Original Articles

Acute Reversal of the Sleep-Waking Cycle in Man

Effect on Sleep Stage Patterns

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PAST studies of the sleep-waking circadian cycle in man emphasized the temporal relationship to other rhythmic physiological and chemical functions.[1] It was implicitly assumed in these studies that sleep is a unitary process. Recent evidence, however, clearly indicates that sleep is composed of recurring short-term physiologic events.[2,3] In man, during each daily sleep period, a consistent sequence of sleep patterns occurs, characterized by four or five recurrent 90-minute cycles. Future studies of circadian phase relationships between sleep and physiologic variables should take into account the qualitative and quantitative differences between sleep stage patterns. We have begun to study the time relation of sleep stages and neuroendocrine processes.[4] The method of cycle phase shift of 180° (sleep-waking cycle inversion) has been used in man.[5-8] This report describes the changes in sleep pattern when normal young adults were subjected to an acute inversion of sleep-waking cycles in a laboratory environment. The effect on other physiologic variables will be described in a future report.

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Method

Five healthy young men lived for three weeks on a metabolic ward. All subjects reported that they normally slept at night and were awake during the day in their prestudy activities. For 7½ days the subjects were allowed to sleep at night for eight hours in an air-conditioned, sound-attenuated, darkened room on a standard hospital bed. Each evening before retiring, standard clinical electroencephalogram electrodes and electrodes for recording the electro-oculogram (EOG) and surface chin electromyogram (EMG) were attached. The electrodes were placed at scalp positions F_3, C_3, and P_3 and referred to both ears, electrically connected ($A_1 + A_2$). One electrode was placed at C_4, to be used if any of the others were faulty during the recording. The EOG was recorded on three channels. The right and left lateral and the left superior orbital electrodes were referred to the ears ($A_1 + A_2$). Two surface electrodes, taped to the chin, were used in a bipolar arrangement for one channel of EMG, recording. The light was turned off at 10 PM, and the sleep period was then interrupted at 6 AM. During each sleep period for 20 days, EEG, EOG, and EMG were recorded. During alternate sleep periods, an indwelling venous catheter was used to withdraw samples of blood every half hour during sleep for four of the five subjects. This catheter extended ten feet via a small wall aperture to an adjoining room so that blood was obtained without disturbing the subject. In addition, for these subjects blood was obtained by direct venipuncture every four hours on alternate days. Every four hours ex-

cept for the mid-sleep period, rectal body temperature (oral for one subject) was measured and voided urine obtained for the entire three-week period. Analysis of body temperature, plasma, and urine measurements will be described in a subsequent report. During the waking period for the baseline week during the day, and at night after inversion, the subjects had no planned activity. They were instructed not to sleep and were carefully watched by the ward staff. On occasion they were allowed to leave the ward for several hours during their waking time.

A standard diet was served at standard meal times. Food and fluid intake was measured, although the subjects were not obliged to eat or drink the same amount each day.

On the eighth evening, the subject remained awake all night under constant observation and was then allowed to sleep the next morning in the darkened room from 10 AM to 6 PM. Sleep was allowed each day during this eight-hour day period for the next two weeks. All meals, measurements, samples, and recordings proceeded in the previous manner, but at a time 12 hours (180°) out of phase with the baseline first week period. Although there was less activity and fewer people were on the ward at night, the unit was well staffed at all hours.

The continuous polygraphic records of monopolar EEG, EOG, and EMG recordings were scored in one-minute intervals by experienced technicians, according to the Dement-Kleitman[9] criteria, into awake and sleep stages 1, 2, 3, and 4, and REM (rapid eye movement, sleep). The criteria agree closely with the recent manual for scoring human sleep stages.[10] The scored data for each sleep period was key-punched onto cards and then analyzed statistically with the assistance of digital computer processing.

