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Source: *Science*, New Series, Vol. 152, No. 3722 (Apr. 29, 1966), pp. 604-619

Published by: American Association for the Advancement of Science

Stable URL: <http://www.jstor.org/stable/1718980>

Accessed: 13-11-2015 18:55 UTC

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Ontogenetic Development of the Human Sleep-Dream Cycle

The prime role of "dreaming sleep" in early life may be in the development of the central nervous system.

Howard P. Roffwarg, Joseph N. Muzio, William C. Dement

Within the last decade new discoveries have forced extensive modification of traditional concepts of sleep. In the past there was always considerable interest in mechanisms of sleep (1, 2), but its function was largely taken for granted. The view prevailed that the role of sleep is self-evidently allied to the need for restitution or, at least, for rest.

Since the demonstration that there are two distinct phases of sleep (3-5) we realize that more than a simple parallelism between rest and sleep is required to elucidate the role of sleep in our biological economy. As a matter of fact, it is probably begging the question of function to discuss *sleep* as a totality at all. For the physiological characteristics of the alternating states within behavioral sleep are so different that it is questionable whether a single designation, purporting to apply meaningfully to the normal condition of the individual when not awake, is any longer adequate. Currently, a "dualistic" hypothesis about sleep mechanisms is widely, though not universally (1, 6), accepted, in which the two major types of sleep are viewed as qualitatively distinct states (7-9). It is likely that a dichotomy will and should apply to the question of function as well.

Owing to its singular properties and recent discovery, the sleep stage accompanied by rapid eye movements (REM sleep) has received a greater share of investigative attention (3-5) than the non-rapid-eye-movement stages (NREM sleep). Most studies have been concerned with the physiological attributes of REM sleep or with the factors that influence its percentage of total sleep. In an attempt to assess the factor of age we began a series of observations on the proportions of REM and

NREM sleep in various age groups. Another reason for our interest in the REM sleep process in preadult groups was the wish to determine the onset of dreaming. Since Aserinsky, Kleitman, and Dement (3, 4) first demonstrated a relationship between REM sleep and dreaming, confirmations of the association have been numerous (10-15). We therefore thought it might be possible to designate when dreaming begins by determining the age when REM sleep first appears. Surprisingly, we found that preschool children had a higher percentage of REM sleep than adults. We also observed REM's in apparently sleeping newborn infants (16). Such unexpected findings suggested the need for a thorough polygraphic investigation of sleep in human neonates.

In this article we shall attempt a new synthesis of current information about the REM state, dream phenomena, and the relationship between sleep pattern and maturation; present our findings in newborns which carry implications with regard to a "functional consequence" of REM sleep; and explore some of the data which lead us to suggest that REM sleep plays an important role in the ontogenetic development of the central nervous system.

Typical Pattern in Sleep

A normal adult, upon falling asleep, exhibits a typical succession of electroencephalographic (EEG) changes (5, 16). After fragmentation and disappearance of alpha activity, the waves diminish slightly in frequency as their amplitudes grow (descending stage 1). High-voltage, notched slow waves, "K complexes," and characteristic trains of

14-cycle-per-second "sleep spindles" invade the background activity (stage 2). Tall "delta" waves (1 to 2 cycles per second) progressively fill the record (stage 3) and finally dominate it in virtually unbroken sequence (stage 4). The distinguishing criteria of these EEG "stages" are arbitrary but the stages are all considered phases of NREM sleep (7, 17, 18).

Approximately 50 to 70 minutes after onset of sleep, the initial REM period of the night begins. Appearing just before the first REM's are manifest and persisting until the last terminate, the characteristic low-voltage, relatively fast, nonspindling EEG of stage 1 sleep resumes, encompassing an interval termed a stage 1-REM period, or REM sleep. Short trains of "sawtooth" waves (2 to 3 cycles per second) invade the stage 1 EEG, presaging or coinciding with the REM clusters (12, 19, 20). The periods recur every 80 to 90 minutes and comprise 20 to 25 percent of the conventional night's sleep of young adults. Short early in the night and longer towards morning, they average 20 minutes in length. Spindle and high-voltage EEG patterns reappear between the REM periods (21).

Although the nocturnal sleep cycle of an individual on a consistent diurnal schedule tends to be fairly constant from night to night (4), it may vary under conditions such as apprehension or anxiety (the "first night effect" in the laboratory) (22), hypnotic suggestion (23), the effects of certain drugs and their withdrawal (20, 24-26), compensation from experimental interruptions of REM sleep (8, 27, 28), and acute and chronic psychotic states (25, 29). Age is also an important variable (16).

The state of the adult in REM sleep is singularly distinct from that in NREM sleep. Hence REM sleep has been classified as a "third" state alongside NREM sleep and waking (7, 8, 30). The physiological characteristics of the REM state have already been extensively reviewed by Jouvet (9), Snyder (7, 30), and Dement (18). We shall attempt here only to summarize the basic phenomena, focusing our attention on the events in the central nervous system.

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Whereas respiratory rhythm, heart rate, and blood pressure tend to be basal in NREM sleep, they display greater activity and greater variability during REM phases (3-5, 11, 12, 31). The fine muscles of the face and extremities contract frequently, though there are few gross body displacements (14). In the absence of movement, however, muscle tone measured from the head and neck virtually disappears in REM periods (20, 32). The extrinsic ocular muscles are an exception to this rule. Before and during shifts of eyeball position, tone may be sustained in uninvolved and antagonist muscles (33). Penile erections are specific to the REM periods, detumescence occurring as NREM sleep ensues (34). Basal skin resistance, which should fall with heightened arousal, has been reported to rise in REM sleep by some investigators (35) but not by others (11, 30). In view of the eye activity and oneiric phenomena during REM sleep, it is intriguing that the REM sleep EEG is remarkably similar to that of a subject awake under circumstances of visual imaging or stimulation, when alpha activity is blocked. Furthermore, cortical responses evoked during the waking state are extremely similar to those evoked in REM sleep (36).

An unexpected finding has been that motor-response and arousal thresholds are no higher in deep NREM sleep than in REM sleep (5, 37). This seems to fit with the finding in cats that during REM sleep there is a high response threshold in the mesencephalic reticular formation to auditory (38) as well as to direct stimulation (39, 40). In spite of the lowered responsiveness to stimulation, however, there is greater spontaneous activity in the reticular formation during REM sleep (39). (It is precisely this aspect of brain functioning in REM sleep which renders "depth of sleep" so difficult to designate.) Huttenlocher has speculated that in REM sleep evoked responses may be *occluded* because of this high level of spontaneous activity. Recently, however, Adey *et al.* (41) were not able to demonstrate higher response thresholds in the mesencephalic reticular formations of chimpanzees during REM sleep.

Studies in Animals

A dual neurophysiological organization of sleep is not specific to human beings. Every species of mammal so

far studied exhibits rhythmically alternating periods of REM and NREM activity which are marked by vegetative alterations similar in most respects to those that are found in man (12, 41-52).

Moreover, animal experimentation has greatly extended our knowledge of the active processes occurring in the central nervous system during the REM state, such as: increase in blood flow to the cortex (47); rise in brain temperature (52); elevation in frequency of spontaneous neuronal firing in the MRF (39), medial and descending vestibular nuclei (53), pyramidal tract (54, 55), and occipital cortex (56); development of monophasic wave aggregates in the pons, lateral geniculate body, and other subcortical areas; continuous theta activity in the hippocampus (even more regular than during arousal) (9, 51, 57-60); and evidence of facilitatory influences at the somatic afferent (61, 62) and visual afferent (lateral geniculate body) thalamic relays (63). During REM sleep, excitability as measured by the evoked-response technique in motor cortex is higher than, and in sensory cortex is at least as high as it is during NREM sleep (40). In both regions, excitability is greater than it is in the waking state (4, 62, 63). A shift in cortical and subcortical direct-current potentials toward the level in arousal and away from that during NREM sleep has also been demonstrated (64). In general, we find, surprisingly, that during REM sleep, thalamic and cortical neurons are more responsive than they are in the waking state. Many of the changes noted are most marked during actual REM bursts. Accordingly, there are both phasic and tonic components to REM-state activity.

Seemingly contrary to the direction of all these changes is a sharp attenuation of spinal reflexes and resting muscle tone in REM sleep, but these phenomena are probably due to an active inhibitory system (12, 65-66). Therein lies the unique quality of REM sleep, that it is a time of considerable excitation within the brain which is largely blocked at the periphery (9, 55, 66-68). Perhaps it is this inhibition of motor and reflex activity that allows perpetuation of behavioral sleep when many areas of the brain are discharging at frequencies approximating those during alert wakefulness (53-56).

The exhaustive studies of Jouvet and his colleagues have provided some understanding of the mechanism of REM sleep. These investigators have demon-

strated an indispensable region for REM sleep in the rostral pons (nucleus pontis caudalis) which appears to be crucial for the entire range of REM phenomena (9). A cat with this area ablated no longer exhibits REM phases or low-voltage fast EEG activity in sleep. It shows only two states, NREM sleep and wakefulness which may gradually progress to insomnia leading to death. Conversely, a decorticated cat shows no evidence of NREM sleep. The mesencephalic EEG never deviates from the low-voltage, fast tracing. However, REM's, myoclonic twitches, respiratory irregularity, and diminished muscle tone continue to appear regularly, in precise periods associated with discharges in subcortical structures identical to the discharges in intact animals during REM sleep. In between the episodes of REM sleep, the decorticate animal appears for the most part awake. Accordingly, Jouvet suggests that the pontine mechanism is both necessary and sufficient for REM sleep, whereas NREM sleep requires the presence of cortical tissue. His studies in decorticate and decerebrate humans indicate that in man there is an analogous dependence of REM sleep upon brainstem and of NREM sleep upon cortex (12, 69). Rossi *et al.* (70) have disagreed with Jouvet as to specific nuclei but have validated his basic finding of an essential area for REM sleep in the pons. There is still some doubt concerning the specific connecting pathways from the pontine center to the midbrain (51, 59, 71). More extensive studies are necessary before we can be certain that, in cats, the exact site of initiation of the REM state discharges is the mid to rostral pontine reticular nuclei or that the mechanism is applicable in every detail to higher forms (41).

