Effects of Method, Duration, and Sleep Stage on Rebounds from Sleep Deprivation in the Rat

Allan Rechtschaffen, Bernard M. Bergmann, Marcia A. Gilliland, and Kari Bauer

University of Chicago Sleep Research Laboratory, Departments of Psychiatry and Psychology, University of Chicago, Chicago, Ill

Summary: Total sleep deprivation (TSD) of rats for 24 hours or less by continually enforced locomotion has consistently produced subsequent rebounds of slow-wave or high-amplitude EEG activity in NREM sleep, which has contributed to the widely held view that this EEG activity reflects particularly "intense" or restorative sleep. These rebounds usually have been accompanied by substantial rebounds of REM sleep. In contrast, chronic TSD (2 weeks or longer) by the disk-over-water (DOW) method has produced only huge, long-lasting rebounds of REM sleep with no rebound of high-amplitude NREM sleep. To evaluate whether the different rebounds result from different methods or from different lengths of deprivation, rats were subjected to 24-hour TSD by the DOW method. Rebounds included increases in high-amplitude and slow-wave activity; ie, the methods produced similar rebound patterns following short-term TSD. (Chronic TSD by continually enforced locomotion would be strategically difficult and severely confounded with motor fatigue.) Rats subjected to DOW-TSD for 4 days, well before the development of severe TSD symptoms, showed primarily REM sleep rebounds. Rats subjected to 1 day of selective REM sleep deprivation, but not their closely yoked control rats, showed large, significant REM sleep rebounds, which evidently were not induced by the stress of the deprivation method per se. The combined findings prompted reexamination of published evidence relevant to "sleep intensity," including "negative rebounds," rebounds in other species, the effects of stress and fatigue, depth of sleep indicators, and extended sleep. The review points out pitfalls in the designation of any specific pattern as intense sleep.
Key words: Sleep deprivation; sleep rebounds; sleep intensity; slow-wave sleep

THE INCREASES (above baseline) in sleep duration during recovery from sleep deprivation are usually only a fraction of the sleep time that was lost. Because it is widely assumed that sleep is homeostatically regulated, many believe that lost sleep is compensated by "intense sleep" that satisfies the unfulfilled sleep need in a relatively short period of time. The empirical identification of sleep-intensity factors might help explain the dynamics of recovery sleep as well as normal sleep patterns; it might also provide clues to the most important mechanistic and functional features of sleep. One clue to sleep-intensity factors is the characteristics of the recovery sleep that follow total sleep deprivation (TSD).

The augmentation of high-amplitude, slow-wave (HASW) EEG activity (also known as "delta" activity) during NREM sleep was early identified as a major feature of recovery sleep in humans[1] and has been repeatedly confirmed; see ref. 2 for recent review. Other features suggesting that HASW sleep is particularly intense include its relatively high awakening threshold, its early appearance and subsequent decline in nocturnal sleep, and its decline following daytime naps.[3] Post-deprivation rebounds of HASW activity have also been described in rats (see ref. 4 for recent review), cats,[5] dogs,[6] and rabbits.[7] As a result of such studies, the acceptance of HASW sleep as intense has become widespread. The major thrust of this paper is to argue that, in several important respects, HASW activity in the rat is not a particularly good measure of sleep intensity.

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Address correspondence and requests for reprints to Allan Rechtschaffen, PhD, Sleep Research Laboratory, 5743 S. Drexel Ave., Chicago, Illinois 60637, e-mail arech@yoda.bsd.uchicago.edu

Part of the argument will be in the form of new empirical data; part will be in reviews of earlier data from our own and other laboratories. Secondarily, the strength of intensity-HASW relationships in other species will be considered.

Many studies have shown initial rebounds of HASW sleep following short-term (24 hours or less) of TSD in the rat.[4,8-20] Various measures of rebound effects have been used. Some studies (eg, ref. 12) have shown the combined effects of prior TSD on the incidence of slow waves and their amplitudes by reporting power in the slow-wave spectral band (eg, 0.75-4.0 Hz). However, there were early clues that high-amplitude and slow-wave components of NREM sleep in the rat could be dissociated, since they showed somewhat different diurnal distributions.[21] Therefore, it was possible that there might also be differences in their rebound patterns.

By demonstrating relatively infrequent post-deprivation crossings of the zero voltage baseline (less than 40 per 10 seconds corresponding to mean wavelengths longer than 0.25 second), several studies[8,13,22] showed rebounds of slow-wave incidence independent of amplitude—except perhaps for a small contribution of amplitude in raising low-voltage slow waves to detectable levels. Conversely, rebounds of amplitude across a large range of wavelengths indicated at least a partial independence of amplitude rebounds from slow-wave rebounds.[8,11] Similarly, in our own laboratory, a period-amplitude analysis of postdeprivation changes across a large range of EEG period lengths[14] showed that wave amplitude in all period bins from 1 to 16 Hz was enhanced during 8 hours of recovery from 4 hours of TSD. The percentage increase in EEG amplitude was as great as that of slow-wave incidence. The magnitude of the amplitude rebound and its appearance at many wavelengths encouraged our separation of rat NREM sleep into low-, medium-, and high-amplitude categories.[23,24] Two studies have shown greater initial rebounds of high-amplitude NREM sleep than medium- or low-amplitude NREM sleep.[9,10] Since EEG slow waves in the rat tend to have higher amplitudes than waves of shorter wavelengths,[8,24] a substantial correlation between slow-wave and amplitude rebounds is expected. Nevertheless, the partial independence of the two rebound effects reported above and the occasional differences between them in response to other variables[8,14] require that at times they need to be considered separately. In the discussions to follow, wavelength and amplitude characteristics will be considered separately when only one has been measured or the parameters do not change in the same direction. The term HASW will designate sleep or EEG activity in which slow-wave and high-amplitude components are combined, not differentiated, or change in the same direction.

Although the evidence is abundant that slow-wave incidence and EEG amplitude show initial rebounds following short-term TSD in the rat, the hypothesis that they reflect sleep intensity is not unchallenged. Some studies have shown that several hours following their initial "positive" rebounds to above baseline levels, slow-wave incidence and/or amplitude may show "negative rebounds" to below-baseline levels for extended periods.[9,13,16,18,25] (Attempts to explain these negative rebounds as compatible with the intensity hypothesis will be discussed later.) Two of these studies which have used "hand deprivation" (see below) to maintain wakefulness have reported relatively small rebounds of slow-wave incidence and EEG amplitude.[13,18] Perhaps most challenging to the intensity hypothesis are the findings that positive amplitude rebounds have been absent during periods when intense sleep would be most expected, ie, during recovery from chronic (several days or weeks) TSD.[26,27] However, some deprivation procedures are not useful for maintaining chronic TSD, and the different rebounds could have resulted from the different procedures that were used.

Three major procedures have been used to enforce TSD in the rat. Most frequently used, probably because it requires little labor and only modest instrumentation, is continuously enforced locomotion maintained by housing rats in or on top of a rotating cylinder. There has been controversy over whether the locomotion has contributed to rebounds from short-term TSD,[14,18-20,28] but there is little doubt that continuously enforced locomotion for several days in chronic TSD studies would compromise any interpretation of rebounds as effects of prior sleep loss.

To reduce possibly confounding effects of motor activity, several studies have enforced short-term TSD by what has come to be known as "hand deprivation" or "gentle handling." By this technique, rats are gently touched, given objects to play with, or fondled as necessary to keep them from falling asleep. It may not be practical or even possible to enforce chronic TSD with hand deprivation. It calls for several experimenters who must struggle to keep themselves awake, and rats may quickly adapt or become unresponsive to even the most ingenious variety of stimulation. One study maintained deprivation by "nonpunitive" procedures for 12 days in one rat and 15 days in another, but immersion in shallow water was frequently used to help maintain wakefulness.[29] Even then, there was evidence of decreasing attention by the experimental assistants.

To reduce both the motor activity and sensory stimulation necessary to enforce TSD, we devised the disk-over-water (DOW) method of sleep deprivation.[30,31] An experimental (TSD) rat and a control (TSC) rat are housed in separate plastic cages mounted over a single plastic disk which serves as a floor for both cages. Under the disk in each cage is a shallow pan of water 2-3 cm deep. Both rats are continuously monitored by EEG and electromyographic (EMG) recordings. When sleep onset is detected in the

TSD rat, the disk is slowly rotated, which forces both rats to walk opposite to disk rotation to avoid being carried into the water pan under the disk. Thus both rats are subjected to similar sensory stimulation and a similarly light locomotor load; usually the disk is rotated only about 20% to 30% of the day for a total of about 1.0 km/day, whereas rats provided with an activity wheel voluntarily run 3.0 km/day.[28] The TSD rat is severely sleep deprived, but the TSC rat can sleep when the TSD rat is spontaneously awake and the disk is still. The DOW procedure makes it possible to sleep deprive rats or selectively deprive them of REM sleep for several weeks.

Most DOW-TSD experiments have been terminated after 2-3 weeks, either because the rats died or were sacrificed for postmortem analyses. In two of the extended disk-over-water studies, deprivation was halted to permit examination of recovery sleep. The first of these studies examined recovery sleep in three rats after 18 or 19 days of TSD.[26] The results were similar in the three rats and not very favorable for EEG amplitude as an intensity indicator. HS2 (our scoring of high-amplitude NREM sleep) decreased from a baseline mean of 19.6% of total time to a mean of 2.1% on the first recovery day. Over the subsequent 14 days, HS2 recovered to near baseline in one rat and to slightly above baseline in a second rat, and remained markedly depressed in the third. The major recovery feature was a huge increase in mean REM sleep to 949% of baseline levels in the first 4 hours, 567% of baseline levels over the first day, and 184% of baseline levels over the next 14 recovery days. (Large rebounds of REM sleep are usually seen after 24 hours of TSD in the rat, but they do not begin approach the magnitude of those following chronic TSD.) Modest increases in total sleep were comprised mostly of the increments in REM sleep.

Because the above study had been carried out in constant light to dampen circadian rhythms, and it was possible that the rebound patterns might have been peculiar to those conditions, three rats were subjected to DOW-TSD for 19, 20, and 21 days while on a conventional light-dark schedule.[27] The results were much the same, except that HS2 during recovery was not significantly different from baseline levels. A third study of recovery following 5 days of DOW-TSD showed a similar pattern of a large (but shorter lasting) REM sleep rebound with little or no NREM rebound.[32] Unfortunately, HS2 was not separately scored in this study.

In the current series, three sleep-deprivation studies were carried out with the DOW procedure to evaluate issues raised by the results reported above.

