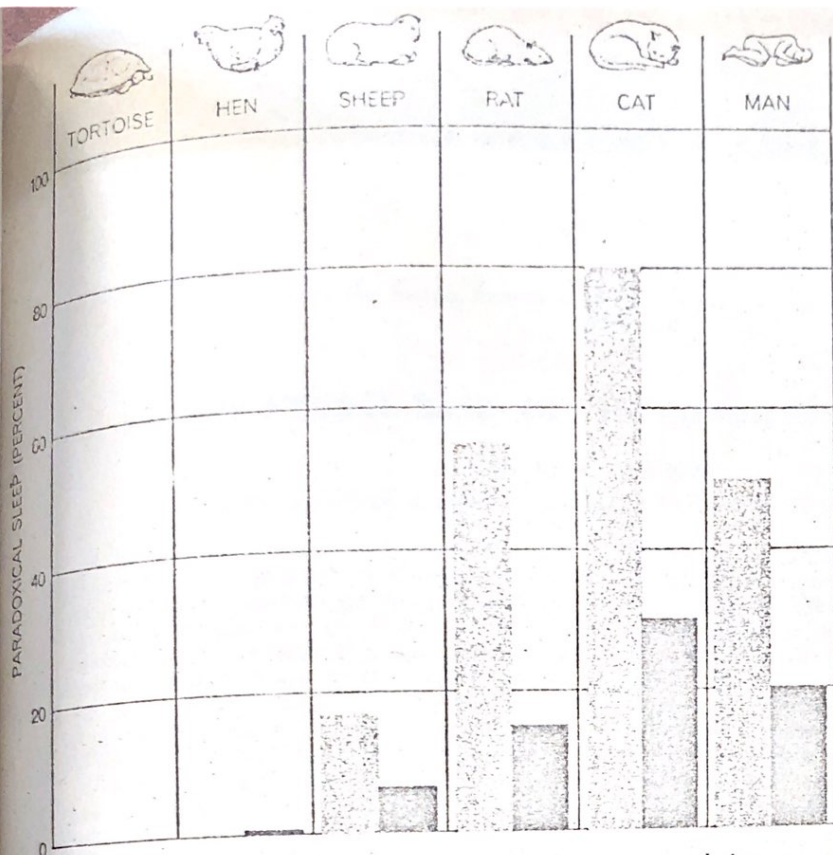
Looking into this question systematically in our laboratory, we failed to find any evidence of paradoxical sleep in the tortoise and concluded that probably reptiles in general were capable only of light sleep. Among birds, however, we start to see a beginning of paradoxical sleep, albeit very brief. In our subjects—pigeons, chicks and other fowl—this state of sleep lasts no longer than 15 seconds at a time and makes up only .5 percent of the total sleeping time, contrasted with the higher mammals' 20 to 30 percent. In the mammalian order all the animals that have been studied, from the mouse to the chimpanzee, spend a substantial portion of their sleeping time in paradoxical sleep. We find a fairly strong indication that the hunting species (man, the cat, the dog) enjoy more deep sleep than the hunted (rabbits, ruminants). In

our tests the former average 20 percent of total sleep time in paradoxical sleep, whereas the latter average only 5 to 10 percent. Further studies are needed, however, to determine if what we found in our caged animals is also true of their sleep in their natural environments.

The evolutionary evidence shows, then, that the early vertebrates slept only lightly and deep sleep came as a rather late development in animal evolution. Curiously, however, it turns out that the opposite is true in the development of a young individual; in this case ontogeny does not follow phylogeny. In the mammals (cat or man) light sleep does not occur until the nervous system has acquired a certain amount of maturity. A newborn kitten in its first days of life spends half of its time in the waking state and half in paradoxical sleep, going directly from one state into the other, whereas in the adult cat there is almost invariably a transitional period of light sleep. By the end of the first month the kitten's time is divided equally among wakefulness, light sleep and paradoxical sleep (that is, a third in each); thereafter both wakefulness and light sleep increase until adulthood stabilizes the proportions of the three states at 35, 50 and 15 percent respectively.

