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Daytime Sleepiness: Quantification of a Behavioral State

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CARSKADON, M. A. AND W. C. DEMENT. *Daytime sleepiness: Quantification of a behavioral state.* NEUROSCI BIOBEHAV REV 11(3) 307–317, 1987.—A neurophysiological technique that quantifies drowsiness as the speed of falling asleep at intervals across a day is used to identify patterns of sleepiness/alertness. The Multiple Sleep Latency Test (MSLT) reveals a daily biphasic organization of sleepiness that is affected in predictable ways by the length and continuity of nocturnal sleep on one or several nights, and by maturation, aging, sleep pathology, and drug ingestion. The systematic nature of these relationships provides impetus to efforts examining the neurobiological mechanisms subserving the delicate balance of sleep and wakefulness.

Sleep Sleepiness Drowsiness Alertness Puberty Aging Circadian rhythms Narcolepsy Sleep disorders Benzodiazepines Insomnia Performance

OVERWHELMING drowsiness in the daytime following a night of little or no sleep is a commonplace human experience. This experience is very unpleasant in the typical circumstance; were this consequence not inevitable, it is a safe assumption that certain members of our society would have long since given up sleep. The daily progression of sleep and wakefulness, however, is an immutable feature of human existence. In the past ten years, great strides have been made in quantifying the relationship of wakefulness to sleep. Most previous attempts to deal with those aspects of daytime functioning primarily determined by nighttime sleep have been off-target. Notions of performance, fatigue, attention, or physiological measures such as body temperature or pupil diameter simply do not probe this quality that provides the background of all waking endeavor: the dimension of alertness/sleepiness.

The range of this dimension is enormous—from irresistible drowsiness with a virtual absence of motivation and function to optimal alertness with energy, clarity, and optimism—and most humans operate across this broad spectrum every day. The purpose of this review is to consolidate a decade of research that has taken this ubiquitous aspect of human function from a pre-paradigmatic status to a field of vigorous, dynamic, and imaginative scientific investigation. We will describe the technique that has provided a neurophysiological tool for measuring this behavioral state, and we will review the application of this measure in ways that establish formal properties governing the relationship of sleep at night to waking behavior. For example, it is now possible to formulate a quantitative definition of the need for sleep; indeed, sleep need can be compared among individuals and across groups. Norms have been established and pathologies defined. Finally, the tools are available to examine precisely the determinants of waking alertness/sleepiness, the consequences of altering nocturnal sleep length, timing, and continuity. These studies have already provided a tremendous insight into adolescence and have also demonstrated that the determinants of this behavioral state can be additive over several days. The investigative horizons opened by this quantitative, neurophysiological approach to a behavioral state are quite broad. This window on waking behavior provides added impetus to the search for an understanding of the functions and mechanisms of the sleeping brain.

MEASUREMENT OF ALERTNESS/SLEEPINESS: MULTIPLE SLEEP LATENCY TEST (MSLT)

Early attempts to quantify daytime sleepiness included pupillometery [44,79], introspective rating scales [40,52], and performance testing [78], none of which achieved widespread acceptance. In the late 1970's, we introduced [13,56] a simple, objective, quantifiable measure of diurnal somnolence, the Multiple Sleep Latency Test (MSLT). The major concept underlying this measure is very simple: the state of alertness/sleepiness is directly reflected by an individual's readiness to fall asleep. The speed of falling asleep measured with standard sleep laboratory procedures [54]—EEG, EOG, and EMG—quantifies this "sleep tendency." Competing stimuli, including internal drive states, are reduced by performing the tests while the individual is comfortable in bed in a darkened, sound-attenuated, temperature-controlled bedroom, having urinated, been fed, and so forth [22]. The test is administered at two-hour intervals across a day, each time with the admonition to try to fall asleep or not to resist falling asleep. Four to six 20-minute opportunities for sleep

