Regulation of Sleepiness in Adolescents: Update, Insights, and Speculation

Mary A. Carskadon, PhD; Christine Acebo, PhD

E.P. Bradley Hospital Sleep Research Laboratory, Brown Medical School, Department of Psychiatry and Human Behavior

WE THANK TOM ROTH, THE EDITOR OF *SLEEP*, AND THE JOURNAL'S EDITORIAL BOARD FOR INVITING US TO REVIEW AND UPDATE THE 1980 PAPER ON PUBERTY AND SLEEPINESS. We appreciate this opportunity and hope to use it effectively to summarize the state of the art and to speculate a bit about the processes that affect the phenomena. We do not have all the answers about adolescent sleep patterns and sleepiness, but we have come a long way since 1980.

UPDATE: ADOLESCENT MULTIPLE SLEEP LATENCY TEST AND SLEEP DATA IN THE STANFORD LONGITUDINAL STUDY

The multiple sleep latency test (MSLT) was first used at the Stanford Sleep Laboratory in the spring of 1976 in a validation sleep-loss study, and the data were presented at the 1977 Associated Professional Sleep Societies (APSS) meeting.[1] The success of that initial study and the desire to learn more about the measure led to the inclusion of the MSLT as a core measure for the Stanford Summer Sleep Camp experiments carried out over the next 10 years. These experiments included the longitudinal assessment of adolescent sleep, as well as a number of studies in which sleep quantity was manipulated, studies in normal elderly persons, and evaluations of patients with narcolepsy and sleep apnea syndrome. These Sleep Camp experiments began in the summer of 1976, and the 1977 APSS meeting also included early reports of MSLT in 10- to 13-year-old adolescents under baseline conditions[2] and following a night of acute sleep restriction.[3] The following summer's study of the adolescent participants included Tanner staging of pubertal development, and the first report of MSLT as a function of developmental stage in this cohort was presented at the 1978 APSS meeting.[4]

The 1980 report in *SLEEP* reprinted for this anniversary issue[5] summarized baseline sleep and MSLT data from the first 3 years of the Stanford longitudinal adolescent study. This project was an important part of Carskadon's doctoral dissertation,[6] completed with the mentorship of a committee comprising William C. Dement, MD, PhD; Helena Chmura Kraemer, PhD; and Thomas F. Anders, MD. Dr. Kraemer's influence is most apparent in the survival-curve analysis of the MSLT data for the dissertation and the 1980 paper. The survival-curve approach remains among the best but most underused methods for analyzing MSLT data, although a resurgence of this approach has recently emerged.[7] In terms of visual display of the data, the survival curves are superior to virtually every other method because they show every data point in the sample. At the same time, however, the survival-curve displays are somewhat inefficient and do not always clearly convey patterns that may be important. Most subsequent studies with MSLT have used a variety of other analysis and display techniques, including simple median and mean and log transform.

In rereading the 1980 paper,[5] several methodologic features stand out. In the first place, this study was a major departure from previous evaluations of normal sleep: sleep schedules were fixed not only during the recording nights, but also for 1 week before in-lab visits and for all the follow-up evaluations. Most sleep studies (either longitudinal or cross sectional) in the 1960s and 1970s evaluated sleep in the context of subjects' "usual schedules." Second, this study was one of the first polysomnographic examinations of human sleep in a 24-hour context, giving equal weight to evaluating the sleeping and waking portions of the day. In contrast to earlier 24-hour sleep-wake studies that used alternative sleep schedules, such as the 240-minute schedule,[8] the 180-minute day,[9] or the 90-minute day,[3,10] this project attempted to examine waking alertness in the context of optimal nighttime sleep. [These innovations came from a collaborative effort of Carskadon and her dissertation advisers: Tom Anders was interested in learning about the "sleepy child" and Bill Dement was interested in sleepiness per se. They determined that a basal protocol run in normal children, stabilizing scheduled sleep at a level that appeared adequate for younger participants, was fundamental to both goals. The collaboration provided Carskadon great latitude in the design and implementation of the protocol: what a wonderful research opportunity for a graduate student!]