(1) Recovery from short-term TSD by either enforced locomotion or gentle handling has produced initial positive and subsequent negative rebounds of EEG slow-wave activity and amplitude. Recovery from long-term TSD by the DOW method has featured huge rebounds of REM sleep, but no increases and variable decreases in EEG amplitude. (Changes in slow-wave activity had not yet been evaluated.) Do the different rebound patterns result from the different lengths of deprivation or from the different methods of deprivation? This first study examines whether recovery from 24 hours of DOW-TSD produces positive and negative rebounds of slow-wave and/or high-amplitude activity like those which follow enforced locomotion and gentle handling. Different results by the DOW method would suggest that the absence of high-amplitude rebounds after chronic DOW-TSD derives from fundamental differences in the physiologic processes induced by the different techniques. On the other hand, similar results by the different methods would indicate that they produce fundamentally similar physiologic effects; ie, there is nothing anomalous about the physiological effects of DOW-TSD. These results would further imply that high-amplitude EEG activity is not a good indicator of the most intense sleep that would be expected during recovery from chronic TSD.

(2) An alternative interpretation would suggest that although the different rebounds from acute and chronic TSD studies might not have resulted from different deprivation procedures, they might have resulted from the severe debilitation of the chronic DOW-TSD rats, which were probably within a few days of death before recovery started. To evaluate this possibility, we examined the recovery of rats subjected to DOW-TSD for 4 days, well before they suffered severe debilitation. In this study, changes in NREM delta power were also evaluated to determine whether the rebound of this activity was also suspended following longer TSD regimes. As noted above, a previous study of 5 days of DOW-TSD[32] had produced rebounds similar to (but shorter-lasting than) those of the longer TSD studies, but the analysis of the 5-day study did not include delta activity in the recovery sleep.

(3) Because EEG slow-wave and high-amplitude activity are defining features of NREM sleep, it has been tacitly assumed that their rebounds from short-term TSD are compensatory primarily for lost NREM sleep. However, the rebounds might be partly responsive to lost REM sleep. Endo et al[4] showed that the addition of 4 hours of REM sleep deprivation to 12 hours of TSD produced further increases of slow-wave activity. To obtain a clearer picture of the contribution of REM sleep loss to rebounds that were uncomplicated by prior TSD, a third study examined recovery from 24 hours of DOW-REMD.

METHODS

Experimental and animal care procedures were approved by the University of Chicago Animal Care and Use committee.

Subjects and Experimental Groups

Rats were Sprague-Dawley males approximately 3.5-4.0 months old at surgery.

Experiment 1 (1-day TSD) used 11 TSD rats, and experiment 2 (4-day TSD) used 6 TSD rats. These two experiments did not use TSC rats because they sometimes lose considerable sleep in the first few days of a TSD experiment, and are therefore not very effective controls for short-term TSD studies. Experiment 3 (1 day REMD) used eight REMD rats and seven yoked-control (REMC) rats. (One REMC rat developed a respiratory infection early in the experiment and was not further studied.) Comparisons with yoked-control rats were appropriate because relatively few disk rotations are required to maintain 1 day of REM sleep deprivation, and the sleep of the REMC rats was not greatly different from baseline values. Comparisons between REMD and REMC rats are relevant to a recent claim that REM rebounds result largely from stress.[33] Two days of recovery sleep were recorded for experiments 1 and 3; 4 days of recovery were recorded in experiment 2.

Surgical and Experimental Procedures

Rats were implanted under pentobarbital anesthesia (55 mg/kg body weight) with electrodes to record the EEG and nuchal electromyogram (EMG) according to procedures previously described.[31] Following at least 1 week of post-operative recovery, rats were placed in the experimental chambers for approximately 1 week of adaptation. When recordings showed stable sleep stage scores for 3 days, that period was used as baseline, and deprivation was initiated. During the adaptation, baseline, and recovery periods, a removable floor was placed over the disks and the trays—ie, conditions were the same for the baseline vs recovery comparisons. Previous pilot studies had shown that the alternative procedure of maintaining rats on stationary disks over exposed trays of water during baseline and recovery produced essentially the same experimental results as when the disks were covered during those periods.

Previous studies have shown that circadian rhythms affect the timing of sleep rebounds, but not necessarily their cumulative amounts.[10,13] To minimize the complicating effects of circadian rhythm modulation on the progression of rebound effects over time, rats were maintained in constant light from the time of their arrival in the laboratory to the end of the experiment. Food and water were always available ad lib. Ambient temperature of the experimental chambers was maintained at 28-29°C.

Scoring of Sleep Data

Sleep stage scoring was done in 30-second epochs by an automatic system.[23] Briefly, wakefulness was defined conventionally by a low-amplitude EEG and relatively high-amplitude EMG, and REM sleep was defined conventionally by low-amplitude lateral EEG, low-amplitude EMG, and high-amplitude theta activity. As noted earlier, NREM sleep was divided into three substages, all with low EMG amplitude. Low-amplitude NREM sleep (LS) has a low amplitude EEG not different from waking or REM sleep, but it has a low-amplitude EMG that distinguishes it from waking and a low-amplitude theta that distinguishes it from REM. It is a transition stage which constitutes about 5% of total time. Except for some reduction early in recovery periods, it is not greatly affected by prior deprivation, and variations in LS do not seem to be important features of recovery sleep. Therefore, LS scores are not separately presented in the results but are included as part of total sleep. The major portion of NREM sleep is designated high-amplitude sleep (HS). HS1 is the fraction of HS with integrated EEG amplitude below the modal HS amplitude. HS2 is the fraction of HS with integrated EEG amplitude above the HS mode. Thus, amount of HS2 was the critical measure of NREM EEG amplitude in this study. To calculate changes in NREM EEG amplitude between baseline and recovery, the baseline HS mode was used to differentiate between HS1 and HS2 during recovery. Amount of slow-wave activity in NREM sleep was calculated from six 4-second 256-sample fast Fourier transforms per epoch as cumulative (1-4.75 Hz) power spectral density (NREM delta). The NREM delta data in experiment 1 are for 5 rats.

Statistical Evaluation

For most evaluations, baseline, deprivation, and recovery days were each divided into 6-hour blocks (starting at the same time each day), which was found convenient for depicting major trends across time in previous studies.[9,10] Most statistical evaluations were by paired (within subjects) *t* tests between baseline and recovery blocks; statistical significance was defined by $p<0.05$, two tailed. REMD vs REMC comparisons were by independent *t* test, ie, rats were not paired. Because of the constant light conditions, there were only minor diurnal variations in sleep stages in baseline days. The last 6-hour block of each baseline day in all three experiments showed less total sleep than the other three blocks, probably because cages were cleaned, rats were weighed, and food and water were replenished during that block. To avoid confounding this small but consistent effect with experimental changes, statistical comparisons across baseline, deprivation, and recovery were made on a block-by-block basis, eg, first blocks of a baseline days were compared with first blocks of deprivation and recovery days, etc. All variance indicators in the figures and text are for standard error of the mean.

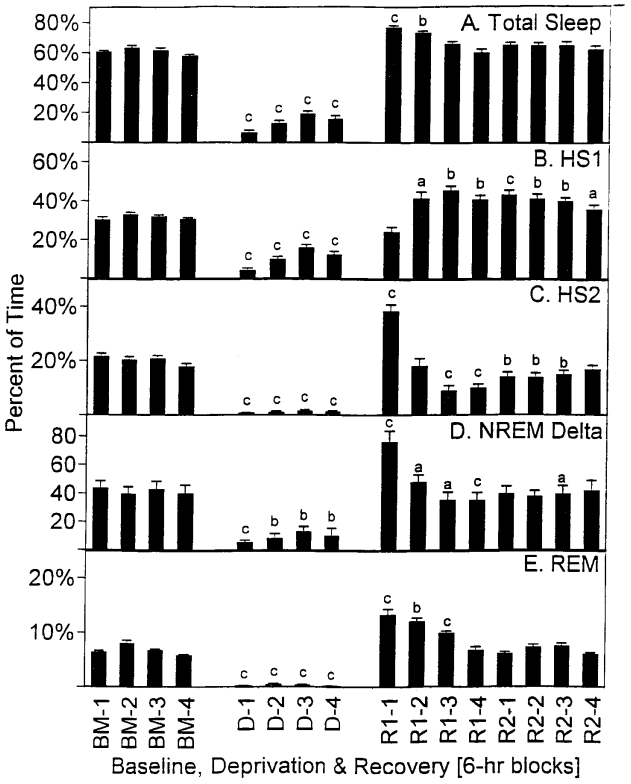

Figure 1.—Mean baseline (BM), 24 hours total sleep deprivation (D), and 2 days recovery (R1, R2), in four 6-hour blocks per day for A) Total sleep; B) High-voltage (below the baseline mode) NREM sleep (HS1); C) High-voltage (above the baseline mode) NREM sleep (HS2); D) Cumulative NREM delta spectral power; and E) REM sleep. All quantities are expressed as mean (n=11 rats) percentages of total time per block except NREM delta (n=5), whose units are proportional to volts^2-second. The letters above the bars indicate difference from the corresponding baseline block significant at ^{a}p<0.05, ^{b}p<0.01, or ^{c}p<0.001.

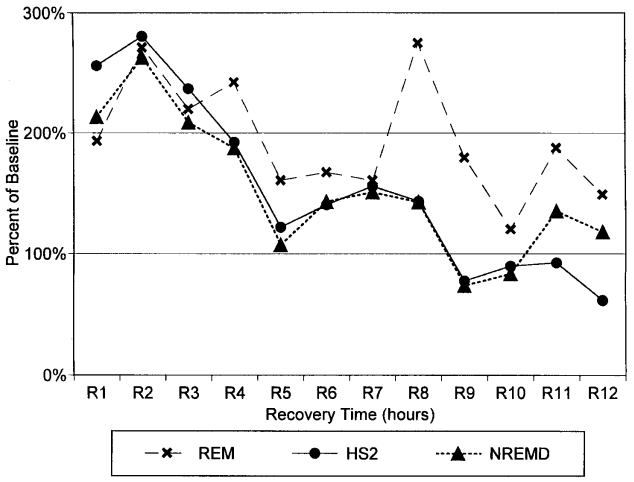

Figure 2.—Mean values for the first 12 hours of recovery (R1-R12) from 24 hours total sleep deprivation for REM sleep (n=11), HS2 n=11), and cumulative NREM delta power (NREMD) (n=5) expressed as a percentage of hourly baseline.

RESULTS

Experiment 1—1 day of TSD

Figure 1 shows that the deprivation procedure reduced all sleep measures to substantially below baseline. Of the 20 *t* test comparisons between the baseline and deprivation blocks (4 blocks × 5 parameters), 17 were significant at p<0.001, and 3 (the last three blocks of NREM delta) were significant at p<0.01. TSD was maintained by rotating the disk a mean of 20.5% of the day, which required the rat to walk a total of approximately 1.0 km during the day.