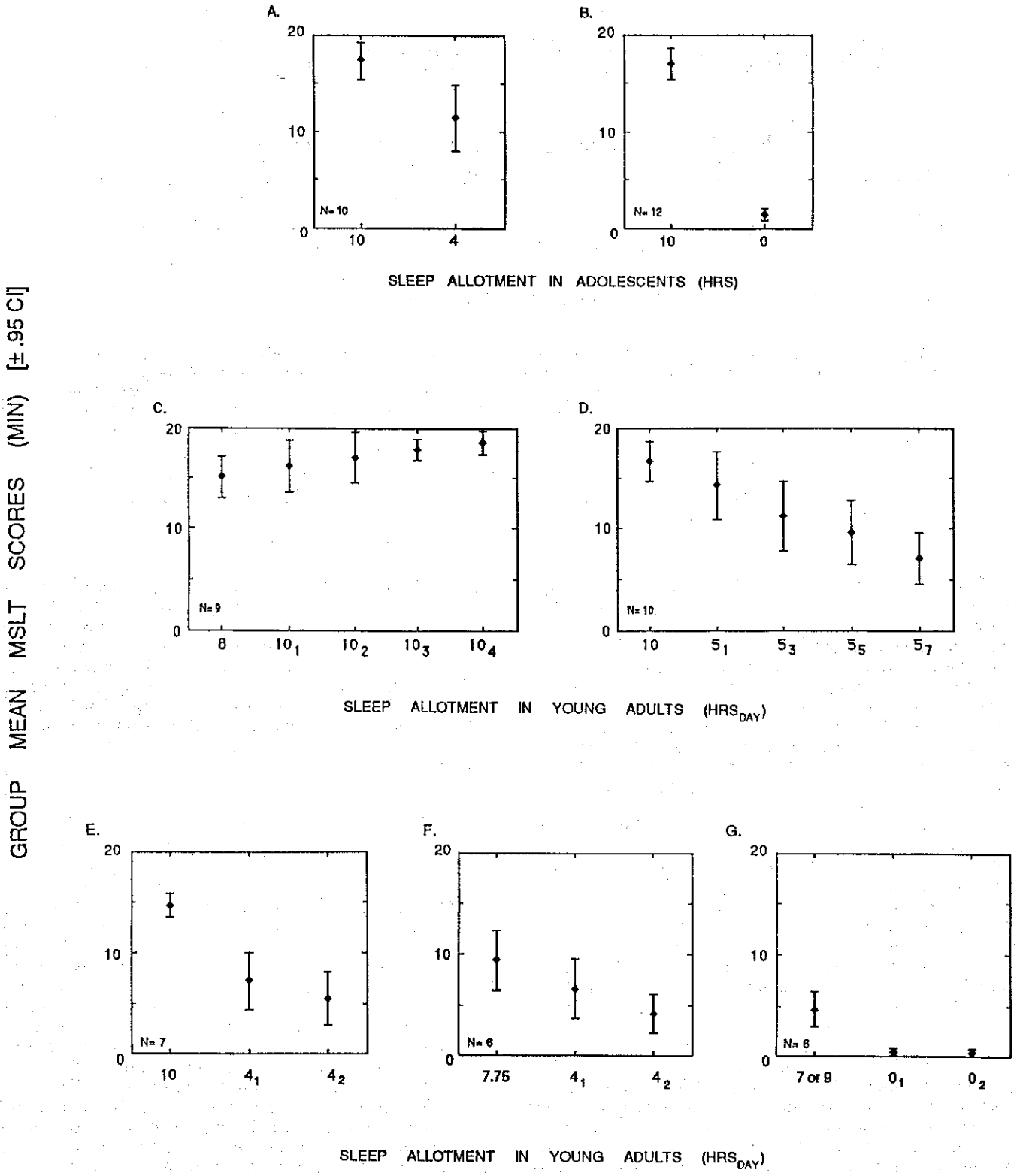
A.
B.
20
10
0
N= 10
N= 12
10
4
0
SLEEP ALLOTMENT IN ADOLESCENTS (HRS)
GROUP MEAN MSLT SCORES (MIN) [± .95 CI]
C.
D.
N= 9
N= 10
8
10 1
10 2
10 3
10 4
10
5 1
5 3
5 5
5 7
SLEEP ALLOTMENT IN YOUNG ADULTS (HRS DAY)
E.
F.
G.
N= 7
N= 6
N= 6
10
4 1
4 2
7.75
4 1
4 2
7 or 9
0 1
0 2
SLEEP ALLOTMENT IN YOUNG ADULTS (HRS DAY)

FIG. 1.

are given, and the results of the tests are generally examined as a profile of sleep latencies across the day or as a mean daily score. In the following material, we will review studies that have used this measure to assess factors thought to influence waking behavior.

LENGTH OF SLEEP ON ONE OR SEVERAL NIGHTS

We have alluded to the common experience that one is less alert during the day following a night of reduced sleep. Experiments using the MSLT have found a predictable relationship of diurnal sleep tendency and nocturnal sleep quotient on a variety of sleep schedules in adolescents and young adults. Examination of sleep tendency in adolescents with sleep allotments of 10 hours, 4 hours, and no sleep [23,24] showed proportional decreases in MSLT scores with reduced sleep (Figs. 1A and 1B). Studies in young adults [15, 16, 18] have included comparison of MSLT scores during sleep schedules of 8 hours versus 10 hours; 10 hours versus 5 hours; 10 hours versus 4 hours; 7.75 hours versus 4 hours; and 7 or 9 hours versus no sleep. Again, appropriate proportional increments or decrements of MSLT scores resulted from variations in nocturnal sleep schedule (Figs. 1C–1G). Furthermore, these studies have provided an assessment of additive changes in MSLT following sleep schedule alterations. The cumulative effects of prolonged sleep extension (Fig. 1C) or prolonged sleep restriction (Fig. 1D) are most obvious, but statistical analysis of the data from more acute procedures (Figs. 1E–1G) also revealed additive changes in MSLT scores.

The findings of cumulative waking responses to changes in the nocturnal sleep allotment have several important implications. For example, a very common organization of sleep patterns for many humans is to restrict sleep on weekday nights and to extend sleep on weekends [20, 41, 74]. Such a weekday-weekend pattern may lead to cumulative effects during the course of a week. Thus, sleepiness may be only minimal or occur in short-lived episodes on Monday or Tuesday, perhaps leading to the assumption that sleep, though restricted, was sufficient. By Thursday or Friday, however, significant impairment may appear, and this impairment may be misattributed to a "tough" week. Similarly, recovery of full alertness, depending upon the extent of the sleep restriction and the degree of compensatory sleep, may take place over one or several nights, and full recovery may not occur before the next cycle of sleep restriction begins. At a more basic level, these cumulative effects and the "memory" process they imply present a challenge for the neurochemical theories of sleep.

MATURATION AND AGING

An early use of the MSLT was a longitudinal evaluation of sleep and waking behavior in normal adolescents [12, 25–27]. Twenty-seven children (12 girls, 15 boys) participated in this study, with 3-day evaluations each summer for as many as six years. Figure 2 illustrates the chief finding from this longitudinal study, showing mean daily MSLT profiles in adolescents grouped by maturational (Tanner) stage [70]. (The "Tanner stages" of maturation rank pubertal status based on pubic hair growth and genital development in boys and pubic hair growth and breast development in girls. Stage 1 indicates prepubertal development, and stage 5 indicates full development of secondary sexual characteristics; stages 2, 3, and 4 are intermediate maturational stages.) MSLT scores displayed a tendency toward decreased diurnal alertness in the more mature adolescents, even though nocturnal sleep amounts remained *virtually unchanged* at slightly over 9 hours per night. This change in sleep tendency that accompanies adolescent maturation is striking. Pre- and early pubescent adolescents (ages about 10 to 14 years) have optimal function: they sleep soundly and well at night and are alert throughout the entire day. By midpubescence, with no change in nocturnal sleep amount, these same adolescents begin to experience bouts of diurnal somnolence. Thus the "need" for sleep, as reflected in producing waking alertness, does not decrease across the second decade, but may in fact increase.