Another striking feature of the 1980 paper was the discussion's extensive apologia of the MSLT as a valid measure of sleepiness. Although the MSLT had been in use for several years and a number of publications had appeared,[11-13] many scientists remained skeptical about the MSLT's utility. This skepticism continued for a number of years. In 1986, however, the American Sleep Disorders Association recognized the importance and usefulness of the MSLT by convening a committee to prepare guidelines for its use.[14]

Data collection from this cohort of normal youngsters continued for a total of six summers, and more of the data were included in two subsequent summaries of the findings. Carskadon's 1982 chapter in Guilleminault's book on indications and techniques[a] provided summary tables by Tanner stage of the nocturnal sleep and daytime MSLT data for each of the three study days.[16] Data from a comparison group of young adults who had been studied under similar conditions were also included in that chapter. (Similar summary tables for children aged 8 and 9 years appeared in a subsequent publication.[17]) Preliminary data from a small sample of children with a family history of narcolepsy who were followed along with the normal adolescent sample were included in the 1982 chapter. Carskadon and colleagues published the final summary of the longitudinal data in another book chapter,[18] which presented the data from all 6 years of the longitudinal study and provided tables and formulas for determining values of sleep and MSLT by age, sex, and Tanner stage. These tabled data were used as the context for interpreting findings from the cohort of adolescents with a family history of narcolepsy.

[a] I note that this book also included a misstatement in the methodology chapter on MSLT in which sleep onset was defined as the "first three consecutive epochs of sleep" or the "first epoch of stage 2, 3, or 4 NREM sleep or REM sleep".[15] The 1986 MSLT guidelines[14] revised the sleep-onset definition as the first epoch of sleep, which was used in the original studies and for which my dissertation clearly outlined the rationale in both experimental and clinical settings.[6] Unfortunately, this misstatement has led to confusion about the MSLT that continues even to this day.

Disclosure Statement

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Address correspondence to: Mary A. Carskadon, PhD, E.P. Bradley Hospital Sleep Research Laboratory, 1011 Veterans Memorial Parkway, East Providence, RI 02915, 401-421-9440, Fax: 401-453-3578, mary_carskadon@brown.edu

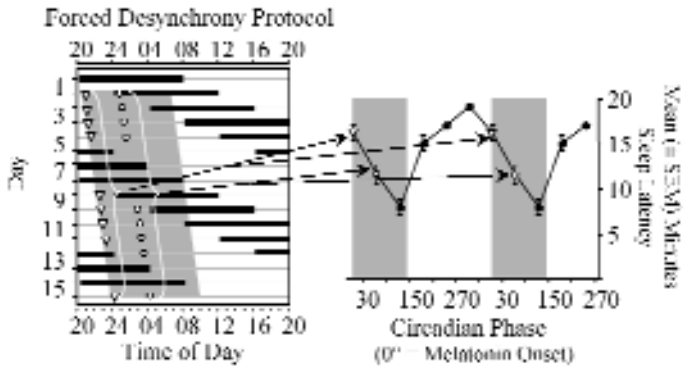

Figure 1—The left panel of the figure illustrates the sleep-wake schedule for the forced desynchrony protocol: Black bars indicate scheduled sleep in <1 lux; gray lines indicate that lighting was <20 lux. Grey shading is a schematic illustration of a free-running melatonin rhythm. Data points gathered near the melatonin-onset phase are indicated by triangles; data gathered at a later circadian phase are indicated by circles. These data points when averaged can be plotted on a diagram illustrating the values for that circadian phase, irrespective of how long the child has been awake. Data on the right panel are double plotted so that the daily cycle is apparent. As before, the gray background is a schematic representation of the phase of melatonin secretion. The averaged data points depicted on the left panel are identified in the right panel by the arrows.