Results

Shifting the sleep period of the five subjects to a day time interval 180° out of phase with the baseline night sleep period had three effects on the EEG sleep records. (1) The proportion of time spent in certain sleep stages was altered. (2) The hourly distribution of certain stages within the sleep periods changed. (3) The usual sequence of stages was disturbed, and the mean duration of continuous intervals of each stage decreased.

Sleep Stage Amounts.—The duration of each stage within a sleep period for each subject varied from day to day both before and after reversal. Therefore, to describe the trends, mean minutes per sleep period for each stage were averaged for sequential half-week intervals (Table 1). From the first to the second half of the baseline week, there was a significant increase in minutes of stage REM from 104 to 125 minutes, and a significant decrease in stage 2 from 217 to 194 minutes, with little change in the other stages. Changes after reversal were compared with the second half of the baseline week, since the data from the first half week are probably more distorted by the "first night effect"[11] and by other adaptational factors.

Stage Wakefulness (W).—There was a significant increase in wakefulness immediately after reversal; after reversal the subjects slept less. The duration of waking time was still higher than baseline in the sixth half week, two weeks after reversal. This effect occurred in all five subjects.

Stage 1.—Despite the decrease in duration of total sleep and specific stages, the amount of stage 1 increased after reversal in all four half weeks. This increase was statistically significant ($P < 0.05$) when calculated individually for two subjects but was not significant when determined for the group.

Stages 2, 3, and 4.—There was no significant change in the amount of time spent in these stages following reversal.

Stage REM.—There was significantly less stage REM sleep after reversal. By the sixth half week, two weeks after reversal, the mean duration of stage REM had increased to a level not significantly different from baseline.

Therefore, the effect of reversal on sleep stage amounts was to increase waking time at the expense of REM sleep, with little effect on non-REM sleep stages. This decrease in REM after reversal was associated with a relatively small decrease in the REM percent of total sleep because total sleep also decreased (Table 2).

Hourly Distribution of the Sleep Stages.—During the first week (night sleep prior to reversal), the distribution of the stages throughout the sleep period was highly skewed (Fig 1) as in numerous other studies.[9,12,13] Stages 1, 3, 4, and awake were all higher in the first three hours, whereas

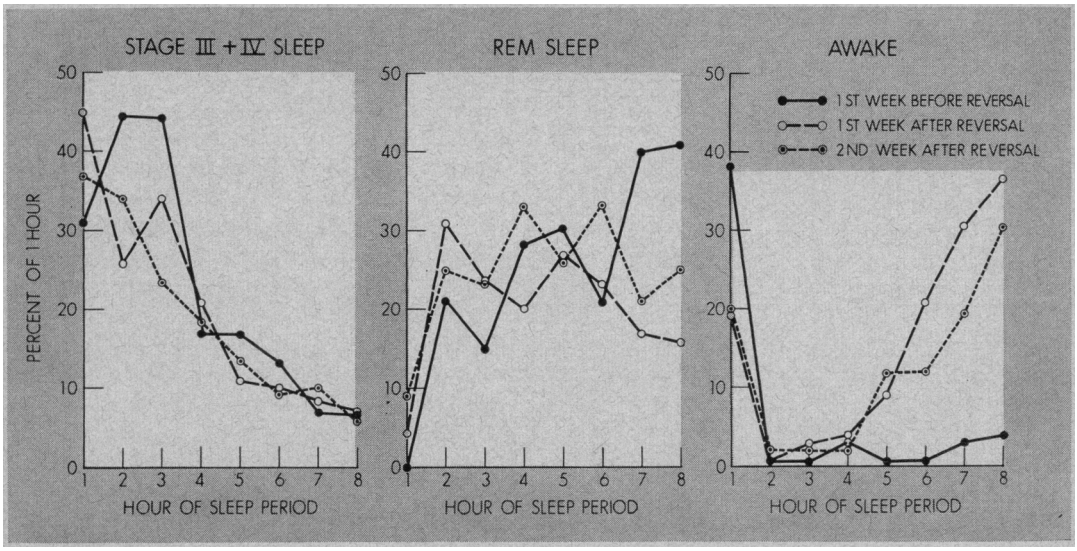

Fig 1.—Mean percent of sleep stages and awake for each hour of sleep period before and after sleep-waking reversal.

