example, during the first shift from depression to mania the MHPG excretion was increased on days 20 through 23, 4 days before the day of behavioral change. Nursing notes during this 4-day period indicate that the patient was nonverbal, sat rigidly in her chair for long periods, and appeared retarded in movements and thought processes. It may also be that the switch from mania to depression was preceded by a beginning decrement in MHPG excretion (Fig. 1). While these changes in MHPG in relation to manic and depressive periods may be coincidental (*19*), they do indicate that the MHPG excretion is not simply a derivative function of the patient's clinical state (namely, more activity during mania), for in this case there would be a close temporal relation between increase in urinary MHPG and the switch from depression to mania. The pattern of MHPG excretion, including changes preceding the behavioral shifts, is unaltered when values are expressed as micrograms of MHPG per milligram of creatinine (not shown). The changes in MHPG excretion and shifts in the affective state are in the expected direction, and the data are in agreement with the comments made by Bond *et al.* (*3*) as well as with the report by Schildkraut *et al.* (*20*) that urinary MHPG excretion is increased during amphetamine-induced hypomania and decreased during the depression which follows amphetamine withdrawal and that the changes in MHPG excretion appear to precede the behavioral shifts.

The pattern of excretion of normetanephrine in relation to the affective shifts is shown in Fig. 1b. The mean normetanephrine excretion by this patient during depressive periods was 99 ± 11 μg in 24 hours, whereas average 24-hour excretion for normal women ($N = 12$) was 191 mg, with the 95 percent confidence interval being 154 to 223 mg (*21*). The mean 24-hour excretion of normetanephrine during the manic phases was 206 ± 22 mg. The relation between urinary normetanephrine and the shifts in the patient's clinical state are less clear than in the case of MHPG. Urinary excretion of normetanephrine was increased on 2 of the 4 days immediately preceding the first switch from depression into mania. During the first manic episode, the urinary excretion increased on the day of behavioral change, but excretion was markedly decreased on the next day despite the moderate amount of activity (Table 1). While these data are generally consistent with the possibility that urinary normetanephrine changes as a function of activity, they also indicate that changes in its urinary excretion may precede the switches from depression into mania and vice versa.

During the second switch from depression into mania normetanephrine excretion was consistently low during the depressive phase (except for 1 day) and increased the day of behavioral change.

In conclusion, the data presented here are considered to support and be consistent with the catecholamine hypothesis of the affective disorders (*4*).

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Sleep and Memory

Abstract. *Two experiments demonstrated that memory over an interval with relatively high amounts of rapid eye movement (REM) sleep was inferior to memory over an interval with relatively high amounts of stage 4 sleep. The results suggest that, at least for humans, REM sleep does not facilitate memory consolidation and that stage 4 sleep may be beneficial to memory.*

Memory for verbal habits is facilitated by sleep occurring during the retention interval (*1*). This simple empirical fact has for some time served as the foundation experiment for an interference theory of forgetting. If forgetting is due to interference from learning taking place during the retention interval, then prevention of this interference, by putting subjects to sleep, would be expected to facilitate recall, and it does just that. We now present evidence which suggests that sleep does not facilitate memory solely by reducing interference.

Physiologists and psychologists interested in sleep and dreaming have attempted to link the beneficial effects of sleep on memory to one particular stage of sleep, rapid eye movement (REM) sleep (*2*). The most general statement of this hypothesis implies that REM sleep is responsible for, or facilitates, memory consolidation. Such a hypothesis has been supported by observations that REM deprivation increases the time interval over which a memory remains susceptible to electroconvulsive shock (*3*) and by a report that REM deprivation during the retention interval interferes with memory for prose passages (*4*). Our own data, on the contrary, suggest that it is delta-wave sleep, particularly stage 4 sleep, that is most beneficial to memory.

The basic paradigm for investigating the effect of REM sleep on memory has involved REM deprivation during the retention interval, an operation

which should impair recall. Subjects are awakened at the onset of each REM episode in an attempt to eliminate REM sleep from the interval. Whereas one or two studies have found such an impairment in humans, there have been numerous reports of failure to find any effect of REM deprivation (*5*). No one has succeeded in demonstrating the impairment in humans, intentionally memorizing associations.