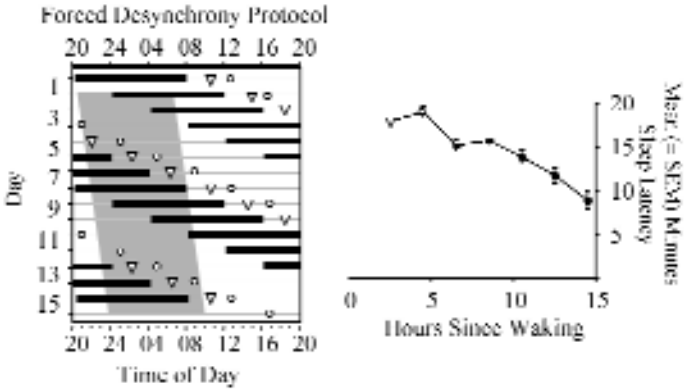

Figure 2—Black bars, gray lines, and the gray background pattern are described in Figure 1. The right panel here depicts MSLTs collected about 2.5 hours after the end of the scheduled sleep (triangles) and approximately 2 hours later (circles). The right panel depicts the curve of sleep tendency when data are averaged across all circadian cycles, with the two points shown in the left panel indicated by the appropriate symbols.

The three summaries of the longitudinal study, including the 1980 *SLEEP* paper, confirmed several general findings about the developmental patterns of sleep and sleepiness in this group of normal adolescents studied longitudinally:

- Sleep "need," operationally defined as the amount of sleep obtained in the 10-hour sleep opportunities for each assessment, did not change across the adolescent span (aged 10 to 17 years). Across age, sex, and Tanner stage, polysomnographically identified sleep was about 9 hours. A slight decline was identified in the oldest girls who were Tanner stage-5[18]; however, children beyond Tanner stage 2 were never awake at the end of the 10-hour bedtime window, so total sleep was truncated by protocol.
- Slow wave sleep (SWS) time decreased by about 40% across this same span, even though total sleep amount was unchanged.
- The MSLT showed an increased level of daytime sleep tendency at midpuberty, which manifested as faster sleep onsets for the afternoon assessments.
- Few consistent sex differences (controlling for age and Tanner stage) were apparent.

The final chapter of the Stanford Summer Sleep Camp assessments of adolescent sleep occurred in the summer of 1984 when a novel experimental paradigm was used to examine the lingering question of whether the midday augmentation of diurnal sleep tendency simply represented a postprandial phenomenon. The constant routine[b,19] seemed ideal for this purpose because a central feature—in addition to constant activity levels, posture, and lighting—was small equal-caloric meals taken at frequent intervals. As presented by Carskadon and colleagues at the 1985 APSS meeting[20] and subsequently reported in this journal,[21] the data demonstrated no significant effects due to the baseline midday meal and a midday augmentation of sleep tendency on the constant routine in postpubertal participants.

Carskadon supervised other Stanford Sleep Camp studies that examined sleep and sleepiness in older persons, and one of these experiments is relevant to the current discussion, although participants were not adolescents, but young adults (aged 19 to 23 years) and elderly persons (aged 60 to 83 years). This study examined the 24-hour pattern of sleep tendency with MSLTs administered during waking hours combined with sleep-latency assessments by waking subjects at 2-hour intervals during a night otherwise spent sleeping.[22] This study led to the conclusion that sleep tendency demonstrated a "biphasic pattern" in both groups, with increased sleep tendency at night and in the midday, as had been seen in the pubertal adolescents. Two explanations for this pattern were offered:

- "Conceivably, the morning and evening peaks in alertness might be the result of two distinct physiological or neurophysiological circadian rhythms that have as their common consequence a decrease in sleep tendency. …A phase-angle difference between the two rhythms would result in a midday trough, during which sleep tendency could increase to nocturnal levels."[22]
- "Alternatively, the sleep tendency rhythm might represent the sum of circadian and noncircadian functions. Specifically, the rising phase of the physiological rhythm indexed by body temperature might reverse the nonrhythmic trend towards increasing sleep tendency as a function of time awake."[22]

Data we have collected in recent years clearly point to the latter explanation as the source of this pattern. Identifying why and how this pattern emerges during adolescent development has been a major thrust of our recent research program.