REM Sleep and Dreaming

It is now widely acknowledged that dreaming sleep and REM sleep are identical, though ideational material and poorly defined imagery can apparently persist through the entire range of sleep stages (11, 13, 72). Numerous associations between dream hallucinations and alterations in physiological systems have been observed in the REM state. Although such correspondences are by no means always demonstrable or precise, they may reach a high order of specificity in the visual system. For example, REM's in abundance are ob-

served at times of frequent alterations of gaze in the dream, whereas the presence of few REM's, or a total absence of REM's (during dreaming sleep), is correlated either with staring at immobile objects or with breaks in the pictorial imagery (10). Roffwarg *et al.* (73) have shown that the number and direction of REM's may be predicted with reasonable accuracy by treating the dream scene as a visual event that the dreamer has scanned as he would the same event when awake. The fact that sequences of REM's associated with visual dream events can be correctly predicted through reference to the REM's expected in replicated waking experience renders the old notion of the instantaneous dream extremely unlikely. Dement and Wolpert (10) fixed particular points in the flow of time in dreams by provoking incorporations of identifiable stimuli into the dream sequence and demonstrated a close correspondence between actual time and the sense of time in dreams. Dream events evidently have a dimension in real time, though intermediary steps in an action may be skipped ("telescoping") (73).

Additional psychophysiological relationships have been suggested by Wolpert's finding (74) of a correlation between dreamed limb excursions and action potentials in wrist muscles. Moreover, when sleep talking takes place in REM sleep (it usually does not), it may relate to the situation in the dream (75). Hobson *et al.* (76) have shown that major respiratory irregularities (such as periods of apnea) are frequently linked to concurrent dream experiences such as talking, laughing, or choking. And penile erections, though typically present in the REM state, show size fluctuations in association with specific dream content (such as sexual activity, anxiety, attack) (34). A single experience in Snyder's laboratory dramatically highlights these correlations. In the middle of a REM period a subject's respirations and heartbeat began to race. When awakened a few minutes later, he recalled that he was dreaming of participating in sexual intercourse. He had experienced a nocturnal emission just prior to the arousal (30).

Other physiological "windows into the dream" may become available as new parameters are studied. The recently reported elevations of gastric hydrochloric acid in peptic-ulcer patients and the increases of adrenal corticoids in

normal subjects during REM sleep (77) may turn out to vary in magnitude in relation to simultaneous dream content. It has already proved possible to derive crude inferences about dream content from variations in physiological activity during the REM period. Additional indirect support for existence of a biological relationship between mind and body events during the REM state is contributed by the finding of heightened vividness of imagery at moments of greatest physiological variation (30, 73, 76, 78). There can no longer be any doubt that a dream, far from being merely a diaphanous and elusive creature of mind, is the sensate expression of a fundamental and rhythmically repetitive, and enormously active neurophysiological state. Hence dreaming, heretofore knowable only via subjective report and intuitive conjecture, is now accessible to more objective investigation.

Hallucinatory Activity

There is general agreement that, with the exception of certain delirious states, dream hallucinations are more encompassing than other hallucinatory events, most of which are merely superimposed on a background of uninterrupted sensory input from the environment. In the dream the total perceptual field is hallucinated. Though predominantly visual, the imagery may include realistic components from most if not all sensory systems simultaneously (79). It is common experience that every nuance of emotion as well as of perception—the full world of our experience—may be reduplicated in dreams. A substantial portion of the brain must be active during this state.

Dement (80) has suggested that dream hallucinations may constitute the only "true" hallucinations because the sensory material in dreams does not depend upon external input at the time of dreaming (although concurrent stimulations may be incorporated into a dream in progress) (10, 81). During REM sleep, the brain appears to be "in business for itself." Blinded individuals continue to experience visual imagery in dreams (19). And input to the central nervous system from the body environment, as for example from a parched throat (10) or an empty stomach (82), does not seem to elicit overtly drive-reducing dream content, at least not in short-term laboratory

experiments. These findings are easily reconciled with data from animal studies. During the REM state the optic tract of intact cats does not exhibit the sharp elevations in discharge frequency that are seen in the lateral geniculate body and occipital cortex (83), and firing in the geniculate body does not diminish as a result of acute enucleation of the eyeball (84). These findings suggest that visual "information" supplying the dream appears to originate within the brainstem and "feeds" into the visual afferent pathway at some intermediary point along its route (8). The fact that the spike discharges in the lateral geniculate body are synchronous with those in both the pontine reticular formation (57, 58) and visual cortex (8, 84) further supports this view.

Just as the dreamer, as an observer of the dream, is confronted by (hallucinated) sensory "percepts," he is also involved as a participant in the dream action in responding to them with (hallucinated) motor activity. The dreamer may experience the appearance and proprioceptive sense of his arm moving to brush away a bee that he hears in flight and sees alighting on his nose. Hence hallucinatory experiences occur not only of sensory objects but also of sensory components of motor performance "evoked" by the hallucinated object. As mentioned above, in REM sleep, upper motor-neuron activity is markedly increased, spikes in the extraocular muscles are coordinated with discharges in the visual afferent system, and phasic bursts of muscle potentials may accompany hallucinated movements (74). We may conjecture, therefore, that impulses are introduced from within the central nervous system into motor as well as sensory pathways, and that the recordable motor discharges may be correlated with hallucinated "percepts" of, or "intentions toward," movement.

Not only, then, is the brain highly activated during REM sleep from a physiological point of view, but as we have just speculated, it seems to be "perceiving" and "reacting" to its percepts much as an awake brain does. If the dreaming brain is in any sense "awake," however, it seems attuned primarily to the compelling phenomena originating and being perceived within itself. On the other hand, under conditions such as direct suggestion (hypnotic or otherwise) or threat of negative reinforcement, subjects in REM sleep

can increase their reactivity to exogenous stimuli to levels greater than during any other stage of sleep (85, 86). Inattention, therefore, may to some extent explain the high arousal thresholds in REM sleep (38, 39, 41). When external events compete with internal events for significance, however, attention may be diverted from the latter (86, 87).

Approaches to Function

Speculations concerning the role of the REM state have risen mainly from two previous lines of study: phylogenetic and deprivational. Because of the location of the pontine REM sleep mechanism, Jouvet first considered REM sleep to be a phylogenetically archaic state. The findings that in the newborn cat the behavioral and EEG characteristics of the REM state mature earlier than those of NREM sleep or waking, and that sustained periods of REM sleep appear directly after arousal without intermediary NREM sleep, initially seemed to confirm the more "primitive" quality of the REM state (44).

Correspondingly, Jouvet believed NREM sleep to be a state which depends on a functioning neocortex, acquired in the course of phylogenetic telencephalization. He therefore referred to it as "neo-sleep" (12). A corollary of this schema is that species having less neocortical tissue would be expected to manifest greater proportions of REM sleep. However, studies on the rat (42, 51), opossum (42), sheep (45, 48), goat (46), cat (12) and monkey (41, 42) have not shown a consistent trend in that direction. The most primitive vertebrates polygraphically demonstrated to have REM sleep are birds, in which the periods are exceedingly brief (0.3 percent) (50). Among the reptiles, the tortoise has been studied but the REM state has not been demonstrated (88). Therefore, only in the ontogenetic sense can REM sleep be considered a "primitive" state (49). More data are needed concerning the phylogeny of REM sleep, but if it is borne out that REM sleep developed later in evolution than NREM sleep, phylogenetic studies may still clarify two important questions: (i) What functional requirement was met by the development of REM sleep? (ii) Why did the rhombencephalon become the site of the REM sleep mechanism?

The attempt to study the function

of REM sleep by experimentally eliminating it was first made by Dement (27). By awakening subjects at the commencement of each REM period he effectively reduced the amount of REM sleep. After a series of consecutive "deprivation" nights the subjects were allowed uninterrupted sleep, and almost all exhibited a dramatic rise in amount and percentage of the REM phase. This was regarded as evidence of a physiological "need" for REM sleep. Additional experiments in humans and animals have confirmed the tendency to compensate for lost REM sleep after artificial interruptions of sleep (8, 28, 89-91).

Suppression of REM sleep by experimental destruction of the nucleus pontis caudalis causes hyperirritability and hallucinating-like behavior in animals (12). These changes are reversible if only small amounts of REM sleep reappear, whereas cats who do not recover any capacity for REM sleep may progress to a state of insomnia and agitation and eventually die. These animals have brainstem lesions, and thus to implicate loss of REM sleep exclusively for these difficulties may not be warranted. In contrast, studies of *functional* deprivation of REM sleep in cats currently being pursued by D. Jouvet *et al.* (89) and Dement (92) reveal surprisingly few overt behavioral changes in the animals even after lengthy periods of complete deprivation, though persistent tachycardia (89) and a faster auditory-recovery cycle (93) have been demonstrated during the deprivation. Hypersexuality is also a feature of the deprived cats, but when awake the animals may appear remarkably unaffected by the deprivation (94). Behavioral changes in humans have been observed only after the 15th day of continuous deprivation of REM sleep in recent studies (9, 28). Therefore, it appears that the function of REM sleep in the intact adult organism is not so immediate that the consequences of REM sleep deprivation are soon apparent or necessarily fatal.

Evolution of Sleep Patterns

Because of the inconclusiveness of phylogenetic and deprivational approaches to the function of REM sleep, we (16, 95) and others (96-100) have begun to examine its role in human ontogenetic development. These observations, as well as those in newborn

and immature animals (44-46, 48-50), reveal that REM sleep assumes a high proportion of total sleep in the first days of life and that its amount and ratio diminish as maturation proceeds (Fig. 1). Earlier work in our laboratory with infants and children pointed to certain relationships among maturation, daily behavior, and evolving sleep patterns (16).

In infancy, when the proportion of time awake is smaller than in any other period of life, there is a large amount of REM activity. REM periods appear soon after sleep begins and are of random duration at any time of the night. Later, when the developing infant spends protracted intervals awake in increasingly active involvement with the environment (particularly when locomotive capacity is attained), the total amount as well as the percentage of REM sleep diminishes.

This evolution in the relative proportions of the sleep stages continues through the period when napping terminates. Long stretches of deep NREM sleep occupy the first hours. Correspondingly, the first REM period in children past the napping age appears much later and is shorter than in children who nap. REM periods become longer toward morning. We have considered it probable that the child's progressively closer approximation of a diurnal pattern of uninterrupted daytime wakefulness causes corresponding changes in the sleep-stage pattern. Post-nappers (4½ to 7 years) average 110 to 120 minutes of deep NREM sleep (stage 4) in comparison to 75 to 80 minutes in the pubescent group. It is of course not yet clear whether these changes are a consequence of lengthening periods of sustained arousal, increased muscular activity, maturation of the central nervous system, or a combination of these factors.