Fig 2.—Results of a binary autocorrelation test comparing percent agreement with lag time for each of five subjects and for group of five subjects as whole. **Uninterrupted line** represents values for first week prior to reversal; **dashed line,** first week after reversal; **dash-dot line,** second week after reversal.

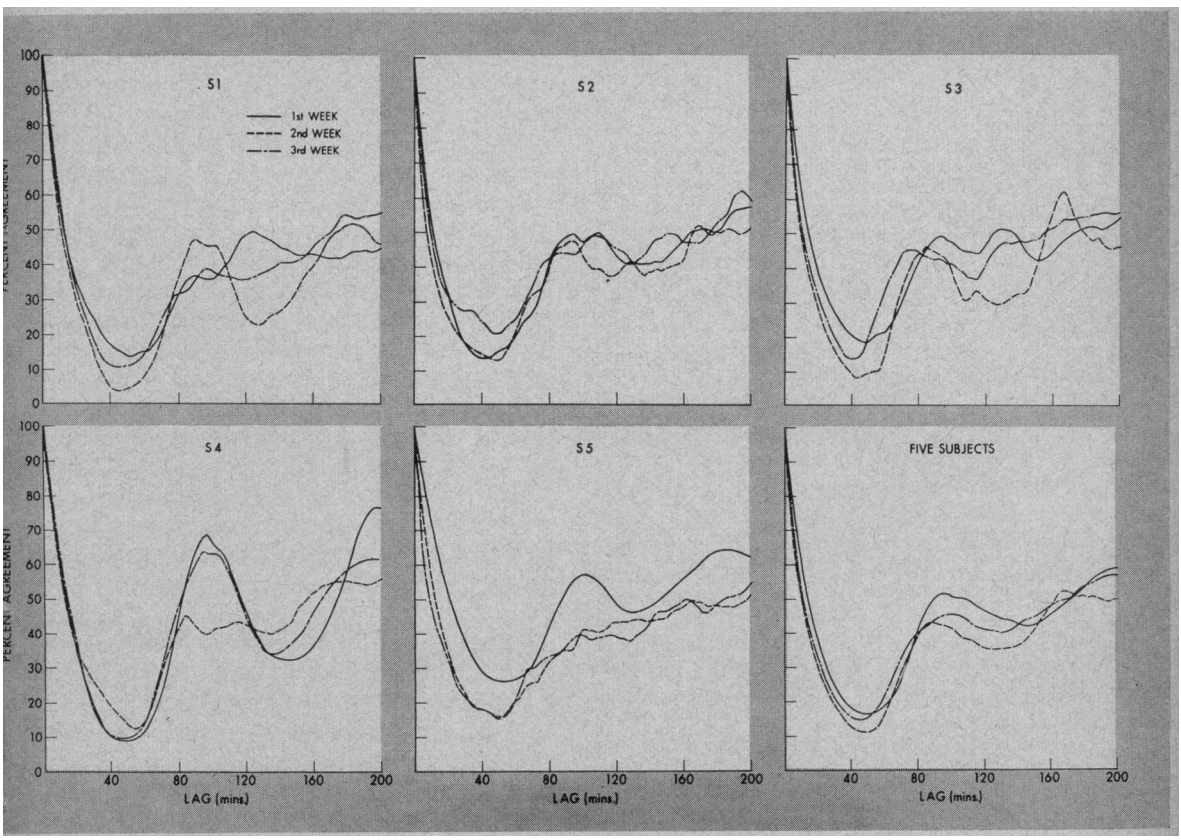

Table 1.—*Comparison of Minutes of Each Sleep Stage Per Eight-Hour Sleep Period by Sequential Half-Week Intervals*

Sleep Stage	Half Weeks (Min) 1	2	Reversal	3	4	5	6
W	31	32		52*	50	48	44
1	7	10		11	14	11	14
2	217*	194		185	201	196	196
3	75	76		75	66	67	63
4	34	35		28	25	29	22
REM	104*	125		99*	91*	104*	119

* Values differ significantly ($P<0.05$) from values of the second half week, latter half of the baseline week.