INSIGHTS AND NEW DATA CONCERNING THE REGULATION OF DIURNAL SLEEP TENDENCY

The primary models describing intrinsic sleep-wake regulation rely on two principal factors, one attributed to the circadian timing mechanism, the other to underlying sleep-wake mechanisms. Borbély was the first to articulate clearly a model identifying these two factors, labeling the circadian process, *Process C*, and the homeostatic process, *Process S*.[23,24] In one description of the model, Process C is modeled by a daily oscillation of one threshold at which sleep can begin and a second at which sleep terminates; process C interacts with Process S, which accumulates as wakefulness is extended and decays exponentially with sleep initiation.[25] According to the model, sleep will begin and end where the two functions cross.

In the years since this model was first described, it has been refined, other models have been proposed, and more has been learned about the interaction of the circadian and homeostatic factors. For example, Åkerstedt and Folkard[26] include in their model a "sleep inertia" factor (Process W) along with the additive circadian and homeostatic factors in order to predict waking behavior better. Edgar,[27,28] by contrast, casts the circadian and homeostatic factors as opponent processes, in which a circadian (clock-dependent) alerting process opposes a wake-dependent sleep-promoting process to maintain wakefulness in primates across the subjective day. Dijk and Czeisler[29] proposed a similar model of opposing processes to describe the maintenance of sleep across the night in humans.

Although these models serve as important theoretical background for our studies, most models of sleep and vigilance regulation (such as those proposed by Edgar et al,[27] Dijk and Czeisler,[29] and Jewett and Kronauer[30]) do not account for the midday increase in sleep tendency, large-

[b]The constant routine is an experimental method for collecting data in the absence of the masking effects of feeding, activity, and sleep. Subjects maintain constant posture, eat frequent small meals, and are prevented from sleeping, usually for 36 hours or longer.

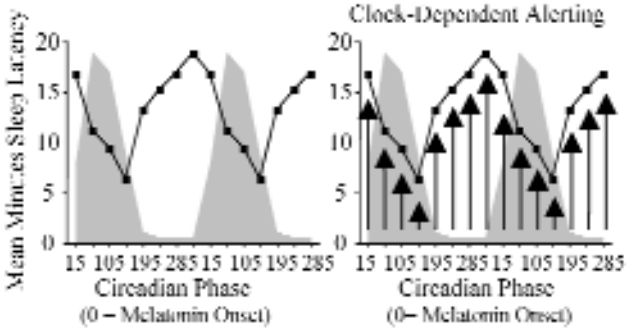

Figure 3—The left panel shows the circadian rhythm of sleep tendency as measured by the multiple sleep latency test on the background of averaged melatonin secretion from 10 adolescents studied in a 28-hour forced desynchrony. As indicated in Figure 1, this rhythm is depicted independent of time awake. The right panel is a schematic of the clock-dependent alerting process: longer arrows indicated greater alerting.

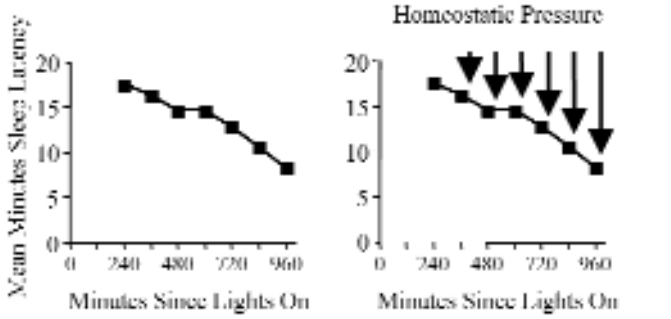

Figure 4—The left panel shows the average sleep tendency (based on the multiple sleep latency test) across the waking day, irrespective of circadian phase. The right panel depicts a schematic of the homeostatic pressure for sleep, with longer arrows indicating greater sleep pressure.

ly because the models are based upon introspected sleepiness. As Richardson and colleagues[22] showed, subjective reports do not manifest the same diurnal pattern of sleepiness as does the MSLT; thus, the midday effect is not represented in most models based on subjective estimates (as, for example, in the Jewett and Kronauer model[30]). Lack and Patrick[31] have presented a model that accounts for the midday alertness trough requiring only an intrinsic circadian rhythm factor. Broughton,[32] however, modeled an afternoon "nap zone" based on an interaction between circadian and homeostatic parameters, a model that is very similar to the predictions we constructed from data of pubertal adolescents.