The first REM period of the night usually appears 50 to 70 minutes after sleep commences, whereas in the 4½- to 7-year-old group, latency of REM onset is 3 to 4 hours. Latency continues to shorten as children mature but it does not assume the adult interval consistently until midadolescence. This phenomenon of a delayed or "missed" first REM period may reappear in adults under conditions of sleep loss (101). Moreover, nocturnal sleepers who nap in the afternoon have a shorter REM latency in their naps than those who nap in the evening (102). These findings suggest that a condition ("fatigue,"

for lack of a more exact term) develops under circumstances of prolonged arousal (and possibly intensive activity) which tips the normal balance between REM and NREM sleep mechanisms, augmenting temporarily the "need" for deep NREM sleep and antagonizing REM sleep processes. We speculate that the immature central nervous system is more vulnerable to "fatigue," though youngsters are unquestionably more active than adults.

Studies of Neonates

Electroencephalograms and electrooculograms from 14 normal full-term newborns were recorded by the usual technique for registration of protracted sleep (5, 73). All but one of the infants, aged 9 days, were under 5 days old and three were only 5, 9, and 29 hours old, respectively, when monitored. Newborns in the Columbia-Presbyterian Nurseries are fed every 4

hours. Their environment lacks major variation, and one period between feedings is essentially like all the others. All the infants had received a high Apgar (103) rating at birth. No attempt was made to select according to the type of obstetrical anesthesia employed. Each infant was recorded once.

Electrode placement required 30 to 45 minutes. In 9 of the 14 cases the electrodes were applied immediately after a feeding, and the infant was then allowed uninterrupted sleep until the next feeding. In these instances the recording period followed an interval of some manipulation which, though generally undisturbing to the infants, caused a postponement of the usually rapid commencement of sleep after feeding. In the remaining infants the electrodes were attached 2 to 3 hours before a feeding. These babies were then allowed to return to sleep. After the next regularly scheduled feeding, there was no need for additional experimental manipulations. This procedure made it

possible to achieve a truer picture not only of post-feeding sleep onset but of the full feeding-to-feeding sleep pattern. Resting muscle activity was recorded with submentally placed electrodes (31) and respiratory rate by means of a 0.5-millimeter thermocouple placed just inside a naris known to be unobstructed. A precordial electrode was used for heart rate. Heart and respiratory rates were tallied during either the first or second half of each minute of recording, whichever contained less muscle artifact. Half-minutes during which gross body movement occurred were not counted. Counting was stopped during small body movements and not resumed for 10 seconds afterwards.

Our observations of the sleep EEG cycles of full-term newborns are consistent in all major respects with the findings of Delange *et al.* (96), Paramelee *et al.* (97), Monod *et al.* (99), and Weitzman *et al.* (100). The sleep tracings, whether recorded day or

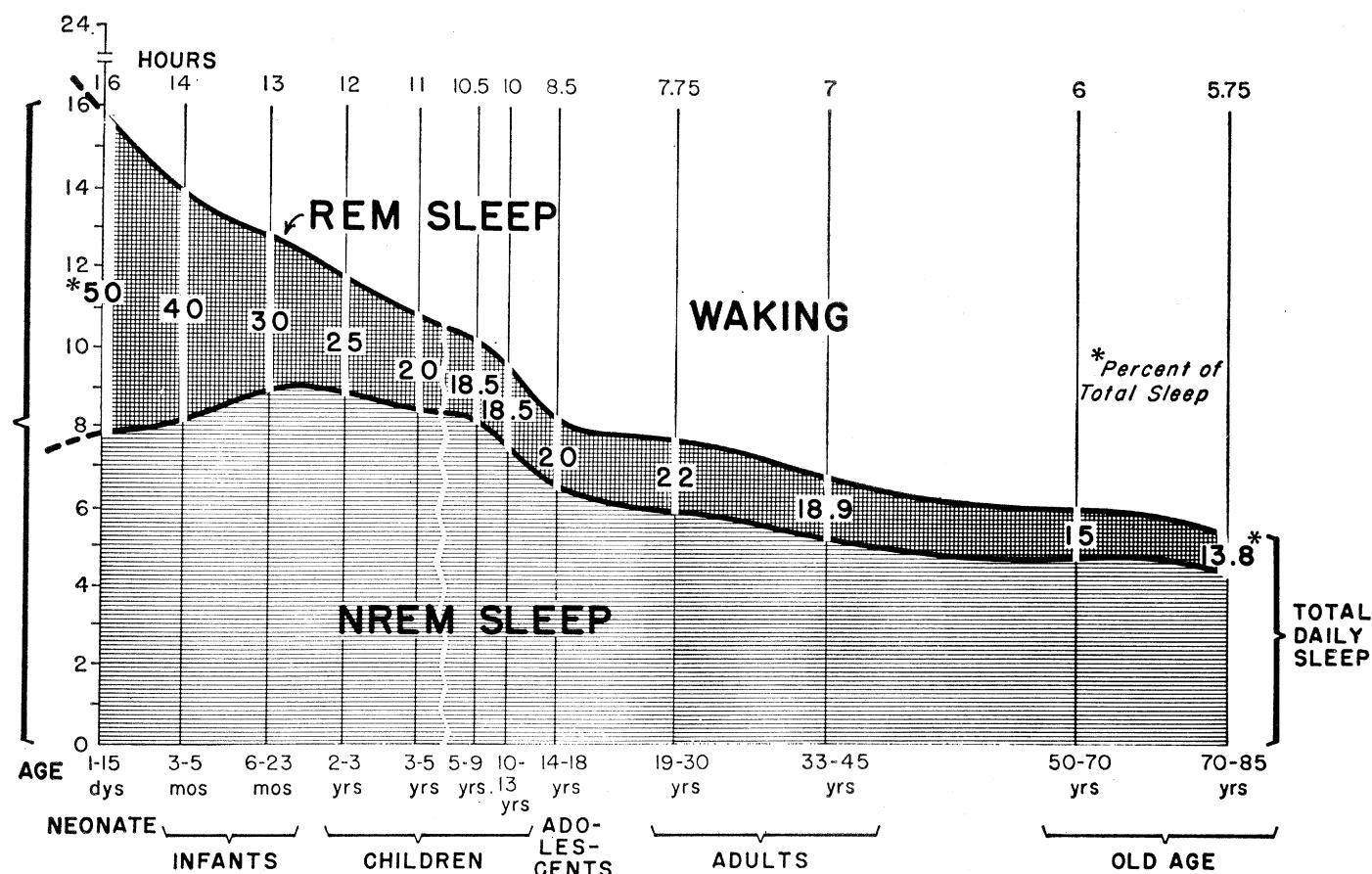


Fig. 1. Graph showing changes (with age) in total amounts of daily sleep, daily REM sleep, and in percentage of REM sleep. Note sharp diminution of REM sleep in the early years. REM sleep falls from 8 hours at birth to less than 1 hour in old age. The amount of NREM sleep throughout life remains more constant, falling from 8 hours to 5 hours. In contrast to the steep decline of REM sleep, the quantity of NREM sleep is undiminished for many years. Although total daily REM sleep falls steadily during life, the percentage rises slightly in adolescence and early adulthood. This rise does not reflect an increase in amount; it is due to the fact that REM sleep does not diminish as quickly as total sleep. Work in progress in several laboratories indicates that the percentage of REM sleep in the 50- to 85-year group may be somewhat higher than represented here. Data for the 33- to 45- and 70- to 85-year groups are taken from Strauch (139) and Lairy (140) respectively.

night, all consist of a succession of alternating REM and NREM periods, each having a distinct EEG pattern (Figs. 2 and 3, see parietal leads). The REM EEG is a low-voltage, relatively fast tracing sometimes appearing a little slower than the waking EEG. Some moderately slow, low-amplitude frequencies are found against the more rapid, low-amplitude background. Amplitude averages 15 to 25 microvolts and reaches a maximum of 40 microvolts. Brief sequences of 3-cycle-per-second "saw-tooth" waves appear over central areas, often just preceding or in conjunction with REM's.

The NREM EEG, by contrast, is characterized by frequent notched, high amplitude slow waves (2 to 3 cycles per second), seen best in frontal leads, against a low-voltage background. Moderately slow frequencies (3 to 8 cycles per second) are often interspersed between the 2- to 3-cycle activity. The NREM EEG has an amplitude averaging 40 to 75 microvolts. Bursts of 13- to 15-cycle-per-second waves were seen in most of the infants over postfrontal and parietal areas. Though lacking the typical "spindle" form and duration, they often follow high-voltage slow waves, having much the same relationship to them as spindles to K complexes in adult stage-2 recordings.

The major distinguishing features of the NREM EEG are the slow, high-amplitude elements and 13- to 15-cycle-per-second bursts. High-amplitude (delta) waves of 1 to 2 cycles per second are occasionally seen, but they are never a continuous or predominant waveform. The NREM EEG of the newborn resembles the adult NREM stage-2 sleep tracing. Frontal, parietal, and occipital areas are all in phase with respect to EEG shifts.

The low-voltage, fast EEG pattern is invariably accompanied by discontinuous ocular deflections. These REM's can be observed grossly through the baby's closed eyelids. Occasionally the eye is open wide enough to allow a direct view of the darting eyeballs. The duration of single REM's ranges from 0.05 to 0.2 seconds. They may appear singly or in clusters (Figs. 2 and 3) and are predominantly vertical. We have never observed a uniform NREM EEG pattern accompanied by REM's in a newborn.

When all sleep onsets are aligned at a point in time (Fig. 4), it is clear that periodic reemergence of REM sleep adheres to a rhythm for the group of newborns as a whole. The

sequence from wakefulness to sleep is the reverse of that in adults. An almost direct transition from the awake state to REM sleep marks sleep onset in newborns. Only after the initial REM period terminates does NREM sleep emerge for any appreciable duration. Conversely, in adults the eventual debut of the first REM period waits upon a 50-to-70-minute period of NREM sleep.

As in the records of older individuals, the EEG of the first REM period (and sometimes of the second) may show some intermingling of high-voltage, slow waves. However, the change in stage is clearly identifiable inasmuch as the EEG of the first-cycle NREM period is of considerably higher voltage and lower frequency than the rather mixed EEG accompanying the first-cycle REM period. After the early sleep cycles, subsequent cycles exhibit the more distinct EEG differentiation with respect to REM and NREM periods described above—that is, a low-voltage, relatively fast EEG in REM sleep, and a higher-voltage, slower EEG in NREM sleep. Figure 5 is a graph of the typical EEG shifts in a newborn.

There is a great deal of variability from infant to infant with respect to sleep-cycle duration and percentage of REM sleep. This is particularly true in the first cycle. The findings for the group as a whole are represented in Table 1. The mean REM percentage is 48.8 (104). As an illustration of variability, Fig. 6 shows the record of a newborn whose feeding-to-feeding REM percentage approached 65. Usually the first sleep cycle in newborns has a shorter mean duration than later cycles. Even if the lengths of sleep cycles are taken into account, the initial REM period is proportionately briefer than ensuing REM periods. Hence the percentage of REM sleep in the first cycle is approximately one-half that in subsequent individual cycles. Duration of REM sleep rises almost threefold in the second cycle and tends to diminish slightly in the third cycle. From the second cycle on, the EEG shifts phase every 20 to 35 minutes. Periods of NREM sleep remain within these limits fairly consistently, but REM periods exhibit greater deviation about the mean (two REM periods exceeding 50 minutes have been recorded).