It is our opinion that the REM-deprivation paradigm has the serious drawback of drastically disrupting normal sleep. Our approach (*6*) has been to attempt to create two relatively normal sleep intervals, differing greatly in the amount of REM sleep present. The first half of a normal night contains very little REM sleep and the second half contains a great deal (*7*). We therefore compared retention over the first and second halves of the night and found that memory was best over the first half, which contained little REM sleep and large amounts of stage 4 sleep. Retention over the second half of the night, which contains large amounts of REM sleep, did not differ significantly from a group which was awake during the retention interval. However, this experiment did not involve physiological monitoring of the subjects. It is possible that awakening the subjects in the second half of the night for learning disrupted their sleep cycle. Another problem was that the subjects tested in the first half of the night learned the material upon arriving at the laboratory, whereas the subjects tested in the second half of the night were awakened from sleep in the middle of the night for learning. Perhaps this difference in state just prior to learning influenced the course of learning and memory. The two experiments reported here attempted to remedy these deficiencies. We also decided to explore the effects of sleep on memory for visual forms as well as verbal paired-associates.

In experiment 1, three groups of college students were the subjects. Two memory tasks were employed, and each subject learned both tasks, the order of both learning and recall being counterbalanced across subjects. Our verbal task consisted of learning a 15-pair, paired-associate list of common words to a criterion of 10 out of 15 correct. Learning was carried out by the study-test method at a 2-second presentation rate. The second task involved paired-associate learning of 10 pairs of "nonsense" shapes, selected because they appeared to be difficult to label verbally. Subjects learned the 10 pairs of shapes to an 8 out of 10 criterion by the study-test method. Study trials involved complete presentation of the 10 paired shapes for 30 seconds, and the 30-second test trials used a complete presentation, multiple-choice recognition procedure.

Table 1. Percent loss in memory as a function of retention-interval condition and type of learning materials; MS_{WG}, mean square within groups from the analysis of variance and represents the best estimate of the population variance.

Learning materials	Loss in memory (%)			MS_{WG}
	First half of night	Second half of night	Awake	
	Experiment 1			
Verbal paired-associates	18.86	35.55	48.24	278.00
Visual forms	26.23	22.40	32.27	510.77
	Experiment 2			
High imagery words	11.85	22.98	33.02	123.72
Low imagery words	29.67	45.89	51.06	

One group of subjects ($n = 16$ per group) learned the materials during the daytime and after a 15-minute rest were released from the laboratory for a 3.5-hour retention interval filled with normal waking activity. They then returned to the laboratory for the retention tests. Thus for this group the retention interval was defined over a period of wakefulness. The subjects in the two sleep conditions came to the laboratory at about 10 p.m. and were prepared for sleep monitoring, after which they went to sleep. For the first-half condition, the subjects were awakened for learning at the first appearance of stage 2 sleep. The subjects went to an adjacent room where they completed the learning tasks. They then returned to bed and spent the next 3.5 hours sleeping, after which they were again awakened and tested for recall. Thus this retention interval was defined over the first half of the night.

For the second-half condition, the subjects were awakened for learning 4 hours after the first appearance of stage 2 sleep. They went to the adjacent room, completed the learning tasks, and then returned to sleep for the next 3.5 hours, after which they were awakened for recall. This retention interval, then, was defined over the second half of the night.

The retention results (percent loss) are shown in Table 1 (*8*). The results indicated a strong memory effect of retention-interval condition for the paired-associate word task, but no effect for the task employing shapes. For the word task on raw recall and percent loss measures, each of the three groups was significantly different from the others, while on absolute loss the difference between the means of second-half and awake conditions did not reach significance (*9*). These results suggest, contrary to our original finding, that subjects in the second-half condition have superior memory to those in an awake condition. They also, however, further document the fact that memory for word pairs over the first half of the night is considerably higher than memory over the second half of the night.

In experiment 2 we manipulated the imagery value of the word pairs. High imagery word pairs are presumably learned with the aid of visual-image mediators, whereas low imagery pairs are learned with predominately verbal mediators (*10*). The experiment was a three (retention-interval condition: first-half, second-half, or awake) by two (high or low imagery words) fac-

Table 2. Percentage of retention-interval time spent in various sleep stages.