If adolescent maturation has an impact on waking alertness, is this maturational change limited to the second decade or does it persist into later life? A number of adult groups have been evaluated to assess this issue. Figure 3A summarizes MSLT data from three adult groups studied in similar experimental settings. Available nocturnal sleep time in these adult volunteers was limited to an amount that corresponds to societal norms—about 8 hours per night. (Young adult and elderly volunteers were given an 8-hour sleep allotment, with bedtime held constant at midnight and rising time at 0800. The older adults were given an 8.5-hour sleep allotment, with bedtime at 2330 and rising time at 0800. For

FACING PAGE

FIG. 1. Effects of sleep quotient on mean daily MSLT scores in adolescents *(A,B)* and young adults *(C–G)*. All subjects were studied under identical conditions, with the exception of sleep allotments (times in bed). Arising time was 0800 in every study, and only those tests given from 0930 to 1930 were averaged for the daily mean. In each graph, the first point represents the mean daily MSLT score for the second or third day under the initial sleep allotment. The deviation bars indicate 95% confidence intervals. *A*. MSLT scores in 12 adolescents (ages 11–13 years; Tanner stages 1–3) at 4 hours differed significantly, $F(2,11)=15.1$, $p<0.01$, from scores at 10 hours [24]. *B*. MSLT scores in 9 adolescents (ages 11–14 years; Tanner stages 1–5) with no sleep differed significantly, $F(3,8)=46.1$, $p<0.001$, from scores at 10 hours [23]. *C*. In 10 young adults (ages 18–20 years), MSLT scores were significantly, $F(6,48)=9.7$, $p<0.001$, greater on the second, third, and fourth days with a 10-hour sleep allotment than with 8 hours [18]. Polygraphically monitored nocturnal sleep times were about 60 minutes longer with the 10-hour allotment than with 8 hours. *D*. Ten young adults (ages 17–24 years) had significantly, $F(4,36)=20.5$, $p<0.01$, lower mean daily MSLT scores on the second (not shown) and subsequent days with a 5-hour sleep allotment than with 10 hours. Trends analysis showed a significant ($p<0.01$) linear decline of MSLT scores across the 7 days of sleep restriction [16]. *E*. Six young adults (ages 18–25 years) had significantly, $F(3,15)=26.7$, $p<0.01$, lower MSLT scores on both days with a 4-hour sleep allotment versus a 10-hour sleep allotment [18]. *F*. Six young adults (ages 17–23 years) had significantly, $F(3,15)=14.4$, $p<0.01$, lower MSLT scores on both days with a 4-hour sleep allotment versus a 7.75-hour sleep allotment [18]. *Post hoc* analysis showed significantly ($p<0.05$) lower scores on the second versus the first restriction day. *G*. In 6 young adults (ages 18–21 years), MSLT scores were significantly, $F(5,25)=24.6$, $p<0.001$, lower on both days with no sleep than with a 7- or 9-hour sleep allotment [15]. *Post hoc* analysis also showed significantly ($p<0.01$) lower scores on the second versus the first sleep deprivation day.

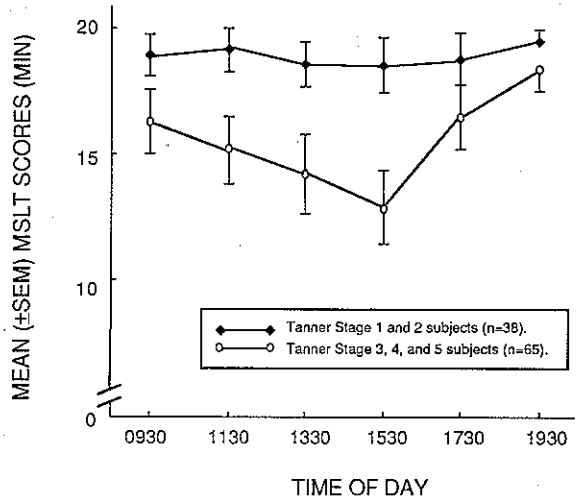

FIG. 2. Effect of adolescent maturation on MSLT scores [12]. Data were obtained in adolescents evaluated for 3 consecutive days on a schedule that included a 2200 bedtime and 0800 rising time. MSLT scores from day 2 were averaged across groups. Subjects at Tanner stages 1 and 2 are at pre- and early pubertal development and were aged 10–15 years; subjects at Tanner stages, 3, 4, and 5 were mid- and postpubertal development and were aged 11–18 years.

all groups, MSLTs began at 0930 and continued at 2-hour intervals through 1930 each day. In each case, MSLT data from the second day in the laboratory on this schedule was used for the analysis.) Not only were most adults somewhat more somnolent on this schedule than adolescents, but the elderly volunteers also showed significantly ($p<0.05$) greater sleep tendency than the younger groups at several times of day (1330, 1730). As a group, however, the elderly volunteers tended to obtain slightly less polygraphically monitored sleep at night. (Polygraphically monitored sleep amounts averaged within each group for the night preceding the MSLT were: young adult mean=438 minutes (SEM=7 minutes); older adult mean=441 minutes (SEM=12 minutes); elderly adult mean=416 minutes (SEM=12 minutes).)

Examining the patterns of diurnal sleep tendency in individuals from these groups (Fig. 3B), only one volunteer (a 19-year-old male) failed to fall asleep on each of the sleep latency tests. In contrast, 15 of 38 early adolescents (Tanner stages 1 or 2) sleeping slightly over 9 hours remained awake on all tests; 95% of these young adolescents and 60% of the older adolescents (Tanner stages 3, 4, or 5) had a mean daily MSLT score of 15 minutes or greater. We find surprising the number of adults on a "nominal" schedule such as this who showed quite high sleep tendency on one or more of the daily tests: one-third of the young adults, two-thirds of the older adults, and nearly 90% of the elderly adults had at least one test with a sleep latency shorter than 5 minutes.