In general, second and third cycles are split almost evenly between the REM and NREM phases, and REM percentage is fairly constant from the second cycle on.

Physiological Characteristics

Except for an occasional gross body twitch and the respiratory excursions of the chest cavity, NREM sleep may be considered essentially devoid of muscular activity. The infant lies passive and motionless, in marked contrast to the almost continuous muscle contractions during the REM state. Grimaces, whimpers, smiles, twitches of the face and extremities are interspersed with gross shifts of position of the limbs. There are frequent 10- to 15-second episodes of tonic, athetoid writhing of the torso, limbs, and digits. Bursts of REM's commonly accompany the generalized muscle contractions, but the former are also present in the absence of other body movements. We have also observed that in the REM state, newborns display facial mimicry which gives the appearance of sophisticated expressions of emotion or thought such as perplexity, disdain, skepticism, and mild amusement. We have not noted such nuances of expression in the same newborns when awake.

Though phasic muscular contractions are extremely numerous during the REM sleep of neonates, we have found a striking reduction in resting muscle activity (RMA) occurring in conjunction with each REM period emergence (Figs. 2 and 3). The amplitude of RMA is greatest in the awake state (40 to 60 microvolts), is slightly lower in NREM sleep (10 to 30 microvolts), and approaches isoelectric levels (0 to 10 microvolts) in REM sleep. Whenever muscle contractions occur, electromyographic potentials appear and disappear instantaneously as the contraction terminates. The activity may be only as brief as 1 to 2 seconds. Hence, there is a fascinating confluence of two skeletal muscle phenomena during REM sleep: suppression of muscle tone punctuated by frequent muscle contractions.

Muscle tone is always present during the body of the NREM periods. But between the well-defined stages of sleep there are transitional phases of approximately 1 to 5 minutes. Usually after an extended period of NREM sleep, RMA amplitude gradually ebbs, though the NREM EEG persists for a few minutes. At the same time there is a sharp increase in frequency of gross body, facial, and sucking movements. Finally, after one of the body movements, the RMA will remain below its premovement base line and, at virtually the same moment, breathing becomes

uneven. The EEG then flattens to the characteristic REM pattern and REM's appear. This sequence—increase in body movement, gradual reduction and the complete suppression of RMA, commencement of respiratory irregularity, appearance of a lower-voltage, faster EEG, and finally REM's—describes the transition stage which heralds (or constitutes) the onset of REM sleep. Figure 7 shows such a transition period. At the termination of a REM period, RMA may not immediately return to the prior NREM level. Even when slow waves have returned to the EEG and REM's have ceased, RMA may remain low for several minutes before a twitch, suck, or other muscular contraction seemingly triggers its instantaneous increase.

The diminution of RMA at sleep onset serves as a specific indicator in newborns that sleep has commenced in spite of an almost negligible change in the EEG from the waking state. If it were not for this substantial reduction, the moment of passage from waking to sleep would still defy exact designation. RMA may be inhibited abruptly or gradually diminish over the course of a few minutes as sleep supervenes, depending on whether the infant has passed directly into the REM phase or through a brief interval (1 to 3 minutes) of NREM sleep. In either case, the diminution definitely establishes onset of sleep. As long as the baby is awake, RMA remains relatively high.

Figures 2 and 3 demonstrate some

differences between the respiratory patterns in the two phases of sleep (105). In REM sleep, respiratory rate is 18 percent greater than in NREM sleep. More critical, however, is the very irregular breathing, which results in significantly greater minute-to-minute variation. Infants commonly display periods of apnea, usually but not exclusively associated with REM bursts, lasting up to 10 seconds (Fig. 3). Contrary to the even respirations during NREM sleep, wide fluctuations in chest expansion characterize REM sleep.

With the advent of REM sleep, respiratory rate increases. With the transition to the next NREM period the rate falls to a new low. Hence rate elevations accompanying REM periods embark from a progressively diminishing base, and there is thus a systematic decrease in rate (Figs. 5 and 6).

As with respiration, there is a cycle-to-cycle decrease in heart rate, though not nearly as sharply defined (Figs. 5 and 6). Mean heart rate is 3.4 percent higher during REM sleep. This difference, though statistically significant, is not so striking as the disparity in respiratory rates. Heart-rate variability is not clearly greater in REM sleep. Analysis of heart rate when the muscular activity of each stage is taken into consideration reveals that the former may not be a truly independent discriminator of REM and NREM stages. During REM sleep the frequent body movements, REM's, and irregular, rapid respirations may account for the apparent elevation in REM heart rate.

Just as a gradual diminution in muscle tone heralds a REM period, so do progressive increases in mouth movements (resembling sucking). This activity may be observed 5 to 10 minutes before a shift to REM sleep. It reaches a crescendo at the commencement of the REM period but continues to be evident throughout the period. At termination, there is again a brief augmentation of sucking which trails off quickly as the NREM phase is definitively established. Hence, sucking activity seems to be connected mainly with the onset of REM sleep.

We have often noted an exception to this general pattern in the sleep cycle just before a feeding. During this cycle, frequent mouth movements persist during the NREM period. This is interesting in light of studies on resumption of gastric ("hunger") contractions in infants after nursing. Gastric contractions resume 150 to 160 minutes after a feeding (106), almost exactly

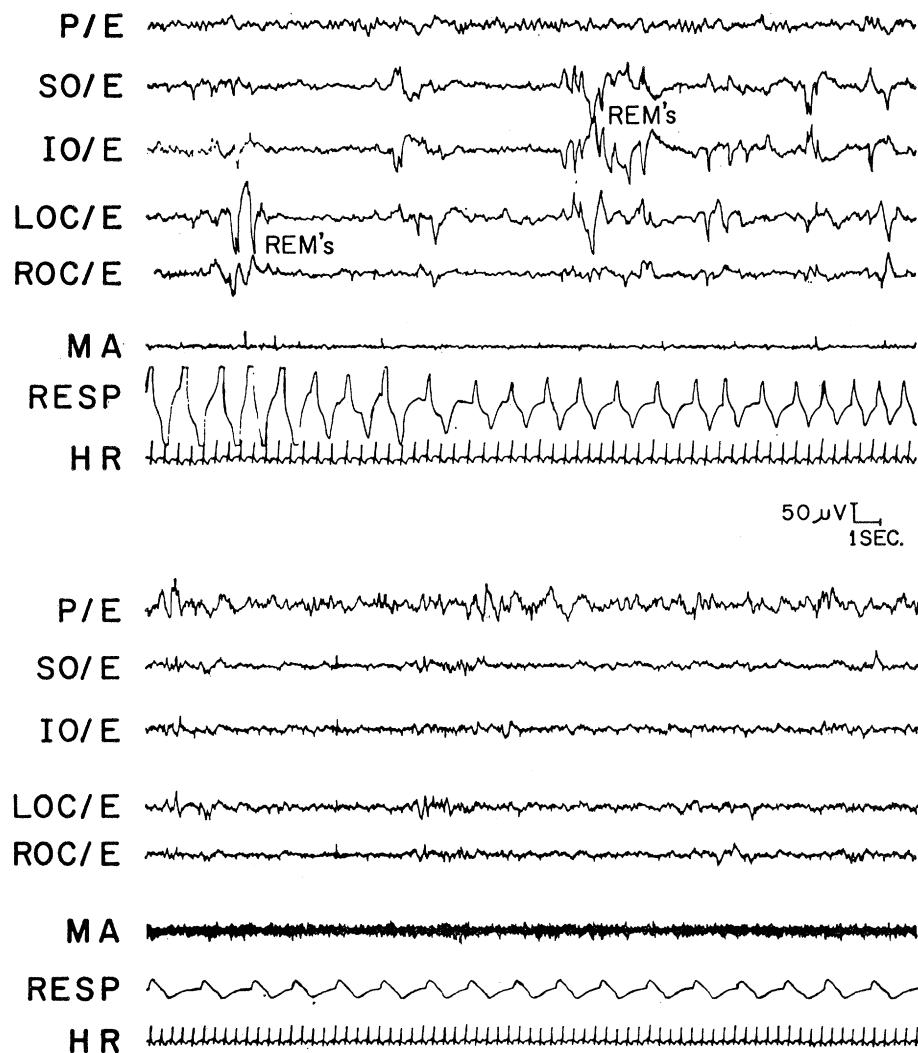


Fig. 2. Recordings of 30-second intervals from the two stages of sleep in a newborn. Top, REM sleep; bottom, NREM sleep. EEG lead: *P/E*, parietal referred to both ears. Eye-movement leads: (vertical) *SO/E*, supraorbital ridge to ears; *IO/E*, infraorbital ridge to ears; (horizontal) *LOC/E*, left outer canthus to ears; *ROC/E*, right outer canthus to ears; *MA*, resting muscle activity (recorded submentally); *RESP*, respirations; *HR*, pulse. The electroencephalogram is low-voltage and fast in REM sleep and higher-voltage, with frequent 1- to 2-cycle-per-second waves, in NREM sleep. There are short trains of saw-tooth waves in upper EEG tracing just preceding sharp vertical and horizontal REM's. Note the absence of muscle activity, the rapid respiratory rate, and the changing respiratory amplitude in REM stage.

the interval before the appearance of sustained NREM sucking. Sucking in sleep may be a manifestation of REM activation, but it continues into the NREM phase under conditions of physiological hunger. Aserinsky and Kleitman had previously reported that spontaneous awakenings in infants generally occur at commencement of REM phases (107). We have confirmed this finding and have further noted that the awakenings generally occur in the REM period that just follows the breakthrough of persistent NREM sucking. Past a certain threshold of activity, therefore, the REM period appears to give way to arousal.

Discussion

The EEG is one of the most widely used criteria for determining change in state of consciousness. However, there has been considerable disagreement with regard to the differentiation of the EEG patterns of wakefulness and sleep in the newborn. Some investigators (108, 109) reported finding determining criteria, but others (110) could not demonstrate fundamental alterations between sleep and waking patterns. With one exception (see 111), most observers had concurred that the neonate's sleep EEG cannot be divided into specific stages.