		Awake	Stage				REM	Body movement
			1	2	3	4		
			Experiment 1					
First half	Mean	11.40	4.60	40.80	4.40	30.60	7.40	0.90
	Variance	1.76	3.14	74.27	3.27	32.86	5.73	.92
Second half	Mean	11.30	7.20	41.40	2.40	5.80	30.20	1.10
	Variance	1.23	3.30	75.34	2.07	2.89	32.82	0.96
			Experiment 2					
First half	Mean	9.80	4.80	39.10	5.40	31.70	8.50	.80
	Variance	1.85	4.16	80.91	4.37	49.37	3.63	.98
Second half	Mean	13.20	4.30	39.30	2.80	10.60	29.50	.40
	Variance	1.51	3.69	79.86	2.78	0.72	36.82	.48

torial design with ten subjects per cell. The details of manipulation of the retention-interval condition were identical to those described earlier. Each subject learned one list (high or low imagery pairs) to a 10 out of 15 criterion and recalled it 3.5 hours later (*11*).

The results in terms of percent loss (Table 1) show that there was a large effect of imagery on memory (F, 1 and $54 = 46.54$) as well as a large main effect of retention-interval condition (F, 2 and $54 = 18.79$). There was no interaction. The pattern of results was essentially unchanged when retention was measured by raw recall and absolute loss. For each of these dependent variables, there was a significant difference between the subjects in the first- and second-half conditions. The difference between the subjects in the second-half and awake conditions was significant when measured by absolute and percent loss.

The results of experiment 2 again document the fact that memory of the subjects in the first half of the night is superior to memory of those in the second half of the night. Both of our experiments also suggest that, contrary to our original observation, retention over the second half of the night is higher than retention over a waking interval. Table 2 shows the sleep-stage analysis from the two experiments. In both experiments, subjects in the first and second halves of the night differed significantly on REM and stage 4 sleep, with no differences on the other categories of sleep.

It is not easy to reconcile these results with an interference theory which states that sleep facilitates memory only by preventing interfering learning during the retention interval. Since subjects in the first- and second-half conditions were sleeping equal amounts of time during the retention interval, prevention of interfering learning should be equivalent for the two groups, but yet they differed reliably in memory. One could argue that the mental activity associated with dreaming, which would occur mainly in the second-half condition, is like being awake; that is, the subject is learning interfering material. However, there is now ample evidence of a great deal of mental activity during the non-rapid eye movement (non–REM) stages (*12*). We suppose, however, that it is conceivable that REM content is like interference whereas non-REM content is not.

Our results suggest that REM sleep is not particularly beneficial to memory or memory consolidation. One could even argue that REM sleep is detrimental, although the numerous failures to find effects of REM deprivation on memory suggest this is not true. We would like to conclude that stage 4 sleep is responsible for the difference between the first and second halves of the night, perhaps because stage 4 sleep facilitates memory consolidation (*13*). Caution is warranted, however, because other interpretations are possible (*14*). Most notable in this regard would be a suggestion that subjects in the first-half and second-half conditions are in different biopsychological states at the time of learning and perhaps at recall. Subjects in the first-half condition have had essentially no sleep at the time of learning and only 3.5 hours of sleep at the time of recall. In contrast, subjects in the second-half condition have had 4 hours of sleep at the time of learning and about 7.5 hours at the time of recall. Although the two groups did not differ in speed of original learning, it is nevertheless possible that different psychobiological states were present and that this could have affected retention. This would mean, however, that the group with prior sleep or more prior sleep (second-half condition) actually was adversely affected by the sleep advantage, that is, it would suggest that prior sleep could interfere with the memory for subsequently learned materials. This is certainly as intriguing a possibility as the hypothesis that stage 4 sleep facilitates consolidation. It will not be easy to distinguish between these two interpretations.

The results also confirm the suspicions of many psychologists and sleep physiologists that sleep and memory are related. We can expect more and more theories of sleep and dreaming to incorporate hypotheses related to memory.

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14. One other potential explanation of the difference in memory of subjects in the first- and second-half conditions has been ruled out by another experiment in our laboratory (T. Barrett and B. Ekstrand, *J. Exp. Psychol.*, in press). This is a circadian rhythm explanation which states that since the first- and second-half retention intervals occurred at different times of the night, the difference may be due to a circadian effect on memory that is independent of sleep stage. We, however, have replicated the difference between the two halves when both retention intervals occurred over the exact same time interval, making a circadian explanation difficult to accept. In both experiments, groups in the first- and second-half conditions did not differ in time to fall asleep after completion of the learning task. This means that the difference in memory between these two groups cannot be accounted for by differential "retrograde amnesia" produced by sleep coming at different times after learning.
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