Recovery patterns resembled those of several rat studies following 24 hours of TSD by other methods. Total sleep modestly but significantly increased for the first two blocks of recovery, and then returned to baseline levels. As in the other studies, HS2 and NREM delta showed large, significant rebounds in the first recovery block, followed soon thereafter by more prolonged negative rebounds. The HS2 increment was primarily at the expense of HS1, which showed a mirror image pattern of a first block negative rebound (not significant) followed thereafter by a long-lasting and significant positive rebound. REM sleep showed the usual strong positive (significant) rebound, with a return to baseline by the last block of the first recovery day. Examination of the distribution of the lengths and intervals between REM epochs (not shown) revealed that REM episodes became both more frequent and longer than during baseline.

The above results can be most directly compared with those of a previous study from our laboratory,[10] which used enforced locomotion as the deprivation method, but was otherwise similar to the present study in several respects; TSD was for 24 hours; the same sleep stage scoring system was used; rats were of the same strain and approximate age; and circadian rhythms were eliminated (in the older study by lesioning the suprachiasmatic nuclei and maintaining the rats in constant dim light). Both studies showed modest total sleep rebounds which were of about the same magnitude, but lasted a bit longer in the earlier study. Both studies showed an approximate doubling of HS2 in the first recovery block, followed by a return to baseline in the second block, and then negative rebounds. Both studies showed a modest depression of HS1 in the first recovery block followed by modest elevations during most of the first 2 recovery days. In both studies, REM sleep was elevated in the first three recovery blocks and then returned to near baseline. For the first recovery day as a whole, REM sleep was 136% of baseline in the earlier study compared to 157% in the 24-hour DOW study; both values were clearly much lower than the corresponding value of 567% of baseline produced by 18-19 days of DOW-TSD.[26] Clearly, DOW-TSD per se does not produce five- to six-fold increases in REM sleep; increases in REM sleep following 24-hour DOW-TSD are much closer to the range of

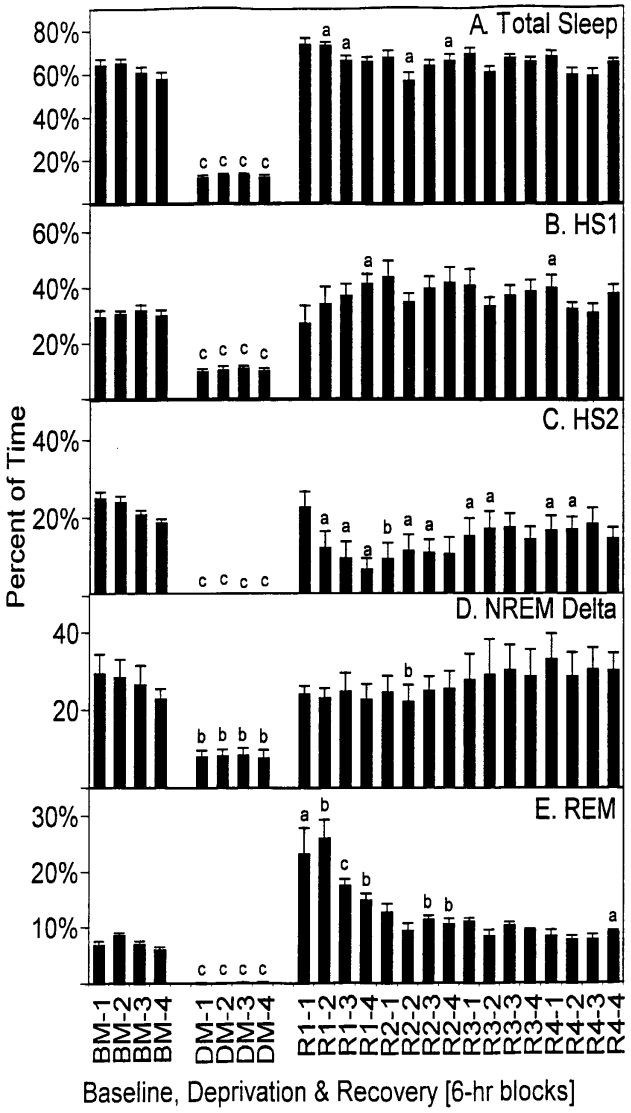

Figure 3.—Mean baseline (BM), 4-day mean sleep deprivation (DM), and 4 days recovery (R1-R4), in four 6-hour blocks per day for A) Total sleep; B) HS1; C) HS2; D) Cumulative NREM delta power; and E) REM sleep for six rats. All quantities are expressed as percentages of total time per block except NREM delta, whose units are proportional to volts^2-second. The letters above the bars indicate difference from the corresponding baseline block significant at $^a p<0.05$, $^b p<0.01$, or $^c p<0.001$.

increases in REM sleep that follow REMD by the other methods. The data as a whole are consistent with the conclusion that method of deprivation was not a major factor in determining recovery patterns.

Examination of hour by hour rebound patterns during the first two blocks of recovery (Fig. 2) revealed no contradictions to the patterns evident in the block-by-block analysis. HS2, NREM delta, and REM sleep were strongly enhanced during the first 4 hours of recovery and then began to drift toward baseline levels—a result of particular relevance (see Discussion) to the issue of possible interactions between the stages. Thereafter, the parameters followed different courses. REM sleep began to decline but continued solidly above baseline, whereas HS2 and NREM delta began to dip below baseline (the apparent beginning of the negative rebound). The strong correlation between the amplitude and slow-wave rebounds is evident from the fact that for most hourly blocks, HS2 and NREM delta showed similar percentage changes from baseline.

Experiment 2—4 days of TSD

The deprivation procedure was also very effective for the 4 day TSD procedure. As shown in Fig. 3, all sleep parameters were severely reduced; in all four blocks (each block represented the mean of four TSD days), the reduction from baseline was significant at $p<0.01$ for NREM delta and at $p<0.001$ for the other four parameters. The disk was rotated an average of 34.4% of the time, which required a total travel distance of approximately of 1.51 km/day. None of the rats appeared debilitated during or after the deprivation procedure. TSD rats that are deprived for 2 weeks or longer generally show yellowed and disheveled fur, severe ulcerative and hyperkeratotic lesions on the tail and paws, and some difficulty negotiating the disk rotation.[34] In contrast, the 4-day TSD rats appeared healthy, their coats were white and shiny, there were no pronounced lesions, and they could negotiate disk rotation with ease.

For the six rats as a whole, the rebound patterns looked much more like those following more prolonged TSD than those following 1 day of TSD. NREM delta showed no positive rebound. The only block that was significantly different in NREM delta from a corresponding baseline block was block 2 of recovery day 2, and in that comparison the recovery-day mean was lower than the baseline-day mean. HS2 block means during recovery never rose above corresponding baseline block means. In fact, HS2 showed a mostly negative rebound recovery pattern without having shown an initial positive rebound. After a near-baseline mean on the first recovery block, HS2 means fell significantly below baseline on the next six blocks. Overall, HS2 means were significantly below corresponding baseline means on 10 of 16 recovery blocks. REM sleep showed a strong and prolonged rebound. It was more than three times baseline amounts on the first two blocks of the first recovery day, more than double baseline amounts on the next two blocks, and was significantly above baseline on 7 of the 16 recovery blocks recorded. The REM rebound was clearly greater than that which followed one day of DOW-TSD, which, although substantial, never exceeded twice baseline amounts for any block. On the other hand, the REM rebound following 4 days of DOW-TSD remained less than following 18 or 19 days of TSD, when REM was more than five times baseline on the first recovery day and averaged about twice baseline levels over the next 2 weeks.[26] The combined data across the different studies strongly suggests that, in the rat, the strength and length of

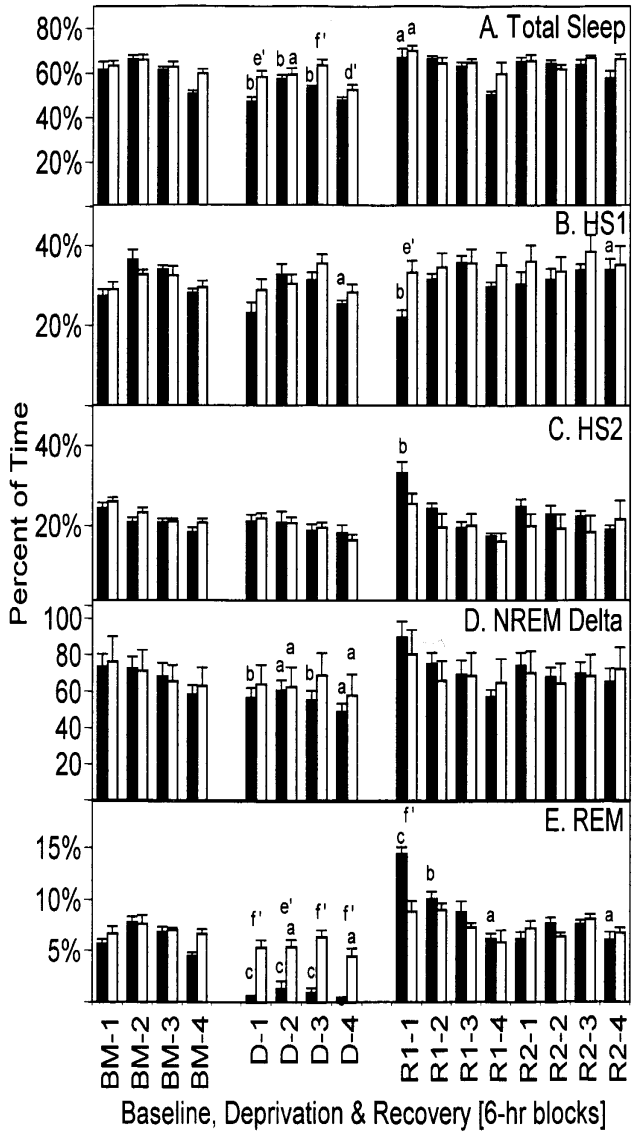

Figure 4.—Mean baseline (BM), 24-hour REM sleep deprivation (D), and 2 days recovery (R1, R2), in four 6-hour blocks per day for A) Total sleep, B) High-voltage (below the baseline mode) NREM sleep (HS1), C) High-voltage (above the baseline mode) NREM sleep (HS2), D) Cumulative NREM delta spectral power, and E) REM sleep for 8 rats (black bars) and 7 yoked controls (white bars). All quantities are expressed as percentages of total time per block except NREM delta, whose units are proportional to volts^2-second. The letters above the bars indicate difference from the corresponding baseline block significant at $^a p<0.05$, $^b p<0.01$, or $^c p<0.001$ or difference between groups at $^{d'} p<0.05$, $^{e'} p<0.01$, or $^{f'} p<0.001$.