The reason for this confusion is now apparent in light of the discovery that one of the EEG stages of sleep in newborns closely resembles the waking EEG. The stage in question is the relatively low-voltage, high-frequency pattern of REM sleep described above. Previous disagreements with respect to EEG differentiation of the stages of sleep and of sleep from waking in the newborn were undoubtedly fostered by the fact that REM sleep directly succeeds waking at sleep onset (unlike the normal adult pattern in which NREM sleep always precedes REM sleep). Infants generally close their eyelids when passing into sleep, but this was probably of little assistance to previous investigators attempting to specify sleep onset, since REM sleep brings with it transient eyelid openings, frequent twitches, body and eye movements, irregular respiration, and vocalizations. Thus actual commencement of sleep, which can now be easily identified in neonates with the assistance of electromyography, was no doubt frequently mistaken for a continuation of the awake state (112).

"Dreaming" in the Newborn

There can be little question that the stage of sleep in newborns that manifests REM's and a low-voltage, relatively fast EEG is related to adult REM sleep. Therefore the REM state must originate from inborn neurophysiological processes, as opposed to being engendered by experience. Important as this finding is, the fact of most significance is that the neonate spends fully one-half of its total sleep, or one-third of its entire existence, in this unique state of activation. In view of this, new questions must be considered. For instance, does REM sleep fulfill a vital function in the newborn? Does the sharp reduction of REM sleep in the first few years of life indicate that its most important function is related to early development?

In order to explore the implications of these questions, we must first deal with certain ambiguities. Since it has been previously established that REM sleep constitutes the time of dreaming in children and adults, does the *de facto* presence of a REM stage at birth indicate that newborns dream? And, if the REM's of adults are related to dream imagery, to what, if anything, are the REM's of newborns related?

If by dreaming one means a succession of vivid, discrete yet integrated, hallucinated images, it is hardly likely that newborns, who have extremely crude patterned vision (113), "dream." Though a most convincing demonstration of the relation of REM sleep to dreaming in adults has been the correlation of the REM's with the spatio-temporal aspects of visual imagery (73), REM's are certainly not unfailing coun-

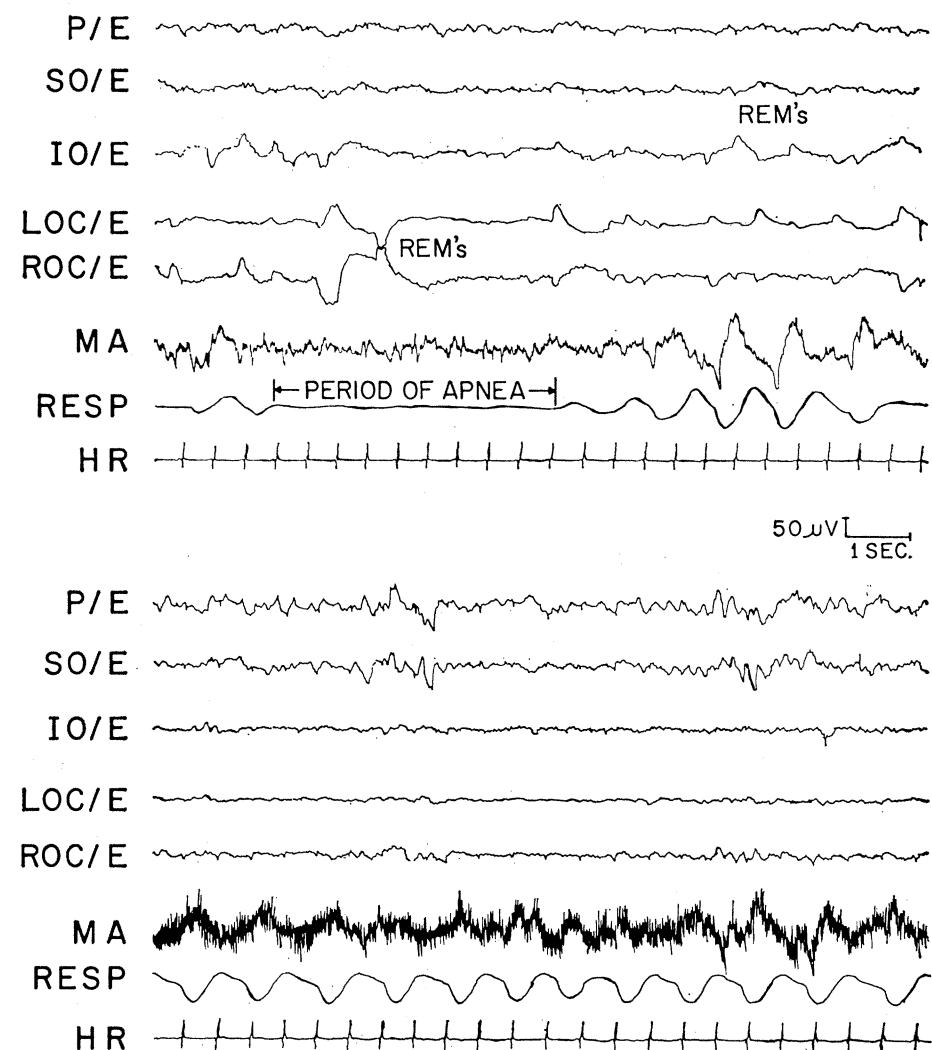


Fig. 3. Recordings of 12-second intervals from the two stages of sleep in a newborn. Top, REM sleep; bottom, NREM sleep. Symbols as in Fig. 2. The SO/E lead picks up the EEG in addition to vertical REM's because of its prefrontal placement. Note the absence of REM's. MA baseline is wavy because of respiration, but resting tone is clearly higher in REM sleep. Apneic periods, as in the above tracing, are common in the REM stages.

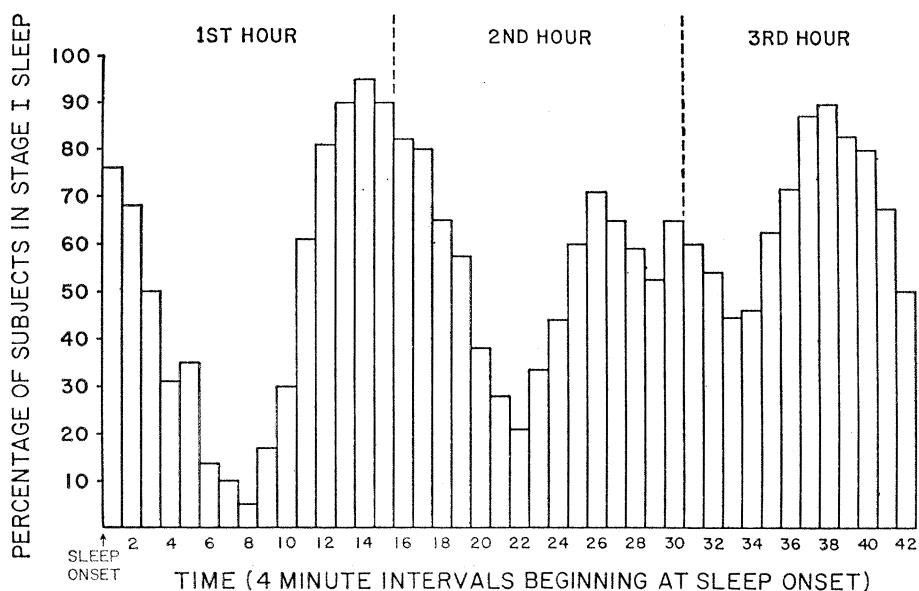


Fig. 4. Bar graph representing the ratio of subjects wholly in REM sleep (stage 1) during successive 4-minute intervals. All times of onset of sleep have been aligned. If subjects were in REM sleep during a portion of a 4-minute interval, percentage was prorated. Hence, in the first 4 minutes of sleep, because of fragmented or slightly delayed REM periods, the percentage of subjects in stage 1 is only 76. Note the rhythmical reemergence of REM periods across the entire group.

terparts of visual imagery under all circumstances. REM sleep is not necessarily associated with the presence of either visual imagery or a functioning cerebral cortex. For example, REM's in sleep have been reported in congenitally blind individuals (114), functionally decorticate humans (69), decorticate cats (115), and newborn kittens (44, 49). Rather than indicating that neonates experience patterned visual dreams or that REM's and imagery cannot be related in the dreams of older individuals, the fact that neonates and decorticates have REM activity indicates that absence of visual phenomena, due to immaturity of the ascending sensory pathways and visual cortex, need not preclude REM-state functioning of the oculomotor apparatus. The REM's, as well as all other phenomena of REM sleep, have been shown to result from activity in the pons. Hence, if the pontine-oculomotor pathways are not cut, the REM's persist (9, 70, 116).

Because the spike potentials in the lateral geniculate body, occipital cortex, and extraocular muscles have the same pontine source (57, 58, 84), it is not surprising that phasic activity in the geniculate body and occipital cortex is synchronous with REM bursts (56, 84). The sensory-motor discharges occurring during REM sleep in the visuo-oculomotor system may therefore be thought of, in their bare essentials, as arising

in the pontine sleep center and traveling simultaneously over separate motor and sensory pathways, eventually reaching the oculomotor nuclei (117) and visual receiving areas, respectively. As long as the common pontine source of stimulation is intact, the sensory routes may be interrupted (as after decortication) or be relatively inoperative (as is probably the case in infancy) without interrupting the functioning of the motor route. It would also be true that interruption of the motor pathways for eye movements should not, in itself, interfere with visual imagery in REM sleep. Accordingly, though the common center subserving a link between visual imagery and REM's is operative before birth, actual visuo-motor correlations must await maturation of the neurophysiological apparatus for vision and visual memory.

The question of whether memory traces are established in humans at such an early age and, if so, whether they are highly transient or permanent is not currently accessible to investigation. It is known that learning, of the conditioned response variety, may be demonstrated at birth and even before (118). Hence, it is not out of the question to speculate that even in fetal life the REM state may provide the neurophysiological setting for hallucinatory repetition of accumulated experience. Prior to the infant's acquisition of visual perception and visual memory,

rudimentary hallucinations might be expressed in sensory modalities in which intrauterine experience had occurred. Speculations aside, however, whether or not "dreaming" understood as subjective sensation exists in the newborn, "dreaming" understood as physiological process certainly does.

REM Sleep in Newborns

If we dismiss the "dream experience" as the vital attribute of REM sleep in the newborn period, we are in a position to consider the possible physiological significance of the great abundance of REM sleep in early life. Parmelee *et al.* (119) have confirmed our finding of approximately 50 percent REM sleep in the newborn at term (95). In premature infants, the percentage of REM sleep is 58 at 36 to 38 weeks, 67 at 33 to 35 weeks, and 80 (one infant) at 30 weeks gestational age. The direction of the data supports the contention that the proportion of REM sleep nears 100 percent before the 30th week (119), but as yet little is known about what processes are responsible for the profusion of REM sleep in the immature organism or, for that matter, for the regulation of the proportion of REM sleep at any age. Nevertheless, at least two possible systems of regulation may be considered: (i) the amount of REM sleep is a "passive" consequence of the relative presence or absence (possibly due to cortical immaturity) of restraining influences on the REM center; (ii) the amount of REM sleep is a product of an "active" system which responds to the specific requirements of the central nervous system for that state in fetal and neonatal periods of development just as it responds to the requirements in later maturational periods.