Considering these facts of evolution and development, we are confronted with the question: What function does paradoxical sleep serve after all? As Kleitman reported in his article "Patterns





PARADOXICAL SLEEP among three vertebrate classes of increasing evolutionary complexity is shown as a percentage of each animal's time spent in light sleep. None is known in the case of the reptile, a tortoise; in the case of the hen it is only two-tenths of 1 percent of the total. In the case of each of the four mammal species shown, the newborn spend at least twice as much time in paradoxical sleep (color) as do their adult counterparts (black):

of Dreaming," Dement found that when he repeatedly interrupted people's dreams by waking them, this had the effect of making them dream more during their subsequent sleep periods. These results indicated that dreaming fulfills some genuine need. What that need may be remains a mystery. Dement's subjects showed no detectable disturbances of any importance—emotional or physiological—as a result of their deprivation of dreaming.

We have found much the same thing to be true of the deprivation of paradoxical sleep in cats. For such a test we place a cat on a small pedestal in a pool of water with the pedestal barely topping the water surface. Each time the cat drops off into paradoxical sleep the relaxation of its neck muscles causes its head to droop into the water and this wakes the animal up. Cats that have been deprived of paradoxical sleep in this way for several weeks show no profound disturbances, aside from a modest speeding up of the heart rate. They do, however, have a characteristic pattern of aftereffects with respect to paradoxical sleep. For several days following their removal from the pedestal they spend

much more than the usual amount of time (up to 60 percent) in paradoxical sleep, as if to catch up. After this rebound they gradually recover the normal rhythm (15 percent in deep sleep), and only then does the heart slow to the normal rate. The recovery period depends on the length of the deprivation period: a cat that has gone without paradoxical sleep for 20 days takes about 10 days to return to normal.

### The Chemistry of Sleep

All of this suggests that some chemical process takes place during the recovery period. Let us suppose that the deprivation of paradoxical sleep causes a certain substance related to the nervous system to accumulate. The excess of paradoxical sleep during the recovery period will then be occupied with elimination of this "substance," presumably through the agency of "enzymatic" factors that act only during paradoxical sleep.

There is reason to believe that certain enzymes called monoamine oxidases, which oxidize substances having a single amine group, play a crucial role in bringing about the transition from light sleep

to paradoxical sleep. We have found that drugs capable of inhibiting these enzymes can suppress paradoxical sleep in cats without affecting either light sleep or wakefulness. A single injection of the drug nialamide, for example, will eliminate paradoxical sleep from the cycle for a period of hundreds of hours. We have also found that this potent drug can suppress paradoxical sleep in cats that have first been deprived of such sleep for a long period in the pool experiment.

The findings concerning the probable importance of the monoamine oxidases in the sleep mechanism raise the hope that it may soon be possible to build a bridge between neurophysiology and biochemistry in the investigation of sleep. If it is indeed a fact that these enzymes play an important role in sleep, this tends to strengthen the hypothesis that serotonin and noradrenalin, which are monoamines, are involved in the two states of sleep—serotonin in light sleep and noradrenalin in paradoxical sleep. There are other bits of chemical evidence that support the same view. For example, the drug reserpine, which is known to prevent the accumulation of monoamines at places where these compounds are usually deposited, has been found to be capable of producing some specific electrical signs of paradoxical sleep in experimental animals. Further, the injection of certain precursors involved in the synthesis of serotonin in the brain can produce a state resembling light sleep, whereas drugs that selectively depress the serotonin level in the brain produce a state of permanent wakefulness.

We can put together a tentative working hypothesis about the brain mechanisms that control sleep. It seems that the raphe system is the seat responsible for the onset of light sleep, and that it operates through the secretion of serotonin. Similarly, the locus coeruleus harbors the system responsible for producing deep sleep, and this uses noradrenalin as its agent. In cyclic fashion these two systems apply brakes to the reticular activating system responsible for wakefulness and also influence all the other nerve systems in the brain, notably those involved in dreaming.

Dreaming itself, particularly the question of its evolutionary origin and what function it serves, is still one of the great mysteries of biology. With the discovery of its objective accompaniments and the intriguing phenomenon of paradoxical sleep, however, it seems that we have set foot on a new continent that holds promise of exciting explorations.