REM rebounds is a monotonic function of the length of prior TSD.

The group data for the 4-day TSD study do not tell the whole story about rebound effects, because there was a striking individual difference. One of the six rats showed a rebound pattern that resembled that following 1 day of TSD. This rat showed slightly more than double baseline NREM delta activity on the first recovery block, followed by a return to near baseline. HS2 started recovery with slightly more than 150% of baseline, followed by a severe negative rebound. On the other hand, if the remaining five rats are considered separately, they showed moderate negative rebounds of slow-wave and high-amplitude activity on the very first block of recovery. Apparently, for most rats, as length of TSD increases, the propensity for initial positive rebounds of delta and high-amplitude activity decreases, but in some rats the shift from one rebound pattern to the other may be more gradual than in others.

It could be reasonably questioned whether the failure to show rebounds of NREM delta activity following long-term TSD might not result from such a strong increase in waking delta activity that total delta activity was not reduced during the deprivation period, thereby obviating the need for a delta rebound during recovery. However, total delta activity in all stages (mostly wakefulness) during deprivation was only 65.5% of total delta activity during baseline ($p<0.01$).

Experiment 3—1 day of REM sleep deprivation

The REM-sleep deprivation procedure was highly effective. On the deprivation day, mean REM sleep was reduced from baseline by 86.0%. (See Fig. 4.) The enforcement of REM deprivation required that the disk be rotated an average of only 1.68% of total time, which required rats to traverse a total distance of about 0.07 km for the day. In some respects, the REM deprivation was highly selective. Total sleep was slightly reduced from baseline, but most of this reduction could be attributed to the loss of REM sleep. There were no significant or substantial reductions in HS2. HS1 was significantly reduced below baseline for the block 4 mean, but the significance resulted from extremely small variances on both baseline and deprivation days rather than from substantial absolute differences. On the other, hand, NREM delta was significantly reduced from baseline on all four blocks of deprivation days; the overall percentage reduction of 17.6% from baseline was much less than the 86.0% reduction of REM sleep. Decreases in HASW activity during REM deprivation protocols have been reported previously; see 4 for references.

As expected, there was a strong rebound of REM sleep. It resembled in magnitude and duration the REM sleep rebound following 1 day of TSD. In both cases the first block of recovery showed roughly a doubling of baseline values, followed by declining rebounds over the next several blocks. The rebound was significant for three of the first four blocks compared to two of the first four blocks in the 1-day TSD study. The rebound in the REM deprivation study could not be attributed to the deprivation procedure per se. Although the yoked-control rats were subjected to the same disk rotations and enforced locomotion, and even though they showed small but significant decreases of REM sleep on two of the four blocks on the deprivation

day, they showed no significant rebounds of REM sleep. On the first recovery block, they had significantly less REM sleep than the REMD rats ($p<0.001$).

Curiously, although disruptions of total and NREM sleep were minimal, the initial rebound patterns of the other sleep parameters resembled in miniature the initial patterns following 1 day of DOW-TSD. Total sleep was significantly elevated on the first recovery block vs the first two recovery blocks in the TSD experiment; the differences in rebounds of total sleep in the two experiments were not nearly so great as the differences in total sleep during deprivation. Even though HS2 had shown no significant or substantial decline during deprivation, it showed a first-block rebound as it had following 1 day of DOW-TSD, but it differed from the TSD rebound in that it was smaller and there was no negative rebound. As in the TSD study, there was a first-block negative rebound of HS1, but there was no subsequent prolonged positive rebound as in the earlier study. As in the TSD study, there was a significant, albeit smaller, first-block rebound of NREM delta, but unlike the TSD study, there was no subsequent negative rebound.

DISCUSSION

The following discussions will range more broadly than specific comparisons across different lengths and methods of sleep deprivation to consideration of the deeper issues of how sleep deprivation and rebound studies bear upon concepts of sleep intensity and sleep function.

TSD by Different Methods

Clearly, rebounds from one day of DOW-TSD were similar to rebounds following one day of TSD by forced locomotion. Both methods produced large initial and subsequent negative slow-wave and amplitude rebounds, small rebounds of total sleep, and large rebounds of REM sleep. There is nothing anomalous about short-term DOW-TSD that precludes initial positive rebounds of EEG amplitude or slow waves. Why should these rebounds be absent after longer TSD when one would expect more-intense sleep? Do peculiarities of the DOW method emerge during sustained TSD that inhibit the expression of high-amplitude and slow waves? This possibility appears unlikely because nothing about the method changes as deprivation progresses. TSD rats do tend to enter the water pan under the disk more frequently in the late stages of deprivation, but such entrances are only partial and brief (total less than 5 minutes/day)[35] during a period corresponding to the 4-day TSD of experiment 2—when slow-wave and amplitude rebounds were already absent. Also, slow-wave and amplitude rebounds were absent during recovery periods when the rats were not exposed to pan water.

On the other hand, there are suggestions that even during rebounds from short-term TSD, the urgency for HASW activity may not be so great as one might expect of intense, need-fulfilling sleep:

(a) Negative rebounds of amplitude and slow-wave activity appear while continuing rebound processes are evident in other parameters. In experiment 1, significant negative rebounds of slow waves and amplitude appeared as early as block 3 of recovery, while there were very significant positive rebounds in REM sleep and HS1 (NREM sleep with EEG amplitude below the HS mode). In fact, there were significant positive HS1 rebounds in the last seven of the first eight recovery blocks, as compared to only one significant recovery block for HS2.

(b) Some short-term TSD studies have produced only negligible and short-lived rebounds of slow waves and/or amplitudes. Feinberg and Campbell[18] found that following 24 hours of TSD by hand deprivation, increases in slow-wave incidence and amplitude above baseline were statistically significant for only the first hour of the recovery period, and were not significant for either the initial 12-hour light period or the following 12-hour dark period of the first recovery day. Another hand-deprivation TSD study found significant positive rebounds in only the lowest (0.25-1.5 Hz) range.[16]

(c) The addition of 2 hours of selective deprivation of slow-wave activity following 24 hours of TSD by forced locomotion produced a smaller rebound of slow-wave activity (power density) than 24 hours of TSD alone.[11] The addition of 4 hours of selective slow-wave deprivation to 12 hours of TSD produced smaller initial rebounds of slow-wave activity (power density) than 12 hours or 16 hours of TSD alone.[4]

(d) In experiment 1 and other studies,[16,18] larger negative than positive rebounds produced net decreases of slow-wave activity and/or amplitude during recovery compared to baseline.

Physiologic Recovery from TSD

If, as our analysis has indicated, the absence of slow-wave and amplitude rebounds from extended TSD is not an artifact of the deprivation method, and if, as shown in experiment 2, the absence does not result from TSD-induced debilitation, then HASW EEG activity has limited generality as an indicator of recovery processes in the rat. Certainly, physiologic recovery from chronic TSD does take place in the absence of a high-amplitude rebound. Rats subjected to DOW-TSD for 18 or 19 days developed a debilitated appearance, decreases in intraperitoneal temperature, increases in energy expenditure, increases in circulating epinephrine and norepinephrine, decreases in circulating thyroxine, and distinctive ulcerative and hyperkeratotic skin lesions on the tail and plantar surfaces—all of which returned to near baseline during the recovery peri-

od.[26] In another long-term study, which subjected rats to DOW-TSD for 19-21 days,[27] hormonal variables were not measured, but—as in the previous study—changes in appearance, skin condition, energy expenditure, and temperature developed during deprivation and returned to near baseline during recovery. In fact, on the basis of results in these and other TSD studies (summarized in 34), these rats would almost certainly have died within a few days had recovery not begun when it did. Rebounds of EEG amplitude did not occur during these recovery processes. Although slow-wave activity was not specifically measured in these recovery studies, given the failure of slow-wave rebound after 4 days of DOW-TSD in experiment 2, it is likely that slow-wave activity also does not rebound during these recovery periods.

Comparison of REM and NREM Rebounds

The absence of amplitude (and probably slow-wave) rebound during recovery from chronic TSD gives reason to question whether the slow-wave and high-amplitude rebounds from short-term TSD represent a recovery process. In the chronic TSD situation, there is evidence of an abnormal physiologic condition that is corrected during recovery, but there is no comparable evidence for the short-term situation. The ubiquity of slow-wave and amplitude rebounds from short-term TSD has lulled many into believing that some critical recovery process must be associated with those rebounds, but we are not aware of any evidence that a deprivation-induced abnormality is reversed in association with a rebound of high-amplitude or slow-wave activity in the rat. Sleepiness may be reversed during recovery from even short-term TSD, but is not clear that this reversal requires rebounds of slow waves or high amplitudes. The release of human growth hormone during high-amplitude, slow-wave sleep[36] suggests a physiologic function for that stage. However, one review indicates that the relationship between slow-wave sleep and growth hormone release has been overemphasized,[37] and one experiment has indicated that the hormone release may be more closely associated with sleep onset than with the slow-wave stage.[38] Furthermore, it is not entirely clear what the function of the nocturnal growth hormone release might be,[39] or whether that function is compensatory to sleep loss.

REM sleep may be a better indicator of recovery processes in the rat than EEG slow waves or high amplitudes. In contrast to the occasionally weak slow-wave and amplitude rebounds in some short-term TSD studies, REM rebounds have been substantial in all 24-hour TSD studies of rats. (REM rebounds have been absent after some shorter TSD regimes,[8,12,15] but physiologic deficits may not result from very short deprivation periods. From a functional perspective, the failure of amplitude and slow-wave rebounds following extended TSD is more important than the failure of REM sleep to rebound following very short TSD periods.) In contrast to the negative amplitude and slow-wave rebounds, REM sleep has not shown negative rebounds, and, as noted above, has remained above baseline during negative slow-wave and amplitude rebounds. In contrast to the absence of positive slow-wave and amplitude rebounds in most rats after 4 days or longer of TSD, REM sleep has shown very large and sustained rebounds. Physiologic recovery from chronic TSD has been accompanied by huge and prolonged increases in REM sleep. Of course, this correlation does not prove that REM sleep was causal to the recovery process, but it makes such a relationship much more plausible than a restitutive role for slow-wave or high-amplitude sleep.