CONTINUITY OF NOCTURNAL SLEEP

Results of studies in elderly volunteers are generally less consistent than in younger individuals. We suspected that this inconsistency might be related to relatively greater sleep disturbance in the elderly, often due to specific occult nocturnal events, such as respiratory disturbances [3, 17, 31, 43]. To test this hypothesis, nocturnal sleep and diurnal MSLT data were examined in 24 elderly volunteers recorded with a 10-hour bedtime (2200–0800) that would tend to maximize individual differences in amount of sleep. Particular attention was also paid to nocturnal arousal events, including breathing disturbances and transient EEG signs of arousal in the range of 2 to 15 seconds, disturbances too brief to be recalled in the morning. Table 1 summarizes these data, showing a clear relationship of brief nocturnal arousals and diurnal alerness/sleepiness, a relationship that was independent of amount of sleep [21].

An experiment by Stepanski and his colleagues [68] extended this work to examine the relationship of nocturnal arousals and diurnal sleepiness in three groups of middle-aged adult patients and normal controls. In patients complaining of excessive somnolence, brief arousals were negatively correlated with MSLT scores; in patients complaining of insomnia, MSLT scores were negatively correlated with longer arousals. This group [69] has also reported a pilot study in which brief arousals were induced by noise during the sleep of young adults. Following two nights in which 8–9 arousals per hour of sleep were produced, 4 of 5 volunteers showed evidence of reduced latencies on the MSLT without any change in total amount of sleep. In another study, which did not use the MSLT, Bonnet [8] woke subjects after each minute of sleep for two consecutive nights; although the total amount of sleep was reduced by only about one hour each night, decrements on tests of performance and on mood scales were greater than after a full night of sleep loss.

From these studies, we conclude that the continuity of sleep at night may be as relevant to daytime function as is the amount of sleep. The likelihood of arousing from sleep due to internal or external stimuli is an age-related phenomenon [45,80]. For example, early adolescents show no behavioral, autonomic, or EEG spectral signs of arousal when subjected to auditory stimuli during the first cycle of sleep up to 123 dB sound pressure [11], roughly equivalent to a jet flyover at 500 feet. Furthermore, the types of spontaneous arousal disturbances common in elderly individuals—periodic leg movements in sleep [3,31] or disturbed breathing—are quite rare in adolescents and younger adults. These differences in arousal and in sleep consolidation may contribute to the age-related changes in diurnal sleep tendency noted previously.

CIRCADIAN RHYTHMS: CYCLIC VARIATIONS IN SLEEP TENDENCY

An ineluctable phenomenon of normal life is the daily cycling of sleep and wakefulness, and presumably of an underlying cycle of sleepiness/alertness. An early examination of this phenomenon used a rather different technique called the "90-minute day," in which young adult volunteers lived for 5 or 6 days on a schedule permitting them to sleep only 30 minutes every hour and one-half [14]. Figure 4 illustrates the sleep tendency on this type of schedule (averaged over 10 subjects during the 2nd and 3rd days, taking each subject's minimum sleep latency value as a reference point). A clear 24-hour pattern of sleep tendency is apparent from this figure, with a trough in the morning and a late-evening peak.

The circadian pattern of sleep tendency has also been assessed using a more traditional sleep/wake schedule, measuring the MSLT as usual during waking hours and waking volunteers for 15 minutes at 2-hour intervals during a night of sleep (2330–0800) to give the sleep latency tests at those times as well [57]. This experiment was performed