Table 2.—*Comparison of Percent of Each Sleep Stage to Total Amount of Sleep Per Eight-Hour Sleep Period by Sequential Half-Week Intervals*

Sleep Stage	Half Weeks 1	2	3	4	5	6
1	2	2	3	3	3	3
2	50	44	46	51	48	47
3	17	17	19	17	16	15
4	8	8	7	7	7	5
REM	24	28	25	23	26	28

Table 3.—*Time of Sleep Onset to the First REM Period

Week	S_1	S_2	S_3	S_4	S_5
1	76±7	83±29	68±15	67±7	62±27
2	60±7	28±30	56±9	55±22	38±28
3	57±28	5±3	60±11	55±26	41±48

* Mean in min ± standard deviation.

Table 4.—*Comparison of the Mean Duration of the Episodes of the Sleep Stages for the Sequential Half-Week Periods of Day Sleep Compared With the Baseline Week of Night Sleep Periods*

Sleep Stage	Baseline Week (Min)	Half Weeks After Reversal (Min) 3	4	5	6
1	3	3	3	2	3
2	18	14*	16*	15*	14*
3	12	12	11	9*	10*
4	16	15	12*	13	17
REM	23	16*	14*	18*	15*

* Significant difference at $P<0.01$ (t-test).

Table 5.—*Number of Interrupted REM Epochs* and Interruptions of REM Epochs**

Week	S_1	S_2	S_3	S_4	S_5
Interrupted					
1	2	5	4	1	3
Reversal					
2	9	17	12	4	5
3	3	15	11	2	4
Interruptions					
1	2	6	4	1	3
Reversal					
2	12	28	13	5	10
3	3	23	16	2	6

* REM epoch is defined as sequential REM period(s) with interruptions $\leqq$ 15 minutes.

REM and stage 2 had higher hourly means in the latter part of sleep.

Stage W.—Before reversal, stage W occurred predominantly in the first hour of sleep. After reversal, the amount of stage W decreased significantly in the first hour and increased significantly in the last three hours. That is, after reversal the subjects fell asleep more quickly, but they tended to awaken intermittently toward the end of the sleep period.

Stage 2.—After reversal, stage 2 was less concentrated in the latter half of the sleep period.

Stages 3 and 4.—These stages predominated in the first half of the sleep period, both before and after reversal.

Stage REM.—After reversal, the minutes of REM increased during the first half of the sleep period and decreased in the final two hours (Fig 1). The time of sleep onset to the first REM period for all nights of all subjects decreased significantly ($P < 0.05$) during the first postreversal week (week 2) and decreased with borderline significance in the second postreversal week (week 3) ($P < 0.01$), using a t-test for correlated means (Table 3). There was more variability in the latency to the first REM after reversal, and some latencies were extremely short. In the baseline week there were no latencies more than two standard deviations below the mean latency to stage REM onset, while after reversal such extremely small latencies occurred for each subject. One subject, who had no very short REM latencies during the baseline week, developed a pattern of first REM periods occurring essentially at onset of sleep or within a few minutes, and this pattern continued through the second week after reversal.

Thus, during the first week after reversal, there was a clear shift of REM and stage 2 toward the early part of the sleep period, and waking shifted toward the latter part.