Across-stage Rebound Substitutions

There is little doubt that REM sleep per se is functionally important. Rats subjected to relatively selective REM sleep deprivation by the DOW method die after about 5 weeks.[40] In rats subjected to DOW-TSD, REM sleep was reduced to a mean of 0.2% of total time; nevertheless, even within this very restricted range, the rats with the most REM sleep survived the longest.[30] The issue before us now is whether REM sleep can also serve functions fulfilled by NREM sleep. The obvious physiologic differences between NREM and REM sleep, the relatively selective rebound of REM sleep following selective REM sleep deprivation, and the relatively selective rebound of HASW sleep following its selective deprivation,[41] have contributed to an implicit but widely held assumption that REM sleep rebounds in response to prior REM loss, and NREM sleep rebounds in response to prior NREM loss. In fact, simultaneous positive rebounds of REM sleep and negative rebounds of NREM sleep have been explained as inhibitions of NREM rebounds by REM rebounds,[4,15,18] although—as shown in Fig. 2—it is clear that at the very start of recovery large positive rebounds of REM sleep, high-amplitude EEG, and NREM delta may all occur simultaneously.

The current results suggest another possibility—that rather than inhibiting NREM sleep or its substages, REM rebounds may be substituting for NREM rebounds. During the recovery from 4 days of TSD (experiment 2), there was only a marginal increase in total sleep, which resulted almost entirely from the very large increase in REM sleep. Delta power was hardly changed, while HS2 mostly decreased. In fact, during the recovery period as a whole, there was a net loss of high EEG amplitude sleep. NREM sleep as a whole was decreased, albeit nonsignificantly; the baseline mean was 54.7% of total time compared to a recovery mean of 50.3% ($p=0.15$). Similarly, during recovery from both of the longer (18-19 day[26] and 19-21 day[27]) DOW-TSD studies, the very small increases in total sleep

were entirely attributable to the increases in REM sleep, which were huge and persisted for weeks in some cases. There was no rebound of HS2 and no net increase in NREM sleep compared to baseline. In effect, the only net positive rebounds were of REM sleep. We are forced to conclude that in rats subjected to chronic TSD, either there is no homeostatic compensation for lost NREM sleep, or that rebounds of REM sleep compensate for lost NREM sleep. There is even some suggestion that NREM sleep may occasionally substitute for lost REM sleep. In experiment 3 (1 day of REM deprivation), although there was no significant loss of HS2, it showed an initial positive rebound during recovery.

The idea that REM sleep may in part compensate for NREM loss is not without contrary indications. Experiment 1 entailed both REM and NREM loss, whereas experiment 3 entailed severe REM loss and only very modest NREM loss (significant but modest declines of NREM delta). REM rebounds were similar in the two experiments, even though NREM loss was much greater in experiment 1. This contrary evidence notwithstanding, the positive evidence for rebound substitutions across stages should at least prod a curiosity about physiologic similarities across stages which could underlie functional communalities. For example, it has long been known that neocortical, thalamic, and brainstem neurons tend to fire in a burst-pause pattern during NREM sleep, and that this pattern is further exaggerated during REM sleep.[42-44] Could the burst-pause pattern serve a function in NREM sleep that is served even better in REM sleep? Monoaminergic neurons of the dorsal raphe[45] and locus coeruleus nuclei[46,47] reduce their firing rates during NREM sleep and then become almost silent during REM sleep. Could this reflect the progressive intensification of functional change? The examination of NREM and REM similarities deserves more attention.

Negative Rebounds

Cross-stage rebound substitutions provide a possible explanation of slow-wave and amplitude-negative rebounds that is more harmonious with previous and current rebound data than some proposed earlier. One hypothesis viewed the negative rebounds as a reaction to the initial positive rebound in sleep duration,[13,16] but does not explain why should there be a negative rebound to a homeostatic process. One of the present authors (AR) previously suggested that while sleep satisfied certain needs, it might also augment processes or substances which militate for its termination, and that the "sleep inhibition" accumulated during early postdeprivation rebounds might produce the later negative rebounds.[9] Feinberg and Campbell[18] argued that "sleep inhibition" could not plausibly explain the strong negative rebounds they observed following only "near-trivial" initial increases in delta activity. To that legitimate objection we can now add the observation that in experiment 2 there was a very pronounced and prolonged negative rebound of HS2, even though there had been no earlier positive rebound of HS2, NREM delta, or total NREM sleep.

A different explanation attributed the negative slow-wave and amplitude rebounds to increases in REM sleep. Feinberg and Campbell studied rebounds of slow-wave activity (incidence and amplitude) following 24 hours of hand deprivation; baseline and 2-day recovery periods were each on a 12 hours light-12 hours dark schedule, with recovery starting at the beginning of a light period. As noted earlier, positive slow-wave rebounds were limited mostly to the first hour of recovery. Negative rebounds started near the beginning of the first dark period and were manifested by failures of slow-wave activity to rise to baseline levels. Feinberg and Campbell theorized that although NREM sleep could increase only minimally in the initial light period because it was already at near-ceiling levels, REM sleep could rise during this period to abnormally high, "pathological" levels that "in some way 'deplete' the systems that generate delta" and render them less capable of responding to darkness with increased slow-wave amplitude and incidence.

Several features of this explanation invite a different perspective. First, the appearance of negative rebounds does not require the same juxtapositions of light and dark periods and rebound events that Feinberg and Campbell described. The first study to describe negative rebounds also used a 12-12 light-dark schedule, but a significant negative rebound did not appear until the light period of the second recovery day.[9] In another study with the same light-dark schedule, a significant negative rebound was apparent during the last 2 hours of the initial light period.[16] Negative rebounds have also appeared in rats maintained in continuous darkness[13] and, in the present study, in rats maintained in constant light. Thus, negative rebounds appear under a wide range of recovery conditions.

More to the point of the role of REM sleep in rebound dynamics, we can examine the Feinberg and Campbell recovery data to determine what in fact does rebound from the previous 24 hours of TSD. Although there were significant rebounds of NREM sleep over baseline in the dark periods of both recovery days, because dark period values are low, the net increment over baseline was not very great. Total NREM sleep was increased over baseline by only 16.1% on the first recovery day and by 15.3% on the second recovery day. On the first recovery day, REM sleep was increased by 112.9% over baseline; figuratively speaking, the REM debt was oversubscribed. On the second recovery day, REM sleep was essentially at the baseline level. Total sleep was increased over baseline by 28.1% on

the first recovery day, but most of the increase resulted from the large increase in REM sleep. Without the REM rebound (increase over baseline amount), total sleep was increased by only 14.1% on the first recovery day. On the second recovery day, when there was no REM rebound, the increase in total sleep over baseline was only 12.1%. Of 20 different comparisons between baseline and recovery on measures of slow-wave incidence and amplitude (5 measures × 2 recovery days × light or dark period), 5 showed a significant net reduction from baseline and 1 (total time in slow-wave band during the dark period of recovery day 2) showed a significant net recovery. (The increased time in the slow-wave band was associated with an increase in NREM sleep during that period; time in band per minute hardly changed from baseline.) The only substantial positive rebounds were in REM sleep. If we accept the Feinberg and Campbell interpretation that the massive REM sleep rebound was a "pathological" release phenomenon, and if we believe that it was not functionally related to the loss of NREM sleep, then we are left with the conclusion that, except for specific REM sleep compensations for specific REM sleep losses, there was little or no substantial homeostatic process during the 2 recovery days.

Thus, an analysis of negative rebounds leads to the same conclusion derived from analysis of rebounds from long-term TSD. If one were to insist that HASW activity is the major vehicle for recovery from total or NREM sleep loss in the rat, then one would be left with the somewhat peculiar theory that this potential homeostatic thrust is regularly thwarted by another, more ubiquitous and sustained process—ie, REM sleep. An alternative, parsimonious interpretation proposes that REM sleep serves a homeostatic function in the regulation of total sleep, including both REM and NREM sleep, thereby permitting it to contribute to the compensation for lost NREM sleep. Compensations for lost sleep may continue during negative rebounds of HASW activity in the form of strong REM sleep rebounds.

Interactions Between NREM and REM Sleep Recovery Processes

If REM and NREM sleep are partly interchangeable in the fulfillment of sleep needs, what determines their juxtaposition during recovery sleep? More specifically, what determines the initial occurrence of HASW sleep at the start of recovery from short-term TSD, the subsequent negative rebound, the early and continued occurrence of REM sleep, and the absence of HASW rebounds during recovery when the TSD period is extended to as little as 4 days? One speculative possibility is that HASW sleep may serve less-essential functions than REM sleep or serve similar functions less efficiently. (Infants, older people, and insomniac patients on certain hypnotic medications seem to survive with little or no HASW sleep.) It might serve primarily as a precursor or primer for the more-important or more-efficient REM sleep. When the need for sleep becomes sufficiently great, such as following more extended TSD, the primer phase may be only briefly expressed or preempted as the animal races to the more important REM sleep. Countering this possibility is evidence of the essential importance of high-amplitude NREM sleep in rats. Relatively selective deprivation of HS2 by the DOW method produced death within 23 to 66 days[48] (although an interaction with an inevitably large REM sleep reduction could not be ruled out as a cause of death). Even during periods of huge REM sleep rebounds, there is continued alternation of REM and low-EEG-amplitude NREM sleep, suggesting either a continuing need or REM-priming function for the latter.

We will probably not understand sleep stage priorities during recovery until we understand the mechanics and functions of sleep stage alternation per se. Whatever the answer, it is likely that the selective loss of HASW sleep during recovery from extended TSD and the selective negative rebounds of this activity during recovery from short-term TSD are based on similar mechanisms.

The Benington-Heller Hypothesis

Based largely on the usual appearance of REM sleep episodes after NREM sleep and the correlation between NREM sleep accumulation and the occurrence of REM sleep, Benington and Heller[49] proposed that the function of REM sleep is to reverse some unspecified consequence of the neural activity of NREM sleep. In addition to criticisms of their theory recently expressed in another paper,[50] reservations arise from the rat TSD studies. According to the Benington-Heller model, REM sleep should occur in proportion to prior NREM sleep. In experiment 2 (4 days of TSD), there are large rebounds of REM sleep throughout the first day of recovery while HS1 and NREM delta remain near baseline and HS2 is mostly far below baseline. According to the model, without prior NREM sleep there should be no stimulus for REM sleep. Why then should rats show large REM rebounds after TSD? Benington and Heller argued that increased sleepiness during TSD could provide the same neural substrate for REM sleep as full-blown behavioral and electrophysiological NREM sleep. However, if this were the case, why should rats subjected to chronic DOW-TSD die? One would have to respond that sleepiness was sufficiently NREM-like to stimulate REM sleep, but not sufficiently NREM-like to prevent death—a response without independent empirical support or rational appeal.