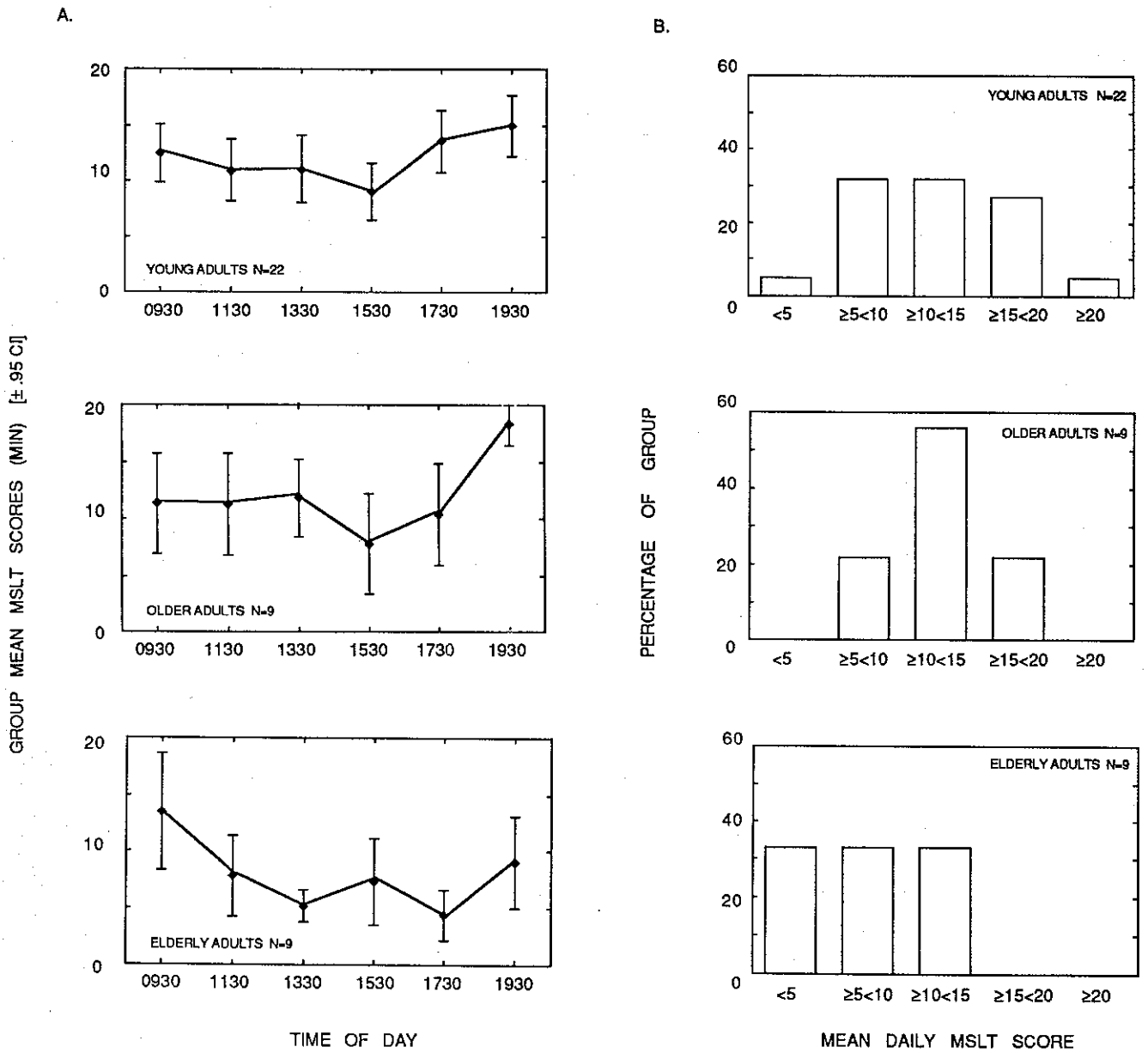

FIG. 3. Effect of aging on MSLT scores. All 3 groups underwent identical procedures, with the exception that the older adults had an 8.5-hour sleep allotment versus 8 hours in the other groups. Data are from the second laboratory day under these standard conditions. Age ranges of the three groups were: young adults=17–25 years; older adults=30–48 years; elderly adults=62–77 years. The deviation bars indicate 95% confidence intervals. *A*. Mean MSLT profiles show greater sleepiness in elderly subjects than other groups at 1330 and 1730. *B*. Individual differences are apparent in this graph showing the percentage of each group whose mean daily MSLT scores are within the indicated limits. The tendency for greater sleepiness in older subjects is also apparent in this plot.

with young adult subjects along with elderly volunteers who were carefully screened for nocturnal sleep disturbances. As shown in Fig. 5, a very clear biphasic pattern of sleep tendency—which was only hinted at in the 90-minute day study—occurred on the more normal schedule. In addition, there were no significant differences between the sleep tendency patterns of the elderly and young adult volunteers.

The nocturnal rise of sleep tendency (decrease of sleep latency) is consonant with everyday experience. The midday enhancement of sleep tendency is also a common experience and is usually considered a postprandial response. We have observed this prominent midday phenomenon in virtually all postpubescent volunteers studied with the MSLT, all of whom were given meals on a relatively normal schedule (breakfast at about 0815, lunch at about noon, and supper at about 1800). The biphasic pattern of MSLT scores has been identified even in aircrew following multiple time zone jet travel [33]. A similar phenomenon—the "post-lunch dip"—has also been reported in various tests of performance [7, 29, 61]. The question remains whether the midday augmentation

TABLE 1

MEAN AND STANDARD ERROR (SEM) OF NOCTURNAL SLEEP AND MSLT SCORES IN 24 NONCOMPLAINING ELDERLY VOLUNTEERS WITH CORRELATION (PEARSON PRODUCT-MOMENT) OF MSLT TO NOCTURNAL PARAMETERS

Measure	MSLT (min)	Total Sleep Time (min)	Wake Time (min)	Number of Wakes >15 sec	Number of Transient Arousals	Number of Respiratory Events
Mean	12.2	426	126	41	160	58
SEM	0.9	15	14	4.1	21.2	14.1
Correlation with MSLT		−0.140	−0.002	−0.386	−0.474*	−0.491*

*$p<0.02$.
(Adapted from [21].)

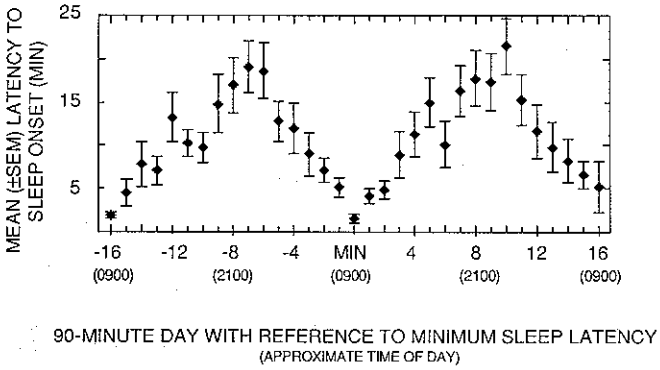

FIG. 4. Circadian effects on sleep latency during a schedule permitting 30 minutes of sleep every 90 minutes in 10 young adult (ages 17–21 years). Data are aligned at the minimum latency that occurred during the third day on this schedule (*min*). Each point represents the mean latency to sleep onset from the sleep episodes occurring 90 minutes before (−) or after the minimum reference episode. The minimum's time of day varied from 0600 to 1030, with a median of 0900, which is used to indicate the approximate times of day.

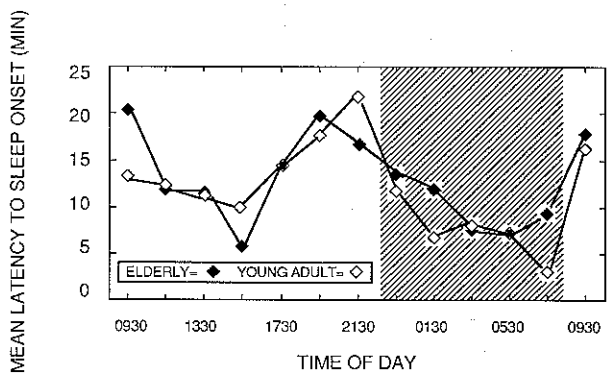

FIG. 5. Circadian effects on sleep latency during a schedule permitting a relatively consolidated sleep episode in 10 elderly (ages 60–83 years; closed symbols) and 8 young adult (ages 19–23 years; open symbols) subjects. The shaded area represents the nocturnal sleep period (2330–0800). Latencies during the daytime were obtained using the standard MSLT procedures. During the sleep period, subjects were awakened every 2 hours for 15 minutes, and latency of the return to sleep was measured. (Figure redrawn with permission from [57].)

of sleep tendency represents a biphasic rhythm of sleep tendency or a postprandial consequence.