The underlying processes that can explain diurnal sleepiness come into sharp focus with MSLT data collected from adolescents undergoing a protocol that allows us to isolate the effects of the sleep-wake homeostatic process from those of the circadian timing system. In order to examine the independent and interactive effects of these systems, one must measure variables or systems at many times and many circadian phases. One way to accomplish such multiple measurement is to vary the length of time awake and asleep, equalizing for time of day[33]; however, such an approach is difficult to implement in a design that is orthogonal both for sleep-wake and time of day. An alternative experimental approach that has recently led to significant gains in human studies is called forced desynchrony (FD).[34]

The term *forced desynchrony* derives from the experimental disruption of alignment between the environment and the intrinsic oscillator that occurs when participants are studied while living on an imposed schedule beyond the intrinsic circadian oscillator's range of entrainment. Thus, physiologic processes maintain their internally generated rhythmicity, but they desynchronize from the imposed environmental cues and run free at the intrinsic oscillatory period. In order to accomplish such desynchrony, a very short (eg, 20-hour) or a very long (eg, 28-hour) cycle of rest-activity can be imposed. In our lab, we use the 28-hour cycle and are able to compute the period of the intrinsic circadian timing system across cycles from several phase markers: melatonin onset, melatonin offset, minimum core body temperature, and cortisol peak.[35] The key feature of the FD protocol, therefore, is that the circadian system runs free from the environmental schedule so that scheduled sleep and waking events occur at varying phases of the internal circadian timing system; conversely, a given circadian phase occurs at varying lengths of time after the offset of waking (or the onset of sleep). By carefully measuring and tracking these parameters, one can determine the "circadian phase" and the "homeostatic time" for any data point based on the time at which it was gathered in the individual. The independent contributions of these processes can then be determined for a variety of measures of interest.

Our MSLT analyses come from children (5 boys, 5 girls; aged 13-15 years; Tanner stages 3, 4, or 5) who participated in an FD study.[36] Participants lived at home on a fixed schedule, with sleep scheduled from 2200 to 0800, for 11 days before the in-lab study. Four children participated together for the in-lab portion of the study, all on the same schedule. Two 36-hour constant routines were performed, one immediately before and a second immediately following the FD procedure. The FD included 12 cycles of 28 hours (11.67 hours asleep; 16.33 hours awake).[36] The "experimental" version of the MSLT procedure[14] was implemented at 2-hour intervals, with each cycle beginning 2.5 hours after the end of the scheduled sleep episodes. We assigned each test score a value based on circadian phase at the time of the test (determined based upon each individual's intrinsic period) and a value based upon the length of time since the offset of the scheduled sleep episode. Thus, each MSLT score has a known circadian phase and a known value for the homeostatic sleep-wake system (time awake).

In order to identify the impact of circadian phase and sleep-wake homeostasis, data are averaged separately for each circadian phase and from each interval of time awake. Figure 1, for example, illustrates the process for determining circadian phase contributions: two phases are highlighted on the left diagram, demonstrating how two data points were derived according to circadian phases, for data collected near the onset of melatonin secretion (triangles) and for data collected from a phase several hours later in each cycle (circles). This diagram shows clearly how the same circadian phase position occurs at a different time relative to the sleep-wake schedule on consecutive cycles because the schedule and circadian rhythms are no longer synchronized. The data acquired at a particular phase for each cycle are averaged together, regardless of how long the participant was awake. The curve on the right panel of Figure 1 is derived from averaged data points and plotted twice so that the cycle is more easily visible. (For this analysis, data were binned into intervals spanning 45° of the circadian day, ie, 3 "circadian hours.") The sleep-wake contribution to MSLT can be assessed in a similar fashion, only now holding constant the interval relative to the sleep-wake schedule. Figure 2 shows how such data points are derived, and the right-hand panel includes the mean values from all data points at specified intervals since waking up, regardless of circadian phase.