Time Sequence of Sleep Stages.—The mean duration of the individual episodes of all sleep stages for the four sequential half-week periods of day sleep were compared to the preceding week of night sleep (Table 4). The duration of episodes of stages REM and 2 decreased significantly in all postreversal periods. Stage 3 decreased in the last three half-week periods, whereas stage 4 de-

creased significantly only in the latter half of the first week postreversal (week 2). The duration of stages 2 and REM were significantly less for both postreversal weeks. Decreases in the durations of the sleep stage episodes are a measure of the interrupted quality of postreversal sleep. To further define the effect of reversal on REM sleep we defined a REM "epoch" as time from the beginning of a REM period to the end of a sequence of REM periods separated by 15 minutes or less. Both the number of interruptions and the number of interrupted REM epochs increased after sleep-wake cycle inversion (Table 5). Although there was a trend to return to prereversal values, the interruptions were still increased in the second week after reversal.

As a corollary to the above findings, there was an increase in the number of changes of sleep stage after reversal. A mean of 30 changes of stage occurred each night during the baseline week, whereas 37 and 39 were the mean values per night for the second and third week. A selective increase in the number of awakenings from REM periods was also noted following reversal. Prior to reversal, 13% of REM periods were followed by awakenings, whereas after, 29% and 36% of REM periods terminated in awakenings in the second and third weeks.

Because REM interruptions might indicate a disruption in the normal rhythmic cycle of stage REM sleep, we applied a test for rhythmicity of REM occurrences. A binary autocorrelation test, supplied by Gordon Globus, MD,[14] was performed on sleep stage data for each subject for each sleep period. An average result was obtained for the entire group for each of the three weeks. Essentially no difference was found between the mean autocorrelation curves for each of the three weeks when the five subjects were treated as a group. All three curves fell off sharply to minimum agreements at a lag of 45 to 50 minutes and then rose to peak agreements at lags of 90 to 100 minutes (Fig 2).

Individual subjects differed considerably (Fig 2). One subject (*S4*) had consistently high agreement in the first and third weeks, at a lag of 90 to 110 minutes. During the second week, however, the curves flattened considerably. Subjects *S1* and *S3* had a consistent 90-minute cycle during week two, whereas this was not consistently present during the first and third weeks. Subjects *S2* and *S5*, on the other hand, had a 90 to 100 minute rythm during the first week, whereas this was not clearly the case for the second and third week.

Therefore, despite significant changes in duration, amount, stability, and timing of certain sleep stages, the basic 90 to 100 minute cyclicity was preserved following acute inversion to day sleep.

Comment

The consistent alteration of sleep pattern after acute inversion of the sleep-waking cycle in these subjects emphasizes the importance of polygraphic definition of sleep stages in studies of circadian cycle shifts. The previous implicit assumptions of a unitary view of sleep can no longer be held in light of the extensive literature documenting the complexity of sleep patterns under a variety of experimental manipulations. Our findings emphasize the differential response of specific sleep stages to an acute inversion of the sleep-wake cycle in a laboratory setting. They demonstrate complex alterations of the phase relations of the sleep stages, the amounts of different stages, and the pattern of sleep stage sequencing.

There was a persistent tendency for spontaneous waking to occur in the latter third of sleep during the inverted sleep period. This was associated with a shift of REM sleep to an earlier time. Further evidence of disturbed REM sleep was shown by the increased frequency of interrupted REM and interruptions of REM sleep epochs. However, the basic 90-minute REM cycle persisted during the day sleep period.

In contradistinction to the disturbances of REM sleep, stages 3 and 4 appeared to shift immediately with the cycle shift. These stages of sleep continued to be present during the first two hours of the sleep period after the 180° shift, as in several previous studies, and suggests that the duration and quality of the waking period may be a factor in determining the timing and amount of stage 3 to 4 sleep.[15-17] In our study a waking period of 16 hours was always followed upon going to sleep by a similar period of stage 3

to 4 sleep, whether the subject went to sleep at 10 PM or 10 AM.

Although our subjects slept in an equivalent dark room during day and night sleep periods, the light intensity and wavelength spectrum differed while they were awake. In addition, since our subjects were not isolated from the environment during the study period, they were subject to a different social and psychological milieu at night. These factors could have a significant bearing upon the change of sleep patterns.