In an effort to answer this question, we administered the MSLT to eleven postpubescent volunteers (5 boys aged 16 or 17 years and six elderly adults, two men and four women, aged 62 to 74 years) confined to bed and fed a standard meal at 1-hour intervals throughout the day. (The experimental protocol for this study involved a "constant routine," which others [30,46] have shown effective in reducing environmental factors that mask the expression of rhythmic circadian function. During the constant routine, volunteers were confined to bed, lights were on continuously, and a research assistant was continuously present (except during MSLTs). Liquid meals in evenly divided portions fulfilling 24-hour caloric and fluid intake requirements were given at one-hour intervals.) As shown in Fig. 6, a midday reduction of sleep latency was present even when food intake was thus controlled. This result lends support to the hypothesis that the diurnal variation of sleep tendency is a rhythmic phenomenon and is not induced by food intake. The findings do not rule out the possibility that food intake can influence the tendency to fall asleep. A number of investigators [6, 37, 67] have reported that certain foods increase feelings of sleepiness and can reduce the latency to sleep onset. The "constant routine" data, which showed no reduction in sleep latency following breakfast or supper, suggest that any susceptibility to food-related sleepiness probably varies with time of day (or phase of the cycle).

Broughton [9] has proposed a 12-hour rhythm in the propensity for slow wave (stages 3 and 4) sleep, which can be seen on occasions when the nocturnal sleep episode is extended, particularly in young adults sleeping on an ad lib schedule [35, 36, 73, 75]. The diurnal augmentation of sleep tendency may reflect this biphasic slow wave sleep rhythm. The converse of this pattern—a biphasic activity rhythm—is well known in many species [4], including several mammals and at least one primate [2]. Such a biphasic activity rhythm has not been reported in humans, but the sleep tendency

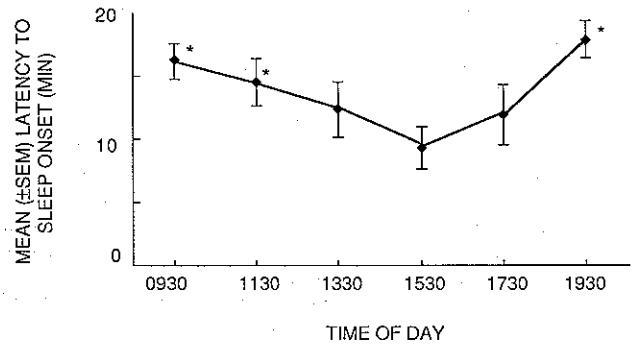

FIG. 6. Circadian effects on sleep latency during a constant routine schedule in which subjects were confined to bed (with head elevated) under constant lighting and with feeding at 1-hour intervals. Data are combined for 5 older adolescent (ages 16–17 years; Tanner stage 5) and 6 elderly adults (2 male, four female; ages 62–74 years). Asterisks indicate those times at which the sleep latency differed significantly ($p<0.05$; matched-pair t-tests, two-tailed) from the 1530 latency on baseline.

pattern may reflect a vestige of such circadian organization in man. These speculations imply that the *siesta* may not be simply a cultural or climatic adaptation, but may reflect a biological rhythm that is also ecologically adaptive in certain environments. Such a rhythm may also be maladaptive, as in Western industrialized societies in which a premium is placed on a sustained level of performance throughout the day.

SLEEP DISORDERS

One of the most common uses of the MSLT has been in the assessment of diurnal sleep tendency in patients complaining of excessive somnolence. Clinical applications of the methodology modify the testing conditions to permit a nap of 15 minutes on each of the testing sessions [22]. This variation has proven particularly advantageous for diagnosing narcolepsy, in which the reversal of normal sleep structure results in the occurrence of REM sleep at the start of a sleep episode. The appearance of two or more of these so-called sleep-onset REM episodes during MSLT testing is diagnostic of narcolepsy [22, 47, 51]. Patients with narcolepsy also generally tend to fall asleep with a latency of 5 minutes or shorter on each test [56].

A number of groups [1, 38, 55, 71] have used the MSLT in attempts to describe other disorders of excessive somnolence. A consistent finding in these studies is that the two sleepiest (mean daily MSLTs=3–5 minutes) groups are patients with narcolepsy or obstructive sleep apnea syndrome (in which hundreds of brief nocturnal arousals are associated with sleep-related respiratory pauses). Patients diagnosed in the nonspecific category of CNS hypersomnolence generally show less impairment on the MSLT, while other diagnostic categories are even farther from the severe degree of sleepiness shown by narcoleptics and sleep apneics. Van den Hoed and her colleagues [71] have suggested a scheme of ranking averaged daily MSLT scores of individuals to indicate the degree of pathology: thus a mean daily MSLT score of 5.5 minutes or less indicates "pathological" somnolence associated with severe impairment; a score of greater than 5.5 but less than 10 minutes is called a "diagnostic grey