With regard to the first possibility, the cortex is known to send inhibitory impulses to many subcortical areas. Recently, Koella and Ferry (120) have demonstrated that the brainstem stimulates both cerebral hemispheres and that each hemisphere feeds back restraining forces upon the brainstem. Such inhibitory regulation may be operative with respect to brainstem centers for REM sleep. And, accordingly, the large proportions of REM sleep in the neonatal period may be "passively" determined by a lack of restriction on the pontine center because of insufficient cortical superimposition.

Data on evoked responses (109, 100, 121) indicate that the human cortex at birth has achieved at least some degree of functional maturity. Furthermore, given such a "passive" mechanism, it should follow that "passive" release of REM sleep processes would be a prominent finding after a mature organism had been subjected to decortication or interference with the NREM sleep mechanism. The fact is, however, that the totally decorticated cat manifests less REM sleep (15 to 20 percent) than the intact animal (25 percent), and the partially decorticated cat shows no change from the normal percentage (9). Where recordings have been possible in decorticate humans (12, 69, 115) the proportion of REM sleep is said to be in the range of 20 percent of the total registration period (69), but because no 24-hour recordings have been published we do not know whether this figure allows for diurnal variation. Still, the overall results are certainly not what would be expected if REM ratios were established solely as a result of the degree of cortical inhibition of the REM mechanism. It has also been demonstrated that when NREM sleep is cut owing to lesions in the basal forebrain area, the time formerly occupied by NREM sleep is henceforth taken up by alert patterns. The percentage of REM sleep does not increase (122). Hence, there is obvious inadequacy in an ontogenetic explanation of high percentages of REM sleep, based entirely on an early paucity of cortical inhibition. It is nevertheless likely that as the brain matures, the REM center may have to "compete for time" in reciprocal interplay with other centers and that it may be subject to some type of regulatory feedback. We have by no means fully ruled out the possibility that the REM center, like other excitatory mechanisms, may achieve functional capacity before auxiliary inhibitory mechanisms and, hence, that the high percentages of REM sleep in early life merely reflect a failure of the pontine system to be turned off or to turn itself off. Our emphasis, however, is not on why the REM mechanism operates so prolifically in the fetus and newborn, but on the functional effects of that prolificacy in terms of the central nervous system.

To turn to the second possibility, there are strong reasons for considering that the pontine mechanism is at least partially autonomous. To put it another way, the output of the REM mechanism may not be subject sole-

ly to greater or lesser degrees of cortical dominance, but may be dynamically reactive to the organism's need for the REM state. As an example, the paroxysmal attacks of sleep in narcolepsy have been identified as REM sleep (123) and may be interpreted as episodes of pathological overactivity or premature triggering of the pontine sleep mechanism. Furthermore, newborns and REM-deprived adults as well as narcoleptics show a forward displacement of the first REM period to the moment of sleep onset (123, 8). Substantial evidence is accumulating that the REM

mechanism can compensate for specific losses of REM sleep by means of subsequent increases in REM time (27, 28, 8, 89-91). Recent studies of cats placed on varying sleep-loss or sleep-excess schedules demonstrate that their REM percentages increase or decrease to effect adjustments toward baseline values (90). Moreover, quantitative alterations may be only part of the readjustment, in that REM phenomena have been shown to be qualitatively more "intense" under circumstances of restricted REM time (94). It is also pertinent to the notion of an "active"

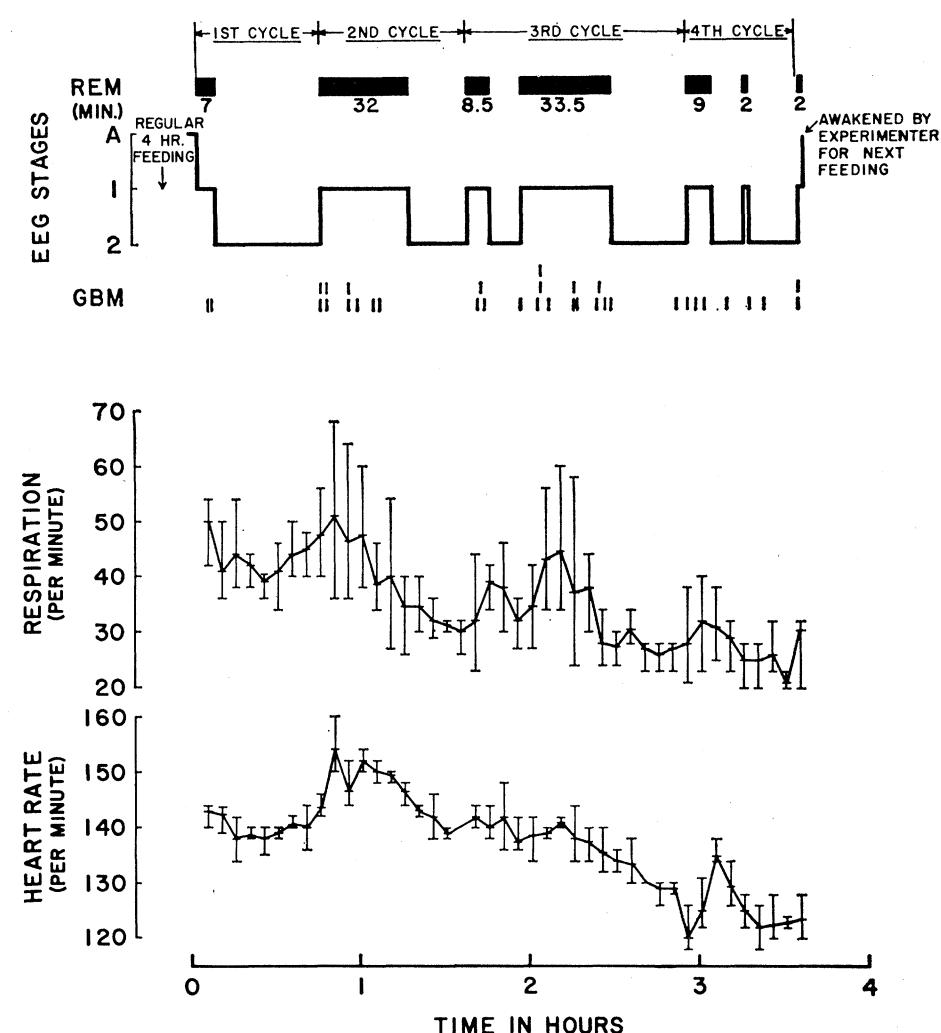


Fig. 5. Graph showing REM periods, EEG shifts, gross body movement (GBM), and respiratory and heart rates during a 3-hour 35-minute period of sleep between feedings in a 4-day-old infant. Each cycle begins with a REM period (stage 1) and ends with a NREM period (stage 2) longer than 15 minutes. Sleep onset is directly from waking to REM sleep (stage 1). Gross body movements occur predominantly at the beginning of and during REM periods. Vertical lines represent successive 5-minute spans of respiration and heart-rate recording. Top of each line indicates the fastest per-minute rate, and bottom of each line, the slowest per-minute rate, in each 5-minute portion. The connecting lines join points designating mean per-minute rates for each 5-minute span. Note, particularly with respiration, the usual increase in rate and widening of range of per-minute rates, commencing with and sustained throughout each REM period. There is an overall slowing of respiratory and cardiac rates as the sleep period progresses. Note that the latter two REM periods are fragmented by NREM intervals of less than 15 minutes. This occurs in one-fifth of all REM periods recorded in this series. Total time of REM sleep is 1 hour 32 minutes (43.2 percent).

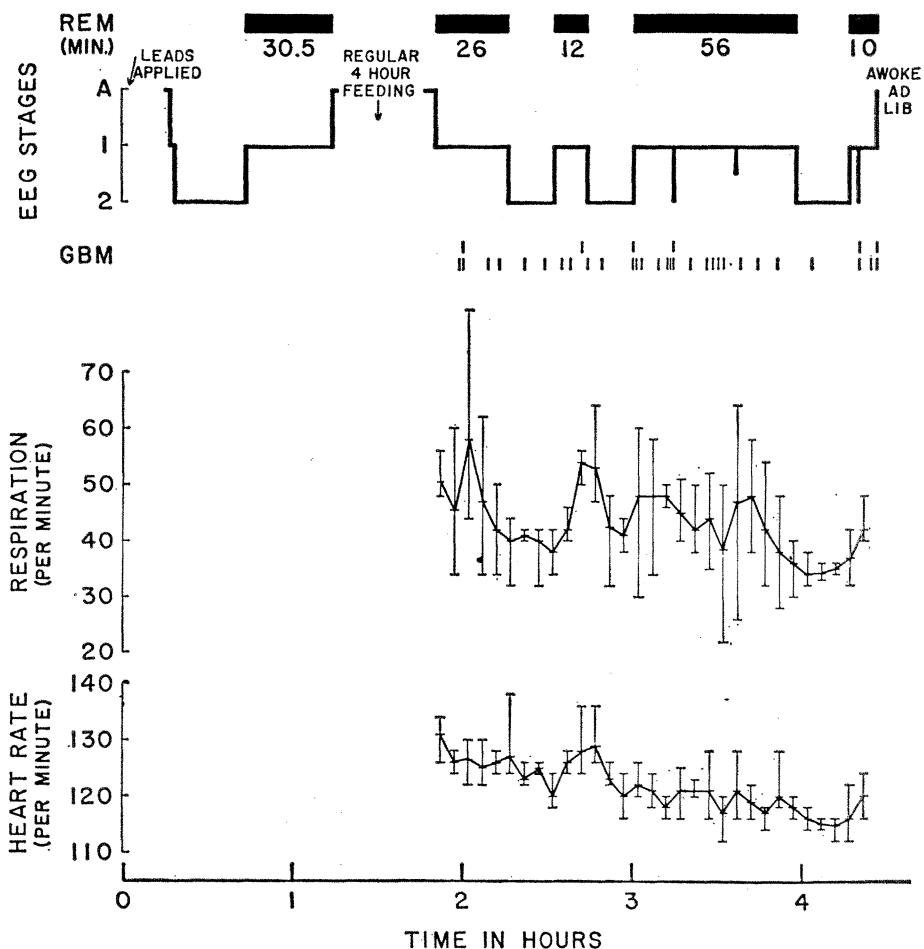


Fig. 6. Graph of another sleep record in a 2-day-old infant, showing REM periods, EEG shifts, gross body movements (GBM), respiration rate, and heart rate. Stage 1 = REM sleep; stage 2 = NREM sleep. As in Fig. 5, vertical lines represent 5-minute spans of respiratory and heart rate recording, and connecting lines join the mean rates per minute for each 5-minute interval. Leads were attached during previous sleep period and infant returned to sleep until feeding. The first REM period is unusually long (26 minutes) after feeding in this infant. Note the higher and more variable respiratory rates during REM periods. This point is less clear for heart rate but both rates show slight decrease during sleep period. Note 56-minute REM period. REM sleep is 64.4 percent of total (2 hours 36 minutes) sleep.

mechanism that a number of drugs such as lysergic acid diethylamide (LSD) (26) and butyrolactone (124) apparently exert a specific stimulating effect on the REM mechanism.