Another approach to the issue is to determine whether measurable NREM-like physiological activity during TSD impacts on subsequent recovery sleep. On this score, the

evidence is somewhat mixed. Higher EEG amplitudes and increased hippocampal spike activity are both features of NREM sleep. One study reported increases in EEG amplitude and hippocampal spiking during wake periods of 1 day of TSD, but these increases were not significantly correlated with increases in total sleep or HS2 during recovery,[9]—ie, there was no evidence that the sleep-like activity during deprivation was sufficient to impact on subsequent recovery. (Unfortunately, the relationship between the waking activity and the REM rebound was not examined.) In a personal communication, Benington suggested that when rats are subjected to TSD by a constant-rotation device, rats deprived at slower rotation rates should have more opportunity for NREM-like neural activity during wakefulness than rats deprived at faster rotation rates. In one study, 14 rats were subjected to 4 hours of TSD at two rotation rates, with one 12 times faster than the other. Rats deprived at the faster rate had greater slow-wave rebounds, suggesting that they may indeed have had less slow-wave activity during the deprivation period. However, contrary to the Benington prediction, REM sleep rebounds were very similar in the two groups.

Some of the results of the current series seem favorable to the idea that delta activity during the deprivation period might serve as a substrate for subsequent REM sleep rebounds. Delta power during the deprivation period was correlated with amount of REM sleep during the first recovery day for experiment 1 ($r=0.79$, $p=0.09$) and experiment 2 ($r=0.90$, $p=0.01$). These relationships are certainly compatible with an effect of prior NREM-like neural activity during wakefulness on subsequent REM sleep, but the nature of the effect is not entirely clear. On the other hand, that the large REM sleep rebounds of the present series did not depend upon accumulated NREM-like activity is indicated by the fact that NREM sleep, HS2, and NREM delta were all severely reduced during the deprivation period of experiment 1 (1 day of TSD) and only slightly reduced during the deprivation period of experiment 3 (1 day of REM sleep deprivation), yet the REM rebounds were similar in the two studies.

The above results suggest that although NREM-like activity during the deprivation period can be associated with greater REM rebounds, similar REM rebounds can occur following little or near-normal NREM and delta activity during deprivation. The apparent paradox might be resolved if we view NREM-like activity as sort of a primer for REM rebounds which are primarily reactive to lost sleep. In other words, once the need for REM sleep is generated by prior sleep loss, then a small amount NREM-like activity generated during the period of sleep loss may act as a trigger for large amounts of REM sleep which are determined by REM deficits during the deprivation period. This interpretation is similar to a model in which REM sleep occurrence is determined by both the need for REM sleep and by the REM sleep-priming action of NREM sleep.[51] The model is consistent with the facts that even when a large REM debt has accumulated, short episodes of NREM sleep usually precede the much larger REM sleep rebounds, and that even huge REM sleep rebounds are usually interrupted by short intervals of NREM sleep.

An alternative interpretation of the apparent paradox is that NREM sleep is indeed the substrate for REM sleep and that NREM-like EEG activity during the deprivation period indicates the accumulation of this substrate, which would account for the high correlations between delta power during the deprivation period and the subsequent large REM sleep rebounds. The total accumulation of delta power during deprivation might be less than normally occurs during normal ad lib NREM sleep and still produce a large REM sleep rebound because it signals a particularly intense form of substrate accumulation. However, acceptance of this argument is tantamount to surrendering the core idea that NREM-like EEG activity quantitatively represents the accumulation of the REM sleep substrate, because the rate of substrate accumulation per unit of NREM-like EEG activity would be variable. Inference of the rate from the magnitude of subsequent REM sleep rebound would amount to a mere tautological argument for the theory.

The Roles of Stress and Physical Fatigue

To what extent are recovery sleep patterns determined by nonspecific stress and/or physical fatigue induced by the sleep deprivation procedure rather than by the sleep loss? Obviously, rebounds from sleep deprivation might be affected by stress induced by the deprivation procedure as well as by sleep loss per se. The literature on stress effects on rat sleep is not very helpful in evaluating this issue because results have varied—as might be expected from the variety of stimuli that have been used as stress-inducers. A provocative study by Rampin et al[33] reported a significant increase in REM sleep during the 12-hour period following 2 hours of immobilization stress, and suggested that the stress of deprivation procedures might be a significant source of REM sleep rebound in all sleep-deprivation studies. Another short-term (1 hour) immobilization study produced an increase in REM sleep during the dark phase of the diurnal cycle,[52] but only the rats with the lowest control values of REM sleep showed this increase—a result which might simply reflect regression to the mean.

Other stress-sleep studies in rats have reported opposite effects or no effect at all. An earlier study had shown that following 5 hours of immobilization stress and TSD, the REM sleep rebound was reduced for 6 hours relative to controls with TSD alone.[53] Rampin et al speculated that the REM sleep rebound might have been reduced in the earlier study by the very brief period of ether anesthetization

required to place the animals in restraint. However, this possibility is virtually nil. Another study[54] reported that deep ether anesthesia for as long as 15 minutes reduced REM sleep rebounds by less than 25% from control values and for only a few hours; during the second 6-hour block of recovery, REM sleep was slightly greater than in nonanesthetized controls. Ether anesthetization for 3 hours had only a slightly stronger REM-suppressing effect.

Inescapable electric foot-shock presented intermittently throughout the day reduced total and REM sleep significantly on the first of 14 stress days, but not thereafter.[55] The spontaneous sleep-wakefulness patterns of rats which received foot shocks during short daily sessions were not different from those of controls.[56]

This mixed bag of results is hardly convincing evidence that increases in REM sleep following TSD resulted from stress induced by the deprivation procedures. Even the earliest REM-sleep deprivation studies of humans indicated that REM-sleep rebounds did not depend upon stress induction. In the very first REM-sleep deprivation study,[57] Dement demonstrated significant REM sleep rebounds after repeated awakenings at the beginning of REM periods, but not after strictly controlled awakenings during NREM sleep. Shortly after that, Rechtschaffen and Maron showed that REM sleep rebounds occurred following drug-induced REM sleep reduction.[58]

The social stress of introducing male rats to the cages of aggressive male conspecifics did not significantly affect amount of subsequent NREM or REM sleep, but it did produce a large increase in slow-wave activity (spectral power).[59] Since this study used a very specific stress stimulus, it is not clear whether the stress of TSD procedures might contribute to subsequent slow-wave rebounds.

Because their hand deprivation 24-hour TSD study and another by Franken et al[16] produced smaller slow-wave rebounds than TSD by enforced locomotion, Feinberg and Campbell[18] questioned whether physical activity and/or emotional stress induced by enforced locomotion might not have contributed to the rebounds in those studies. There is little doubt that hand deprivation involves less locomotion for the rat than the enforced locomotion deprivation procedure, so the issue they raise with respects to the effects of physical activity is well taken and will be discussed at greater length below. However, the relevance of the hand deprivation results to the role of stress in rebound effects is more problematic because the widely held assumption that sleep deprivation by so-called "gentle handling" is without stress may not be fully warranted.

First, we know of no reports which have described the frequency of stimulation. Second, the variety of stimuli used have not been well described. Feinberg and Campbell[18] reported only that rats were "picked up and fondled." Franken et al[16] reported that "rats were given objects to play with and activated by acoustic and if necessary tactile stimuli." Some studies[15,33] reported only that rats were deprived by "gentle handling," with no further elaboration. Third, as noted earlier, attempts at maintaining long-term TSD by hand deprivation revealed a growing resistance to the stimulation—to the point that immersion in shallow water had to be used to maintain wakefulness.[29] We know of no accounting of how resistance to arousal may have developed even in short-term hand deprivation.

In our own efforts at hand deprivation, it often seemed that after several hours the need to stimulate the rats became almost incessant, and they became agitated and irritated at almost any intrusion. Although these observations may be little more than anthropomorphic inferences, they are no more prejudicial than the implied suggestion that all of the many "gentle" stimuli delivered to the rats are cheerfully accepted.

The empirical data on how much emotional stress may be induced by hand deprivation procedures are not conclusive. Twenty-five years ago we gave up on hand deprivation as a neutral TSD procedure, after observing that 24 hours of it produced significant increases in brain 5-hydroxyindoleacetic acid (5-HIAA), then widely considered as a stress indicator (unpublished observations). Very recently, small but statistically significant increases in 5-HIAA concentrations in several brain regions were reported following 3, 6, or 12 hours of TSD by "gentle handling."[60] Our own examination of the data showed no increasing trend of higher concentrations with increasing sleep deprivation, suggesting that the 5-HIAA levels might reflect a continuing response to the handling procedure rather than to the sleep loss. In support of the sleep-loss interpretation, the authors cited another study,[61] which showed that various forms of stress increased regional brain 5-HIAA concentrations as determined by in vivo voltametry, but "gentle handling" alone did not. However, in the cited study, "gentle handling" was applied only for 10 minutes, and even then there were clear, although not statistically significant, trends toward higher brain 5-HIAA during and following the handling procedure than in control rats. (We suspect that the failure of significance resulted from the pooling of determinations across time in each group. In fact, in 36 determinations made at 5-minute intervals after the handling procedure, the handled rats always showed higher 5HIAA than control rats.) Another recent study reported that TSD by "gentle handling" produced greater increases in brain c-fos mRNA, an indicator of brain activation, than sleep deprivation by intermittently enforced locomotion by the DOW method.[62] However, others have suggested that stress and sleep loss increase c-fos in different brain areas.[63]

Murison et al[64] evaluated the effects of 24 hours of hand deprivation on conventional stress indicators in six

40-hour-food-deprived rats. Only one of the sleep-deprived and none of the six normally sleeping rats developed stomach erosions. On the other hand, plasma corticosterone levels were almost twice as great in the deprived rats as in the control rats, but the means were not significantly different, probably because of the small samples and a huge (significant) increase in the variance of the handled rats (which in itself suggests a large stress effect in at least some of these rats). A study of plasma corticosterone levels in rats subjected to TSD by enforced locomotion showed percentage increases over control rats of similar magnitude as the increases following TSD by "gentle handling."[65] On the whole, there does not appear to be strong, convincing evidence that stress-free TSD can be reliably produced by hand deprivation, or that the induced stress is significantly less than any produced by forced locomotion. Plodding along in a slowly rotating cylinder may be no more emotionally stressful to a rat than an array of varied sensory stimuli, all of which frustrate the impulse to sleep.

The DOW method presents advantages in controlling for method-induced stress. First, the physical stimulus is benign. The disk is rotated only when the experimental rat enters a "forbidden stage" (NREM or REM sleep in TSD experiments, or REM sleep in REM deprivation experiments); it typically awakens the rat when rotation starts or a few seconds later, and is maintained only until the rat has been out of the forbidden state for 6 seconds. Except for experiments in which deprivation is maintained until the rats are near death, the slow rotation rate of 3.33 rpm is easily negotiated by the rats; they need walk at only a moderate rate to avoid being carried into the water. (Because the inner cage wall is less than halfway across the disk, movement of the disk produces forces both perpendicular and parallel to the wall when the rat comes in contact with it. The parallel force pushes the rat toward the disk edge.) The rats are not, as has been described in some reports, spun at a high rate and dashed into the water; such reports are entirely the construction of the writer's imagination.