These findings may be compared to the pattern of sleep disturbances in patients with narcolepsy or endogenous depression. Characteristically, patients with endogenous depression awaken spontaneously during the latter third of the night, and the total sleep time is decreased. Their sleep pattern is altered by more frequent sleep stage shifts and a tendency for REM sleep to occur earlier.[18-20] Many chronically depressed patients have partial phase shifts of their sleep-waking cycle, sleeping during the daytime. These similarities raise the question whether some of the physiologic and psychologic changes associated with endogenous depression could be secondary to the disturbed phase-shifted circadian cycle.

Studies of the nocturnal sleep pattern of patients with narcolepsy have shown that sleep-onset REM periods occur frequently, with a significant decrease of the time from onset of sleep to onset of the first REM period.[21] This is similar to the pattern of our subjects following sleep-wake inversion. In one subject (S2) there were REM periods at onset of sleep throughout the second-week day sleep period associated with vivid dreams. Narcoleptic sleep attacks, cataplexy, or sleep paralysis were not induced in any of these subjects, however. Repeated or irregular phase cycle shifts might induce a more permanent disturbance of sleep stage timing and lead to the narcoleptic syndrome; Mitchell and Dement[22] reported that in narcoleptic patients, a high incidence of nocturnal sleep disordering and deprivation preceded and occurred with the onset of narcoleptic sleep attacks.

The differential pattern of response of various sleep stages to the cycle phase shift indicates the importance of correlating these changes to other physiological systems. Sassin et al[23] found an immediate shift of both stages 3 and 4 and plasma growth hormone during sleep when the sleep cycle was reversed in contrast to studies indicating a significant delay of a phase shift of cortisol secretion.[4,7,24] Investigations relating cerebral biogenic amines to sleep stages, neuroendocrine control systems, and biological rhythms may increase understanding of the physiologic and biochemical mechanisms of the effects of cycle phase shift.[25]

There is an increasingly important problem of the effects of rapid sleep-wake cycle shift entailed by industrial work shifts and geographical time zone shifts. Alterations in psychological function, work efficiency, and somatic symptoms accompany rapid sleep-wake phase shifts.[26-28] Our findings of a significant delay in the reestablishment of normal sleep patterns indicate the possible importance of correlating sleep-stage changes to specific occupational work-rest cycle changes. Monitoring sleep patterns and other physiological variables with cycle shift experiments may lead to more rational schedules for work-activity patterns. In the field of occupational medicine there is a substantial body of literature indicating health hazards in situations involving repeated reversals of sleep-waking patterns. Delays in physiologic cycle correspondence have been implicated in the disruption after air and space travel,[29] with symptoms of fatigue, urinary irregularity, appetite changes, and major disruption of sleep-waking patterns. Alterations in adrenal function and water and electrolyte excretion have been found in transmeridian air flights. The list of occupations involved in sleep-waking reversals is long: airplane pilots, maintenance and traffic control personnel, medical interns, residents and nurses, radar operators, truck drivers, taxicab drivers, postal employees, police and fire department workers. As man works increasingly in situations without regard to a repetitive sleep-waking cycle, the disruption of physiologic circadian rhythms affects mental and physical health, especially if complicated by environmental isolation or mental and physical stress.

Summary

Five healthy young men were subjected to an acute sleep-wake cycle reversal (a phase

shift of 180°) in a laboratory. The subjects slept for one week at night (10 PM to 6 AM) followed by two weeks of day sleep (10 AM to 6 PM). A significant increase in waking and a decrease in REM sleep time occurred during the inverted sleep period. No change in the amount of time spent in stages 2, 3, and 4 was noted. After reversal there was a shift of REM and stage 2 sleep toward the early part of the sleep period, and waking shifted toward the latter part. In addition, the duration of episodes of all stages of sleep decreased, and the number of changes of sleep stage increased after reversal. Despite these changes in duration, amount, stability, and timing of sleep stages, the basic 90 to 100 minute cycling was preserved following acute inversion to day sleep.

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