Of course, if the REM state is an expression of a process, autonomous in the sense that it is not completely under cortical control, to what is it responding? Jouvet (9) and Dement (8) have both proposed that the REM mechanism is triggered by a neurohumoral substance which accumulates to a critical threshold level and is then released. This hypothesis would account for the heightened REM percentages following deprivation of REM sleep, on the basis of overaccumulation or "back-up" of the specific agent. Correspondingly, the effects of pharmacologic substances on REM sleep could be treated as instances of blockage, neutralization,

early release, or enhancement of the action of the endogenous agent.

Evidence for a neurohumoral process is scant. Nevertheless, such a mechanism is suggested by the finding that short stimulations of the nucleus pontis caudalis can induce long periods of REM sleep followed by intervals of temporary refractoriness to further triggering (9). The study of Dement *et al.* (125), demonstrating that the compensatory increase in REM time following REM deprivation may be delayed but not vitiated, also lends support to a hypothesis that allows for accumulation and storage of some substance. Preliminary data reveal that a specific agent may be found in the cerebrospinal fluid of cats subjected to long REM-deprivation schedules (126). There is as yet little information about the chemical properties of the proposed agent,

whether it accumulates intracellularly or extracellularly, and what type of transport is involved. Of course, any hypothesis which purports to account for the regulation of REM sleep will eventually have to explain the great quantities of REM sleep during early development.

Function of REM Sleep in Early Development

Between the newborn period and young adulthood, mean REM sleep diminishes approximately 80 percent (8 hours to 1 hour 40 minutes), whereas mean NREM sleep diminishes only 25 percent (8 to 6 hours); that is, of the total reduction in all sleep in that period, 75 percent is in the REM portion (Fig. 1). Accordingly, in answer to the possible contention that there may be more REM sleep in infancy merely because infants sleep longer, it might well be argued that the sleep requirement in infancy is a function of the requirement for the REM stage. As stated earlier, we believe that the diminution of REM sleep in ontogenesis does not reflect merely a maturation of inhibiting centers. Rather, the drop-off may signify a reduced requirement for REM sleep after one of its most important early functions has been fulfilled.

Irrespective of the processes regulating proportions of REM sleep, the functional consequences of the protracted REM upheavals in the immature organism must be considered. Accordingly, we have suggested (16) that in early infancy, when waking life is limited in time and scope and offers little occasion for stimulation, the REM periods may allow a substantial (and necessary) discharge of activity. Now we would like to develop this formulation further.

Has it not formerly been our tendency to think of the fetus as receiving only those stimuli which are available to it from the protected uterine environment, and of the newborn as exposed to sensory excitation only by virtue of the provocations provided by waking life? Have we not traditionally considered the sleep of babies as well as of adults to constitute a surcease from excitation, a time of rest, a reversal of fatigue, and an opportunity for metabolic restitution? In this conventional view the infant either sleeps and is separated from external stimulation, or he is awake and receptive to it.

But we now are aware that during REM sleep brain activity is vigorous.

Spontaneous electric discharge is at peak rates in many and diverse areas of the central nervous system (39, 53–58). Reports that intense hallucinations are experienced in various sensory modalities indicate excitation over widely separate cortical regions. It is not likely that these hallucinatory phenomena simply result from spontaneous and unprovoked discharges in an excitable cortex during the REM phase, for recent data do not indicate a great increase in the excitability of sensory cortex during REM sleep over that during NREM sleep (61–63). Hence consideration of more specific pathways of cortical activation seems justified.

Indeed, the hallucinatory activity and heightened discharge frequencies may be comparable to the active perceptual and processing activities taking place in the awake brain in response to large volleys of incoming impulses. Already there is evidence that the normal neuroanatomical routes to the cortex are traveled by REM-state impulses in the visual sensory system after they arrive at the lateral geniculate body from the

pons (57, 58, 83, 84, 8), and that they do not descend from suprapontine structures but travel only in an ascending direction (58, 84). There is other evidence which suggests that the thalamus is the site of introduction of brainstem influences on their way to higher sensory centers during REM sleep (61, 62). We believe, consequently, that the active discharges in diverse brain sites during REM sleep originate in the phasic and tonic impulses which emanate from the pontine REM center; some ascend to the thalamus and course along the primary thalamocortical projection pathways traversed by environmentally induced impulses until they reach the cortical sensory receiving areas. Dement has suggested elsewhere that once this "internal sensory input" is "substituted" in the "stimulus-response chain," higher centers interpret and react to it as if it were a set of true percepts impinging on the central nervous system from without (80, 8). The pontine REM center also appears to have important links to excitatory and inhibitory efferent centers for eye movement, motor activity,

muscle tone, spinal reflexes, respiration, heart rate, and probably others (9). It apparently sends excitations into sensory channels directly, and into motor channels directly as well as indirectly (in that some motor responses may result from typical reactions in higher centers to the receipt of "sensory" material).

On the basis of this schema we hypothesize that REM sleep affords intense stimulation to the central nervous system, stimulation turned on periodically from within it by a mechanism capable of stimulating the rest of the central nervous system. This is probably the pontine REM mechanism which functions largely independently of factors external to the central nervous system. The intervals of intense activity during sleep would be available in great quantity to the developing organism *in utero* and later in its early extrauterine life when stimuli are limited. Measures of the systematized qualities of this activity are the sustained, realistic, and sequential attributes of dream images (10, 73) and the seemingly purposeful associated activity in motor (94) and

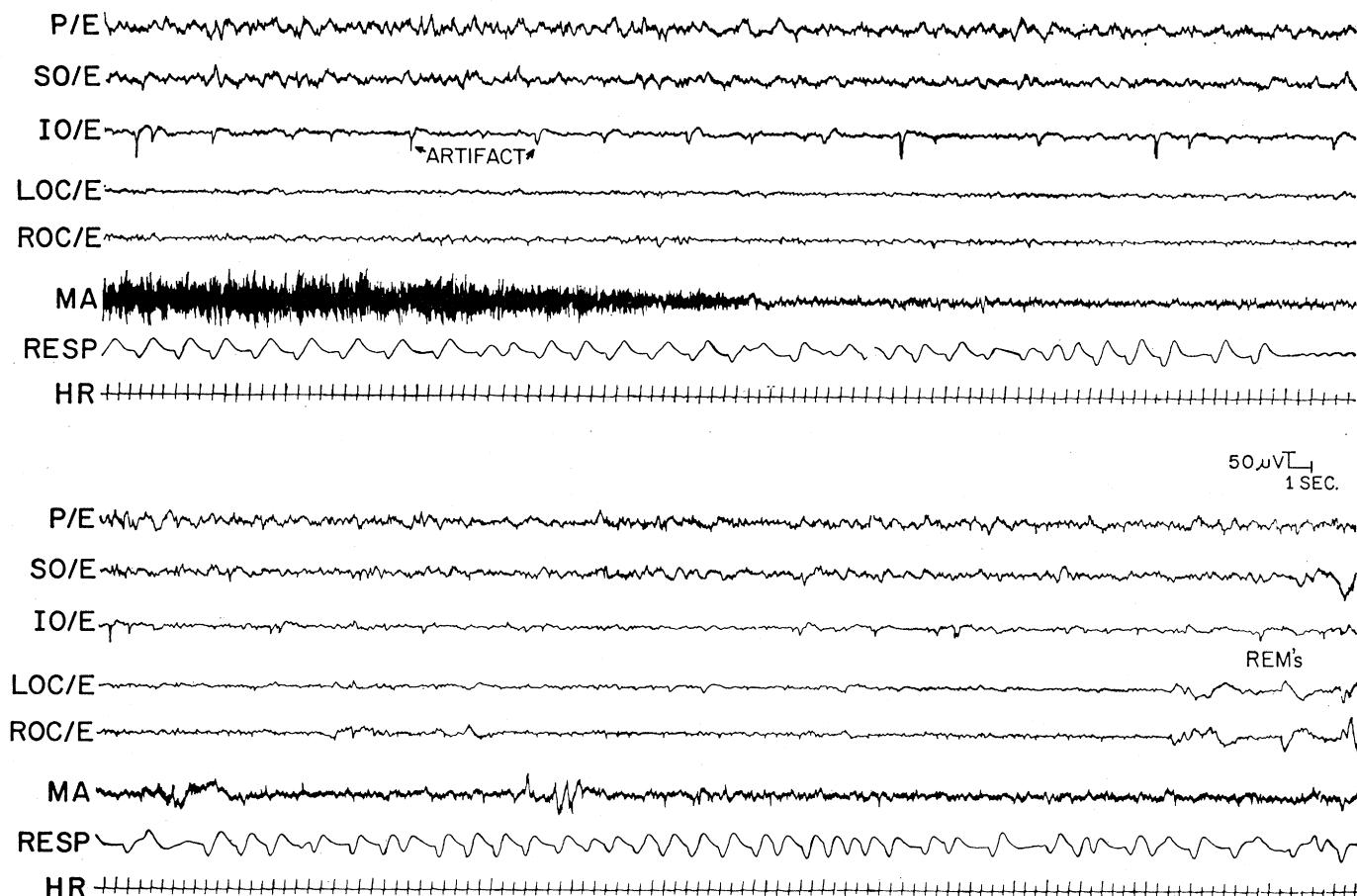


Fig. 7. Continuous 2-minute recording from a newborn infant. Top, first minute; bottom, second minute. Symbols as in Fig. 2. Note transition from NREM to REM pattern. As resting muscle activity attenuates (upper trace), respiratory rate and amplitude become irregular. EEG flattens to REM pattern just before first REM's appear (lower trace). EEG channel contains some EKG artifact. MA in lower trace shows some irregularity and increased amplitude during sucking.