An even greater advantage of the DOW method is that the effects of the deprivation method are controlled for by the use of a yoked-control rat which receives almost the exact physical stimulation as does the deprived rat. Thus, whatever stress is induced by the deprivation method per se should be equally experienced by the deprived and control rats, and should equally affect their sleep patterns during recovery periods. In experiment 3, REM-deprived and control rats were subjected to equivalent disk rotations, yet the deprived rats had large and significant REM sleep rebounds, while the control rats did not. In an earlier study of rats subjected to 19-21 days of DOW-TSD,[27] even though the control rats suffered a partial loss of REM sleep during the deprivation period, their REM sleep during the recovery period was not significantly greater than during baseline. In contrast, REM sleep of the deprived rats during the first recovery day was significantly greater than during baseline and more than double the level of control rats. Over the next 12 days, REM sleep in control rats returned to near baseline, while deprived rats showed significantly elevated REM sleep levels which averaged 79% above baseline. Clearly, the huge rebounds of REM sleep did not result from the specific deprivation procedure.

There have been arguments for and against a confound between sleep loss and the motor fatigue by enforced locomotion. Against the motor fatigue factor have been reports of little difference in rebound effects following sleep deprivation at two different speeds. Friedman, Bergmann, and Rechtschaffen[9] found little difference in post-TSD rebounds after walking speeds of 0.34 and 1.03 km/day, and Borbély and Neuhaus[11] reported little difference after walking speeds of 1.81 and 3.62 km/day (our calculations). On the other hand, Mistlberger, Bergmann, and Rechtschaffen[14] found that the number of EEG slow waves, but not EEG amplitude, was greater during rebounds after deprivation at 1.76 km/day than after 0.15 km/day. Franken et al[16] and Feinberg and Campbell[18] reported that TSD by hand deprivation produced smaller rebounds of slow-wave activity and EEG amplitude than the forced locomotion procedures. A fair integration of the above results might be that forced locomotion, even at very slow rates, induces some increment in slow-wave activity independent of sleep loss, or that some threshold level of motor activity is necessary to prevent the accumulation of slow-wave activity during the deprivation period. However, small increments above those speeds seem to have little further effect. None of the locomotor speeds cited above can be considered exhausting, since rats provided with an exercise wheel voluntarily ran 3.0 km/day without a significant increase in daily slow-wave activity,[28] implying that the increased slow-wave activity in the TSD studies did not result from the enforced motor activity alone. (Studies of sleep deprivation by enforced locomotion might do well to permit voluntary locomotion in the control condition.) REM sleep was associated with reduced voluntary motor activity, indicating that rebounds of REM sleep following TSD by enforced locomotion also do not result from prior motor activity per se.

Comparisons with Other Species

The present results show that in contrast to the rebounds of HASW activity and REM sleep which follow short-term (24 hour or less) TSD in the rat, rebounds from longer-term TSD show mostly large, prolonged rebounds of REM sleep. Is there a comparable shift in other species? There are few animal studies with more than 1 day of TSD and rebound data. In one unique study, cats were kept awake for 5 to 7 days by electrically stimulating the midbrain reticular formation either continuously or contingent

upon EEG signs of NREM sleep.[66] The continuous method produced a mean first recovery day rebound of 38.6% for NREM sleep (which was not further differentiated by EEG frequency or amplitude) and 116.2% for REM sleep. The contingent method produced corresponding values of 11.6% for NREM sleep and 181.8% for REM sleep. Even if HASW activity had been differentially favored in the NREM rebound, the total NREM rebound of NREM sleep was so limited that HASW rebounds could not have been very great. These results appear to favor a priority for REM sleep rebound following extended TSD in the cat. It is possible that the postdeprivation increment of REM sleep did not result as a homeostatic rebound, but only as a result of prolonged electrical stimulation of the brainstem. This alternative appears unlikely, however, because another cat study of 3 days of TSD by very gentle "natural" stimuli—eg, feeding the cat or bringing it into a new environment—also produced very large rebounds of REM sleep (initially at about 300% of control values), while the proportion of NREM sleep was reduced from baseline.[67]

Other cat TSD studies have limited the amount of daily sleep and noted the distribution of sleep stages when sleep was permitted. In one large-scale early study,[68] the proportion of REM sleep increased as a function of sleep restriction, while the proportion of NREM sleep decreased. The authors acknowledged that the residual NREM sleep might have special restorative quality, but with NREM sleep severely reduced in the most stringent deprivation schedule, it was again difficult to believe that an increase in the quality of that sleep could have had a very major restitutive effect. Their own results and the absence of NREM rebounds in other TSD studies led the authors to question the functional necessity of NREM sleep. Two other short-term cat TSD studies separated "light" and "deep" (HASW) NREM sleep. In one,[5] both 12-hour and 24-hour TSD produced rebounds of both HASW and REM sleep, but not of "light" NREM sleep. In the second study, mean percentage of REM sleep increased significantly as available sleep time was limited, but HASW sleep did not.[69] Taken together, the cat TSD studies, like the rat TSD studies, indicate that even that even though HASW sleep may rebound following short-term TSD in some studies, there is also a rebound of REM sleep, which predominates in recovery from longer TSD regimes.

To the best of our knowledge, TSD studies in other animal species have all been short-term, and have generally shown rebounds of both HASW and REM sleep in various juxtapositions. For example, dogs subjected to 12-hour TSD showed an initial rebound of HASW sleep followed by a rebound of REM sleep during the 24-hour recovery period.[6] Rabbits subjected to 24-hour TSD also showed immediate, simultaneous rebounds of both HASW activity and REM sleep.[7] Similar to the rat studies, TSD of rabbits of only 4 hours produced only rebounds of HASW activity but not of REM sleep.[70] On the other hand, a review of relevant studies by Opp et al[70] indicated that after TSD, rabbits show peak increases in slow-wave spectral power of only 10% to 32% above baseline compared with peak increases of 80% to 250% in the rat. In fact, the rabbits subjected to 24-hour TSD[7] showed peak increases of only about 20% over baseline during the first 12 hours of recovery (corresponding to the light period), while REM sleep was 62% above baseline during the same period. Evidently there are species differences in which kind of sleep dominates the recovery period for a particular TSD duration.

Most TSD studies have been conducted on rats and humans. All short-term (less than 2 days) studies in humans have shown rebound priorities for HASW sleep (as reflected in sleep stage scores and/or computer analysis), with only modest increases or decreases or no change in REM sleep, eg refs. 2, 71-73.

Based on the short-term human TSD studies, the priority for HASW sleep over REM sleep may appear much greater in humans than in rats, and it has been suggested that HASW and REM sleep might perform different physiological functions in rat and man.[18] However, meaningful comparisons of recovery functions across species should start from comparable levels of need; the chronological duration of sleep deprivation is probably not a very precise indicator of sleep need. Given that rats sleep almost twice as much as humans and—judging from the short length of their NREM-REM cycles—may have accelerated sleep processes, it is likely that the need for sleep accumulates much faster in the rat. One day of sleep loss in the human may be functionally comparable to only a few hours of sleep loss in the rat—a duration that produces only high-amplitude, slow-wave and no REM sleep rebounds in these animals. (In analogy, survival in food deprivation is 16.7 days in rats[35] and 61.6 days for humans.[74] The number of days without food has a different biological significance in rats and in humans.) At the present state of our knowledge, we have no way of determining when biological sleep needs are comparable in rats and humans, or whether humans have ever endured the same severity of sleep loss as rats in laboratory studies—eg, in contrast to the deaths of all rats subjected to unrelenting sleep TSD, no humans have ever died in laboratory sleep-deprivation studies. What can be meaningfully examined is whether humans have shown the same pattern of relationships between amount of sleep loss and rebound characteristics as rats. Specifically, do humans, like rats, tend to increase rebounds of REM sleep as TSD becomes more severe?

The conclusions of the classic Berger and Oswald study of 4 nights of TSD in humans[1] were that HASW sleep (stage 4) rebounded on the first recovery night (when it was at 450% of baseline); that REM sleep was reduced on the

first recovery night; and that REM sleep did not show a positive rebound until the second recovery night. This widely quoted conclusion was based on an analysis of only the first 7.43 hours of recovery sleep, because that was the mean duration of total sleep on baseline nights. The REM sleep percentage of total sleep during that early recovery period was only 7.4%, far below the baseline percentage of 22.5%. However, subjects averaged 4.14 hours of sleep beyond the 7.43-hour cutoff, and it is difficult to understand why that extended sleep should be excluded entirely as part of the recovery process. By our calculations, subjects averaged 38.4% REM sleep during the extended period. For the first recovery night as a whole, REM sleep was increased by an average of 24%. Some part of that increase might reflect more or less baseline amounts of "normal" sleep extension. However, there is little doubt that the very large increase in REM sleep during the extension period in the Berger and Oswald study was largely a rebound effect, because several studies showed that in the absence of prior, specifically enforced TSD, extended human sleep features a decreasing trend of REM sleep,[75-80] not the large increase seen in the Berger and Oswald study. That study certainly showed a delay of REM-sleep rebound during the early portion of the first recovery night, but there was a rebound of REM sleep for the night as a whole, which is consistent with expectations of greater REM sleep rebounds as TSD increases.

A study of 2.67 days of TSD in humans[81] limited total sleep on each of the 2 recovery days to about 7 hours. For that recovery period, the results were similar in several respects to those of Berger and Oswald for their limited sleep period of 7.43 hours. HASW sleep (stage 4) showed a large rebound on the first recovery night to 200% of mean baseline and a lesser rebound on the second recovery night. REM sleep (19.4% of total sleep time) was not significantly reduced on the first recovery night as it had been in the limited sleep period of Berger and Oswald, but, as in the earlier study, it did not show a significant positive rebound until the second recovery night, when it was at 132% of the baseline mean. Since no recovery sleep was permitted beyond 7 hours, there is no way to determine what total rebounds might have been.

In a particularly well-analyzed study, Kales et al reported on the effects of 8.54 days of TSD in human subjects.[82] Kales and colleagues found that HASW sleep (stage 4) during the first 9 hours of the first recovery night was at 365% of the baseline mean; the HASW sleep percentage of total sleep for the first recovery night was similar to those of the two studies reported above. Smaller rebounds of HASW sleep persisted on the second and third recovery nights; the earlier studies did not report second- and third-night recovery values. In contrast to the 7.4 REM sleep percentage of total sleep reported for the first 466 minutes of sleep the first recovery night reported by Berger and Oswald, Kales et al reported 30% for the same sleep period. During an "additional" 3-hour sleep period, the REM sleep percentage increased to 52.8. For the entire 12-hour period in the laboratory on the first recovery night, REM % of total sleep was 35.5, compared to a baseline average of 21.9.