These MSLT data acquired from the FD protocol can be mapped onto the theoretical constructs. Thus, as Figure 3 shows, the circadian pattern (independent of sleep-wake homeostasis) shows greatest alertness near the onset of the circadian "night" (marked here by the onset of melatonin secretion, which is depicted by the gray background pattern) and least alertness toward the end of the circadian "night." The right side of Figure 3 is a schematic depicting the strength of clock-dependent alerting as illustrated by the upward arrows. This paradoxical circadian pattern—sleepiest at the end of the circadian nighttime and most alert at the end of the circadian day—makes eloquent sense if circadian and homeostatic factors are conceptualized as opponent processes. Figure 4 shows the "pure" homeostatic or wake-dependent sleep-tendency curve for these youngsters. As predicted by the two-process and opponent process models, alertness associated with the sleep-wake process is greatest in the hours closest to sleep offset (excluding a sleep inertia window) and declines monotonically across the waking day. On the right side of Figure 4, the homeostatic drive to sleep is portrayed with downward-point-

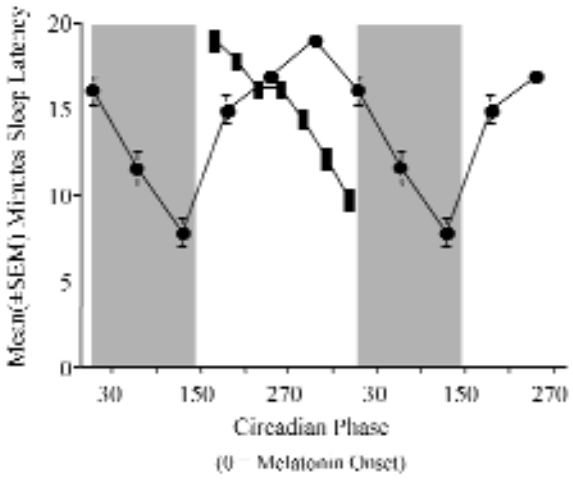

Figure 5—Multiple sleep latency test values for the circadian and homeostatic components of the regulatory process are juxtaposed, with the homeostatic curve (see Figure 4) drawn to overlay the waking part of the circadian cycle.

ing arrows depicting the relative strength of the wake-dependent process. When circadian and homeostatic processes are linked in the normal waking day (Figure 5), one can clearly identify how humans are able to sustain alertness across an extended daytime waking interval: low homeostatic sleep tendency in the morning after a night of sleep opposes the early-morning circadian trough of alertness; the circadian (clock-dependent) alerting signal rises across the day to the onset of the circadian night opposing the "weight" of increased sleep tendency associated with prolonged waking.

Because the homeostatic component of the model is "reset" by a night of sleep,[23] the alignment of sleep (particularly sleep offset) to the circadian timing system is a key determinant for the course of sleepiness across the day.[c]

SPECULATIONS: DEVELOPMENT, PHASE ANGLE DIFFERENCES, AND THE IMPACT OF INSUFFICIENT SLEEP

The question remains how to fit the theoretical constructs with observed changes in MSLT pattern across adolescent development. In order to put our current perspective into the analysis, we must first describe a number of findings about the adolescent sleep-wake and circadian timing systems from the last two decades. Sleep-habits survey data acquired in the late 1980s and 1990s fill in some gaps and characterize more richly what adolescents say about their "real-life" sleep-wake patterns. These data from a number of other groups studying adolescents in industrialized countries[38-44] confirm several major developmental trends in adolescent sleep practices.