Table 1. Mean duration of sleep cycles and REM periods and mean percentages of REM sleep, in 14 human neonates. Standard deviations appear in parentheses.

Sleep cycle	Duration of cycle (minutes)	Length of REM period (minutes)	Percentage REM
1st	43.4 (11.4)	12.6 (10.7)	29.1* (15.2)
2nd	61.2 (17.8)	33.9 (15.2)	55.0* (12.6)
3rd	54.1 (13.3)	29.8 (8.4)	57.0* (6.6)
<i>All cycles</i>			48.8† (10.3)

* Weighted means. † Four infants fell asleep before all leads were in place. Data for their first sleep cycle are hence incomplete and have been omitted. Because percentage of REM is appreciably less in the first cycle than in subsequent cycles, omission of these infants' first-cycles slightly raises the ratio of REM to total sleep for the whole group. If all data for these infants are dropped, REM sleep is 46.4 percent (S.D. 6.9) of total sleep.

autonomic systems (77) which it can provide.

The REM's of neonates, which likely have no counterpart in patterned vision, are extraordinarily similar to those of sleeping adults (though they are somewhat more clustered and vertical). In view of this fact, we wonder whether the eventual development of dream imagery may involve a process by which the cortex "fits" sensory images to discharge patterns of brainstem origin established before the accumulation of sensory experience. The cortex may develop some modulating influence over these pontine discharges, but the basic discharge rhythm probably has a brainstem genesis. In this sense, the dream would truly appear to be born in the brainstem but clothed in the cortex.

Structural Growth, and REM Sleep

Although nerve tissue is able to differentiate somewhat in the absence of any external input (127), many studies *in vivo* have demonstrated that structural maturation and maintenance are seriously impaired by lack of stimulation (128, 129). Moreover, there is considerable evidence that functional stimulation potentiates structural growth in the nervous system; that, for instance, activity may precede myelinization (128, 130-132). This is extremely significant, we believe, in that functional stimulation commences in fetal life and may result not only from actual sensory stimulation but perhaps also from the REM sleep process, which begins to operate at some point in fetal development. The ascending impulses originating in the pons during the REM state may be useful in assisting neuronal differentiation, maturation, and myelinization in higher centers. In addition, the downward discharges from the REM center, such as those found by Gassel *et al.* (68) to be activating the peripheral

musculature, may provide activation to the neuromuscular apparatus. Could these downward discharges account for Langworthy's curious early finding that ventral root nerves display myelinization before dorsal root nerves (131)?

The demonstration in the fetus of myelinization in tactile, auditory, gustatory, and proprioceptive pathways comes as no surprise, because a degree of sensory stimulation and development in these systems can be assumed during the intrauterine period. But why, if stimulation and development are linked, should there be substantial myelinization in the visual system before birth without exogenous stimulation to the retina save that from physical pressure (131)? And why before birth should the sensory neurons of the striate cortex be second in development only to the Betz cells of the pyramidal tract (133)? We would contend that structural building has occurred in the visual sensory system in response to the afferent or afferent-like excitations periodically provided to it by the pontine REM mechanism.

Romanes's conclusion (134), growing out of his finding that myelinization begins in the visual pathways of the sheep 50 days before birth, seems germane to our proposal: "It may be that the development of myelin in the optic system is initiated by factors quite different from those found elsewhere in the nervous system, but it is clear that the transmission of impulses resulting from light reaching the retina is *not* a factor in the sheep or in man. . . ." Structural maturation in the other sensory systems during fetal life may also substantially depend on discharges emanating from the pontine center.

If we accept the concept of "stimulus-induced" development, to use Riesen's term, we should not overlook REM sleep as a prime source of cortical stimulation in early ontogenesis. Its hypothesized role may offer a new ap-

proach to the processes of growth and maturation in higher brain centers. It makes all the more meaningful the somewhat unspecific but undoubtedly true suggestions of Carmichael (135), Dodgson (136), Riesen (132), and others that the immature central nervous system can "anticipate" or "prepare" for its future active role long before such functions are called into play. The abundance of REM sleep in early development also fits with the tremendous growth of the central nervous system during the first year or two of life. We conjecture that the REM mechanism became necessary in phylogenetic evolution at the time that extensive telencephalization began because of the need for maintenance of large masses of neural tissue not directly involved in motor and sensory reactions taking place during the progressively longer periods of sleep manifested by evolving species.

It is noteworthy that the areas in the central nervous system which are myelinated *in utero* either receive afferent fibers directly from subcortical centers or are principally related to them (137). Conel's descriptions of cortical histology in the newborn place the most differentiated and mature cells in the brain within the primary sensory receiving areas, principal motor areas, limbic system, and rhinencephalon (133). All these areas are intimate participants in the neurophysiology of the REM state. Therefore it is plausible that the REM mechanism is responsible for the first appearance, in ontogenetic development, of a "state" of the central nervous system which recurs throughout life. The mechanism may then function to bring higher brain centers to an operational capacity requisite to handling the rush of external stimulation in waking experience.

If REM sleep delivers significant functional stimulation to the cortex in infancy, then it probably maintains this role throughout life. It might even be conjectured, on the basis of the large reduction in REM sleep and the augmentation of time awake in the adult, that the need for endogenous stimulation becomes negligible, owing either to the maturity of the cortex or to a surfeit of exogenous input. On the other hand, many would argue that dreaming, the epiphénoménon of the REM state, is not a process without a purpose, and that it, indeed, serves a necessary psychological function in the adult. A physiological system that remains active throughout life probably continues

to execute physiological as well as other functions. It is known that deprivation of REM sleep induces certain behavioral and (in humans) psychological aberrances (27, 28, 8, 92, 93). This information, however, does not clearly indicate the natural physiological function, if any, of REM sleep in the adult. One possibility we are considering is that frequent excitation of higher brain centers during sleep, accruing from periodic activation of the REM process, serves to maintain the central nervous system in a state of physiological readiness so that it may react swiftly to the exigencies of the real world. Extended interruptions of excitation may be injurious to optimal responsiveness of neural structures. [It is interesting that accuracy of depth perception is considerably weakened after one eye has been covered for a matter of hours (138).] In this sense, then, the stimulating function of the REM mechanism may remain important to the organism throughout life.

We hope that embryologists and experimental neurophysiologists will give consideration to the possibility that REM sleep plays a role in stimulating structural maturation and maintenance within the central nervous system. If our hypotheses have any validity, then a developing fetus should show critical failures or lags in maturation of certain neural systems if deprived of the REM state. Another corollary of our proposal is that a significant reduction of external sensory input to the developing central nervous system might, by means of a feedback system, retard the rate of diminution of the REM moiety. However, if the normal fall-off of REM sleep were programmed by an autonomous REM sleep mechanism, lack of external sensory input and a failure of nervous tissue to develop during critical growth periods might not substantially affect proportions of REM sleep. Certainly, further experimentation is required in order to distinguish, separate, and quantitatively assess the specific part played by REM sleep in the maturation of central nervous structures.

Summary

When the means for physiologically identifying rapid-eye-movement (REM) or "dreaming" sleep became available and sleep-dream patterns were first investigated, it was totally unexpected that more REM sleep would be found in

younger individuals than in adults. However, this fact has been demonstrated in both humans and animals. We have presented data indicating that normal newborns spend one-third of their day and one-half of their sleep in the REM state. This high ratio diminishes progressively with maturation. The early large percentages of REM sleep compel us to look to early development for the most important function of REM sleep.

This activated phase of sleep is a state during which the central nervous system is functioning at intensities as great as or greater than during arousal and in which vivid hallucinations (dreams) are experienced. Accumulating data suggest that centers in the pons constitute the REM mechanism and that the pontine area sends impulses to motor as well as to sensory areas of the brain. After reaching the thalamus from the pons, the impulses appear to traverse the usual pathways to cortex.

We have hypothesized that the REM mechanism serves as an endogenous source of stimulation, furnishing great quantities of functional excitation to higher centers. Such stimulation would be particularly crucial during the periods *in utero* and shortly after birth, before appreciable exogenous stimulation is available to the central nervous system. It might assist in structural maturation and differentiation of key sensory and motor areas within the central nervous system, partially preparing them to handle the enormous rush of stimulation provided by the postnatal milieu, as well as contributing to their further growth after birth. The sharp diminution of REM sleep with development may signify that the mature brain has less need for endogenous stimulation. Proof that the critical function of the REM sleep mechanism during development is the one of "auto-stimulation" of structural and responsive capacity in the central nervous system must await future experimentation.

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 141. This and our other related studies are supported by grants MH-18,739 (NIMH Research Career Development Award, level I), MH-06383, and MH-06858 to H.P.R., and grants MH-08185 (NIMH Research Career Development Award, level II) and MY-3267 to W.C.D. We thank Dr. Gilbert W. Mellin of the Department of Pediatrics, College of Physicians and Surgeons, Columbia University, for enabling us to use the newborn nurseries of the Columbia-Presbyterian Medical Center; the nursing supervisors and staff nurses of the Presbyterian Hospital newborn nursery for indispensable help; Dr. Joseph Schacter of the Department of Psychiatry, Columbia University, for making laboratory facilities at Presbyterian Hospital available; Joseph Fleiss for help with some of the computations; France Burke and Harriet Phillips for preparing illustrations; Mildred Pleasant for invaluable secretarial and editing assistance. The thermocouples used to record respiratory rate were furnished by Capt. Roland A. Bosse, MSC, USN, Director of the Naval Air Engineering Center, Air Crew Equipment Laboratory, Philadelphia, Pa.

Adaptations of Amphibia to Arid Environments

Novel physiological mechanisms not seen in fish aid frogs and toads to conserve water and live in deserts.

P. J. Bentley

Amphibia—frogs, toads, newts, and salamanders—have a worldwide distribution which excludes only the antarctic continent and most oceanic islands. There are three groups within the Amphibia, but they are unevenly distributed geographically and show

some interesting differences with respect to the areas where they are principally found. Thus the Urodela (newts and salamanders) are nearly all found in the Northern Hemisphere and do not cross the equator, the little-known Apoda (coecilians) are confined to

certain tropical equatorial regions in central Africa, South America, and southeast Asia, and the Anura (frogs and toads), which have the widest distribution, extend from arctic regions such as Alaska into the hot, dry deserts of Africa, Australia, and America.

People generally associate Amphibia with moist, cool areas, and it is at first somewhat surprising that they successfully occupy dry areas. Although certain physiological characteristics of Amphibia might be expected to result in hardship in such environments, small modifications of the basic physiological pattern result in an animal well able to survive in such hot, arid regions.

The principal problems of animals living in hot, arid areas arise from high environmental temperatures and

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