Gulevich et al[83] reported on the longest human TSD study on record—11 days of TSD in a single human subject. They noted that the rebound increase of stage 4 was no greater than it had been in the Berger and Oswald study, but that the REM rebound was greater. By our calculations, mean time in stage 4 on 3 recovery nights was at 375.1% of control nights, while mean REM sleep time was at 282.4% of the control values. Both the Kales and Gulevich papers noted that although the longer TSD times in their studies did not produce greater rebounds of stage 4 than in the shorter TSD studies, the REM sleep rebounds were greatly increased.

Some studies of sleep apnea patients with presumably chronic impairments of sleep have shown that on the first night of treatment with continuous positive airway pressure, REM sleep is increased to well above normal values for that age group[84,85]; in other similar studies, the return of REM sleep is only to about normal levels for people without apnea.[86,87]

On the whole, the extended TSD human studies did not produce the complete rebound dominance of REM sleep seen in the rat studies, but they did produce the same kind of shift toward greater REM rebounds with increasing TSD seen in the rat studies.

Other Evidence Relevant to the Issue of Sleep Intensity

One of the arguments that HASW sleep is particularly intense has been its regular appearance early in the sleep period shortly after a day of wakefulness, and its subsequent decline over the remainder of the sleep period—ie, another indication of its response to prior wakefulness. However, there have been several reports that HASW activity may reappear during extended sleep, particularly after 12 hours of sleep, indicating that variables other than preceding wakefulness, eg, ultradian rhythms or total elapsed time—may participate in its occurrence.[77,78,80,88-90] Reports of the reappearance of HASW activity in extended sleep have been criticized by Dijk et al[91] because the scoring had been by visual recognition of stage 4[92] rather than by more precise computer analysis. This is an unfortunate critique. Although scoring of HASW activity by computer is undoubtedly more precise, the observations of reliably scorable stage 4 in extended sleep by several experienced investigators were sufficiently robust that they could not be discounted as measurement errors. Neither does the development of more-precise measurements obviate the many fundamental discoveries about sleep characteristics and

organization that were made before the computer age. There has been no corresponding hesitancy to accept data on stage 4 when it has fit the HASW-intensity model. Getting back to the substance of the matter Dijk et al did not (by spectral analysis) find a return of HASW activity in extended sleep. However, the more recent study of Christ et al did find a HASW return with spectral analysis. They suggested that its absence in the Dijk et al study may have resulted from the fact that their extended sleep period followed a period of sleep deprivation, which might have affected the dynamics of subsequent extended sleep. On the other hand, there have been studies in which extended sleep without prior deprivation did not show late returns of HASW activity.[76,79] In general, although the return of HASW activity in extended sleep challenges the sleep-intensity hypothesis, these returns are not very powerful effects. They do not appear in all studies or in all subjects; when they do appear, the magnitude of the effect is always just a fraction of the HASW activity in early sleep. It is conceivable that there is a major early effect of prior waking time, and, in addition, a later return stimulated by lesspowerful determinants.

Depth of Sleep

Borbély has made the reasonable suggestion that high-intensity sleep should be a "deeper" form of sleep, and has cited high arousal thresholds during HASW sleep as evidence of its intensity. The problem is that "depth of sleep" does not behave reasonably. Depth of sleep has varied within species according to the measures used, across species, and across laboratories. A complete review of the relevant literature would be very lengthy and unnecessary; examples will suffice. One study of humans showed that, as measured by the behavioral response of awakening in response to sound stimuli, stages 2 and REM were relatively light, while stages 3 and 4 were relatively deep.[93] However, another human study showed that (by the behavioral response of pressing a finger switch) stage 2 was the lightest, while stages 3, 4, and REM followed in descending order.[81] By the criterion of electroencephalographic responses, stage 3 was the lightest, followed by stages 2, 4, and REM, while by the criterion of vasoconstriction, stage REM was lightest, followed by stage 2 and then stages 3 and 4. In rats, one study showed that by the criteria of EEG and muscle arousal to acoustic stimuli, NREM sleep with relatively more HASW activity was deepest, while NREM sleep with less HASW activity and REM sleep shared a lower arousal threshold.[94] Other rat studies cited in this paper and one from our own laboratory[23] showed that arousal thresholds in REM sleep were higher than in NREM sleep (which was not differentiated by amount of HASW activity). In cats, REM sleep has proven to be deeper than NREM sleep by response to reticular stimulation[95] and auditory signals.[96,97] In these cat studies, NREM sleep was not divided according to amount of HASW activity. However, the REM vs NREM differences were so large that it is unlikely that there would be a segment of NREM sleep with less responsiveness than that seen during REM sleep.

Particularly telling would be the response of putative depth measures to TSD. (If sleep intensity increases following TSD, then depth measures should change accordingly.) Humans have shown decreases in behavioral responses, vasoconstriction responses, and EEG responses during recovery from TSD.[81] However, different response measures have not changed in unison in other species. Following 4-hour TSD, rabbits showed reduced behavioral arousal responses to auditory stimuli and shortened latencies to return to sleep after arousals. However, while the shortened latencies were related to HASW activity before the stimulus presentation, behavioral responsiveness was not.[70] Following 12 hours of TSD, rats showed elevated awakening thresholds to auditory stimuli but not to trigeminal nerve stimulation.[98] In view of the great variations in response across sensory modalities, response mechanisms, species, and levels of response to prior TSD that are invoked in determinations of depth of sleep, "sleep depth" may not be a firm foundation for supporting the selection of intense or recuperative sleep.

CONCLUSIONS

Over the past few decades, a groundswell of opinion has developed in support of the belief that HASW activity identifies the most-intense, most-restorative sleep. Two lines of evidence have been presented to support this view. One is that this sleep is "deeper" than other stages. Not only is the generality of this evidence suspect, but the idea that deep sleep is particularly restorative is inferential. The second, somewhat less inferential line of evidence for the special functional value of HASW sleep is its priority in time and amount in response to prior wakefulness—including its early and large rebound following sleep deprivation, its early appearance and its subsequent decrease over the course of nocturnal sleep, and, conversely, its reduction during nocturnal sleep following daytime naps. A major support for the special homeostatic value of HASW sleep has been the many reports of its early and large rebound following short-term TSD in the rat. The current studies have shown that short-term TSD by the DOW method has produced essentially the same kinds of HASW rebounds as short-term TSD by the other deprivation procedures. Unlike the other procedures, however, the DOW method permits longer-term TSD. Recovery from longer-term TSD has been characterized by decreased HASW activity and massive, sleep loss dependent rebounds of REM sleep. These data weaken the argument for HASW sleep as the

most intense, need fulfilling sleep.

Other weaknesses in the argument gleaned from past literature were also noted, including the negative rebounds of HASW activity in short-term TSD studies; the increasing rebound of REM sleep in long-term TSD of humans; the appearance of HASW activity during extended sleep in humans; and the mixed evidence on the relationship of depth of sleep measures to sleep stage and prior TSD. We can also ask why, if HASW sleep is so need-fulfilling, it comprises so small a portion of total human sleep? Stages 3 and 4 in humans typically comprise about 15% to 20% of total sleep compared to 50% to 60% for stage 2 (the NREM stage defined in part by the paucity of HASW activity). One would think that evolution might have maximized productive wakefulness by concentrating the fulfillment of the sleep need into shorter, more efficient sleep periods comprised mostly of stages 3 and 4.

We do not intend the above to rule out a homeostatic role for HASW sleep. There is still considerable support for such a role: its early rebound from short-term TSD in the rat; the physical demise and eventual deaths of rats subjected to relatively selective, chronic deprivation of high-EEG-amplitude sleep by the DOW method,[48] and the rebound of this activity during the recovery sleep of one of these rats[26]; the large rebounds of HASW sleep in humans; the concentration of HASW sleep during the early portions of sleep. Neither do we wish to encourage a war over which sleep stage or activity is most intense. Debates about rebound priorities such as those reflected in the present paper engage us in a seemingly vital conceptual sport, but they still skirt the fundamental issues of what the functions of the different stages may be and, even more important, of which causes, correlates, or effects of the stages might be the critical functional components.

Even if a particular EEG-defined stage of sleep were defined as most intense or functionally important, it would constitute only a minimal first step toward understanding functional dynamics. The EEG patterns of sleep are only observable manifestations of complex physiological processes which must lie at the heart of homeostatic adjustments. The introduction to this paper expressed the idea that the identification of "intense" sleep might provide clues to functionally important underlying features. But much more attention has been directed to surface manifestations than to putative underlying functional processes. For example, EEG slow-wave activity has many known physiological correlates and determinants. It is generally believed that the slow waves of the cortical EEG reflect postsynaptic potentials of assemblies of cortical neurons and dendrites[99] which are driven synchronously via projections from the reticularis nucleus of the thalamus.[100] The release of acetylcholine from cells in the midbrain and dorsal pons blocks the rhythmic firing of the reticularis neurons, thereby diminishing HASW activity and producing the desynchronized, low-voltage EEG characteristic of waking and REM sleep. Accordingly, HASW activity can be elicited or suppressed by the administration cholinergic blockers or agonists respectively, independent of behavioral state (see review in 101). Cortical neurons also exert a modulatory control over thalamic oscillators.[102] It is also known that HASW sleep can be augmented by several hormones or is correlated with their release,[103] and cerebral oxygen metabolism and blood flow are substantially reduced during HASW sleep.[104] So which are the functionally important features of HASW sleep—the neuronal activation or blockade that causes or is correlated with it? the synaptic potentials that produce its visible EEG features? the hormonal release that affects it or is produced by it? the associated reduction of cerebral metabolism and blood flow? If we could direct more attention to and resolve some of these more basic issues, the debates surrounding the intensity of HASW sleep and its priority relative to other stages would retreat from the limelight of current controversy.

Since we have little but diverse theories for the function of any sleep stage or its components, none of which has achieved very wide acceptance by sleep researchers,[50] we do not feel very comfortable about asserting the relative values of any sleep stages. Others have accepted HASW sleep as the most intense and restorative; eg, ". . . it is now generally accepted that it is primarily slow-wave or non-rapid eye movement sleep that is restorative for the brain and that the recovery process is most intense during high-amplitude delta sleep."[105] The major message of this paper is to counter the reification of this kind of thinking.

Sleep intensity may be a natural and easy way of thinking about sleep. But sleep may involve a very complex interplay of mechanisms and functional attributes that defies such easy description. It would be a bit like asking which aspect of wakefulness was most intense or important. There are so many different kinds of waking activity with so many different functional targets and different dimensions of intensity that the question becomes silly. Sleep appears less varied than wakefulness, but it may have complexities of its own that make it impossible to describe sleep by unitary dimensions of intensity.

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