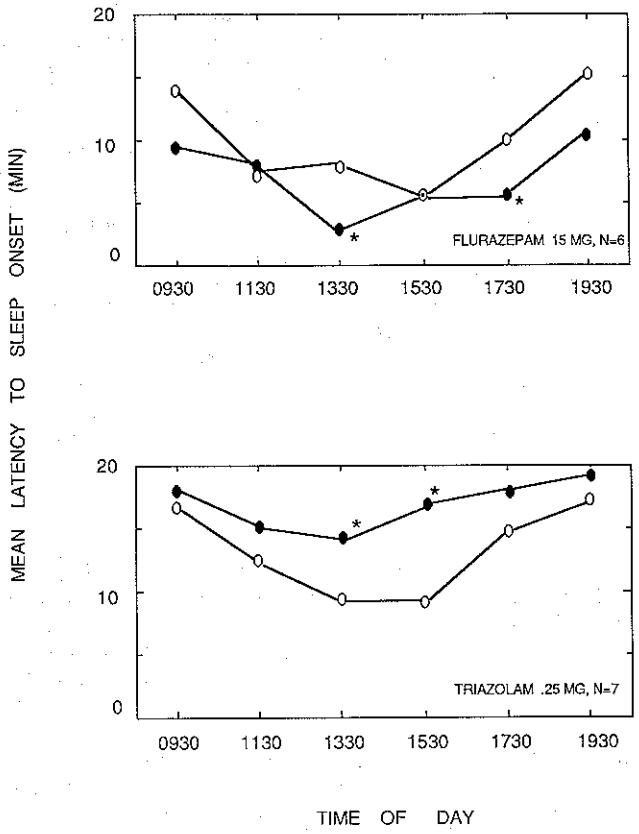

FIG. 7. Effects of flurazepam 15 mg (top graph) and triazolam 0.25 mg (lower graph) on MSLT scores in 13 elderly (ages 64–79 years) volunteers with chronic complaints of insomnia. Open symbols indicate scores with placebo (single blind) treatment; closed symbols, drug treatment. Asterisks denote the times of day at which the sleep latency with drug differed significantly ($p<0.05$) from the placebo scores. (Redrawn with permission from [28].)

area," and the authors suggest that other problems (psychiatric, drug abuse) are present; scores above 10 minutes are considered to be in the normal range.

Another variant of the MSLT has been used by several groups, particularly in the assessment of response to treatment. In this variant, called either the Repeated Test of Sustained Wakefulness (RTSW) [39] or the Maintenance of Wakefulness Test (MWT) [10,48], all procedures are identical to the MSLT except that patients are requested to remain awake and, in the MWT, are tested while sitting comfortably. Results using these techniques have varied. Hartse *et al.* [39] were able to extend sleep latency in normal individuals on a nominal sleep schedule using the RTSW, but found no differences from MSLT in sleep-deprived normals or in narcoleptic patients receiving treatment. Mitler *et al.* [49,50], on the other hand, found significant improvement on the MWT in narcoleptics after treatment. These methods are attempts to evaluate the ability to remain awake in a low-stimulus environment, and they may provide a method of assessing subtle differences in persons whose sleep tendency is in the "pathological" range.

A more recent clinical application of the MSLT has been in the assessment of patients who complain of insomnia [62,72]. One might expect that, as in noncomplaining indi-

viduals whose sleep allotment is experimentally reduced, patients whose sleep is pathologically disturbed would experience an increased diurnal sleep tendency. In a study of Seidel and Dement [63], only 7% of insomniacs were in the "pathological" range on MSLT (≤5.5 minutes), while 17% were in the "grey area" (≥6≤10 minutes), and 41% had scores ≥15 minutes. These data suggest that "insomniacs" are a heterogeneous population and that many respond abnormally to restricted nocturnal sleep. Seidel and Dement [63] suggest that the "alert" insomniacs may suffer from a chronic "activation," which disturbs sleep at night but prevents excessive somnolence from accruing during the daytime. An alternative explanation is that these individuals are simply natural "short sleepers," whose sleep need is fulfilled with relatively short sleep at night. We feel that the diurnal sleep tendency of insomniac patients as measured by MSLT may eventually yield clues to underlying pathologies in these groups.

DRUGS

Another major thrust of research using the MSLT has been to assess the impact of various pharmacologic agents, primarily the benzodiazepine hypnotics [32, 58, 66]. Until the late 1970's, studies of sleeping pills focused almost exclusively on changes in nocturnal sleep: was sleep onset faster? Was sleeping time increased? Were there fewer intrasleep arousals? Was the structure or the amount of various sleep stages altered? Few experiments were designed to evaluate the effects of these compounds on waking behavior. The current view of hypnotic efficacy, however, includes a consideration of diurnal as well as nocturnal effects, e.g., is waking function impaired or improved? The ideal sleeping pill, according to this conception, would increase the consolidation and amount of nocturnal sleep, which should consequently improve waking alertness if alertness is impaired, or at least should not further compromise alertness.

Figure 7 illustrates an example of MSLT findings from a study of a short-acting (triazolam) and a long-acting (flurazepam) benzodiazepine hypnotic in elderly patients with chronic complaints of insomnia [28]. Both compounds increased nocturnal sleep amount by approximately one hour. Daytime sleep tendency, however, was differentially affected by the two compounds: the flurazepam group had shorter diurnal sleep latencies with drug than on baseline, while the triazolam group had longer sleep latencies with treatment. We interpreted this result to suggest a carry over of sedating effects of the long-acting compound and improvement of diurnal alertness with the short-acting drug that was attributable to improved nocturnal sleep. Others [5,42] have suggested that the differential diurnal response is related to the anxiolytic effects of the benzodiazepines, persisting with the long-acting flurazepam but no longer present with the shorter-acting triazolam. Several factors favor the first explanation over the second. First, we have been unable to show any relationship between MSLT scores and paper-and-pencil measures of anxiety [65]. Second, referring to Fig. 7, it is apparent that similar diurnal patterns of sleep tendency are maintained on baseline and with drug. This consistency suggests that the circadian "program" of sleep tendency is unaffected, but a level-setting process is effected by the hypnotic treatment and its prolonged action in the case of flurazepam or by the preceding sleep quotient in the case of triazolam. Finally, another study by Seidel *et al.* [64] evaluated a nonsedating anxiolytic using the MSLT and showed no reduction of diurnal sleep latencies with this compound.

The MSLT has also been used in the assessment of other types of compounds that may affect diurnal somnolence. Antihistamines, for example, are commonly associated with sleepiness [34] and are usually accompanied with an appropriate warning. Roehrs *et al.* [60] evaluated two antihistamines—diphenhydramine (150 mg) and terfenadine (120 mg)—using a modification of the MSLT and found that significant daytime sleepiness occurred with diphenhydramine, in this case confirming a common subjective report. This type of experiment underscores the potential of the MSLT as a valuable tool for assessing many types of compounds, not just those for which the primary action or desired effect is hypnotic or sedative. The MSLT detects levels of sleepiness that may not be apparent with subjective measures or performance tests (see below), but which nonetheless may have significant impact on daytime well being. Furthermore, the assessment of varying drug administration regimens using a sensitive measure of diurnal somnolence may indicate treatment strategies that can reduce sleepiness-inducing side effects.

PERFORMANCE TESTING AND THE MEANING OF THE MSLT

A problematic area with regard to interpreting MSLT scores concerns relating them to other known measures of behavioral functioning. In several studies in which performance tests and MSLT have been run concurrently, the measures have been uncorrelated [16,24]. This is particularly true when the changes in MSLT, though statistically significant, have been relatively small and when performance test scores have not shown statistically significant changes. When MSLT scores achieved "pathological" levels, such as with one night or more of sleep deprivation, correlations with performance decrements have been found [15,23]. How can this relationship be explained? It is important to keep in mind that the MSLT measures one's tendency to fall asleep, and it is readily apparent that this tendency will not necessarily affect the ability to perform. Many tests of performance are, in and of themselves alerting, and thus the impact of a high sleep tendency is offset by the stimulating circumstances of the performance setting. A consistent conclusion of investigators assessing the effects of changes in sleep quotient on performance has been that the most sensitive tests are those that are long, unstimulating, repetitious, and simple [53, 76, 77]. Williams and his colleagues [78] were among the first to suggest that "lapses" in performance were most likely to be affected by sleep deprivation.

When performance testing results are examined in relation to MSLT scores, it is clear that these factors are relevant. At MSLT values above the "pathological" level, performance on many types of tests is unrelated to MSLT scores—volunteers can apparently offset, or the experimental situation itself offsets a slight sleep tendency. When MSLT scores achieve "pathological" levels, performance on brief, stimulating tests may be maintained at basal levels, but significant impairment occurs on long, dull tests. When EEG is continuously monitored during performance tests, performance lapses following sleep deprivation are directly related to intrusive episodes of sleep [15, 19, 23].

These data suggest to us that the MSLT-measured sleep tendency is most predictive of the *vulnerability* to fall asleep in a low-stimulus environment, such as that found in the "sensitive" performance tests. In a nonlaboratory setting,

such low-stimulus performance settings might include highway driving, certain industrial tasks (e.g., assembly line quality control), and other positions requiring prolonged vigilance (e.g., air traffic control, power plant control rooms, student). A recent description of sleep written by an 18-year-old university student, who reports sleeping about 7.5 hours a night, provides a vivid characterization of this phenomenon: "Getting to sleep [at night] is never a problem for me, but during the day it is hard to stay awake in lectures and while I read. If I don't engage in either of these activities, I would be fine [20]."

Although an MSLT level in the "pathological" range, that is, a mean daily score of 5.5 minutes or less, clearly indicates such vulnerability—and most patients report incidents of unintended sleep—a daily MSLT level that is in the grey area or even the normal range may be associated with vulnerability at certain times of day. Thus, even on a "nominal" sleep schedule in a normal individual, episodes of vulnerability can occur (see Fig. 3B). In this regard, a change in mean daily MSLT score that may be as little as 3 or 4 minutes—such as seen with one or two nights of slight reduced sleep—may well indicate marked impairment at certain times of day.

CONCLUSION

The experiments reviewed here provide clear parametric descriptions of factors affecting waking alertness. Of fundamental relevance to behavioral organization is the biphasic daily rhythm of sleepiness/alertness that appears with a specific relationship to maturation. The level of this rhythm can be set by altering the quantity of sleep over one or several nights, by varying the structural integrity of sleep at night, or by administering drugs that impact directly on sleep tendency. Certain pathological conditions, whether because of a probably direct biochemical lesion—e.g., narcolepsy—or because of probable secondary effects of a sleep fragmenting disturbance—e.g., sleep apnea, also vary the level of this underlying rhythmic process.

On a behavioral level, it seems likely that misattribution of the day-to-day occurrences of sleepiness is quite common. Drowsiness is blamed on such situations as a warm room, a boring lecture, a heavy meal, a few drinks, a monotonous automobile ride, and so forth. An overarching conclusion from the past decade of research is that these situations do not *cause* sleepiness, but they *unmask* a high underlying physiological sleep tendency or may *interact* with and exacerbate a moderate level of physiological sleepiness. The optimally alert individual—one with zero sleep tendency—would not be vulnerable to sleep or sleepiness in the circumstances listed above. Roehrs *et al.* [59], for example, have shown that high doses of alcohol do not produce sleepiness unless there is a pre-existing vulnerability. Yet the pervasiveness of misattributions suggests that the fully alert individual is indeed unique.

The quantification of sleepiness/alertness has set the stage for future investigations that will examine the specific processes regulating this exquisitely balanced interaction of sleep and wakefulness. Among the issues remaining to be assessed on the behavioral side include the role of sleepiness as a motivator for sleep; the long-term impact of chronic sleepiness on behavior, learning, and performance; the level of alertness providing optimal function; and the role of napping. Neurobiological questions include the specific molecular mechanisms by which sleep is able to relieve daytime sleepiness, the neuronal substrates of the system(s) underlying sleepiness, the neurochemical processes involved in producing sleepiness or providing alertness, and the interaction of circadian oscillatory processes with the sleep/wake homeostatic mechanisms. The final question is one of function: What is the work of the sleeping brain that creates the necessity for such an urgent signal?

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