- Bedtimes delay markedly across the adolescent span, especially on weekend nights
- Rise times also delay on weekend mornings; however, the delay of rise times on school days is held in check by early school starting times
- The amount of sleep on school nights declines precipitously, while weekend night sleep time changes much less
- The discrepancy between school night and weekend sleep patterns grows markedly across adolescence
- The magnitude of the school–night-to-weekend discrepancy is linked to problematic outcomes, including impaired school performance and depressed mood

The delay of sleep patterns across adolescent development has been

[c]In circadian rhythm terminology, this alignment is usually quantified as a "phase angle" difference. The phase angle is "the value of the abscissa corresponding to a phase of the oscillation, usually given in degrees, where the whole period is defined as 360 degrees and the zero point is arbitrary." A phase angle difference is the "difference between corresponding phase angles in two coupled oscillations, given either in degrees or units of time".[37]

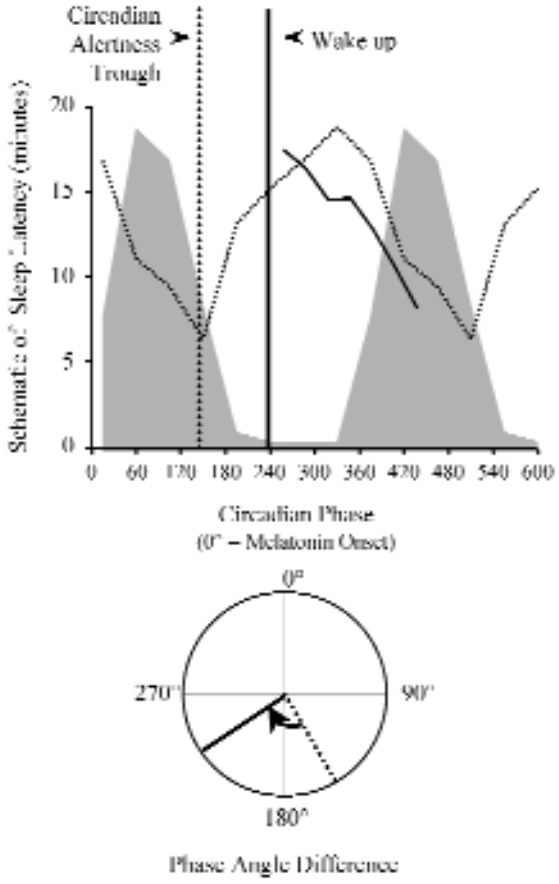

Figure 6—As detailed in the text, the phase angle difference between usual time of waking and the internal circadian phase determines the point at which the homeostatic drive for sleep intersects the circadian rhythm of clock-dependent alerting. The top panel shows that waking up (solid line) far from the trough of the circadian rhythm of alertness (dotted line) produces a large phase angle difference (bottom panel) and moves the homeostatic drive for sleep into the phase when it is opposed by the circadian process.

recognized for many years and was generally attributed to psychosocial factors (growing sense of autonomy, increasing opportunities for evening social interactions, more homework, after-school employment, and so forth). When the social restraint on sleep patterns—going to school—is removed, the delay of sleep patterns is also associated with a change in markers of circadian phase. For example, we showed in a group of mid-adolescents (aged 14 to 16) that summertime sleep onset was 1.5 hours later and sleep offset nearly 2 hours later than during the previous school year, and dim-light melatonin onset phase was about 1.25 hours later.[45] Laberge and colleagues found similar summertime delays of sleep and circadian phase in adolescents and young adults.[46] Because the circadian phase marker moves with sleep-wake under these relatively unconstrained circumstances, the question arises: is the adolescent delay of sleep patterns solely due to psychosocial factors, or do the underlying biologic regulatory processes also contribute to the delay? Further, does sleep-wake homeostasis or circadian timing contribute most to the developmental changes?

Several findings point to the involvement of adolescent changes in the sleep-wake homeostatic process as favoring a later bedtime. The adolescent decline in SWS under "optimal" sleep conditions,[5] for example, may indicate that sleep "pressure" accumulates at a reduced rate for older adolescents. Data from a study of sleep loss indicate that older adolescents have a diminished SWS response to sleep deprivation.[47] These data are suggestive of developmental changes in the sleep-wake homeostatic process but are not yet conclusive.

The effects of aging on circadian rhythms have been widely studied for many years. This research, while not central to the adolescent story,

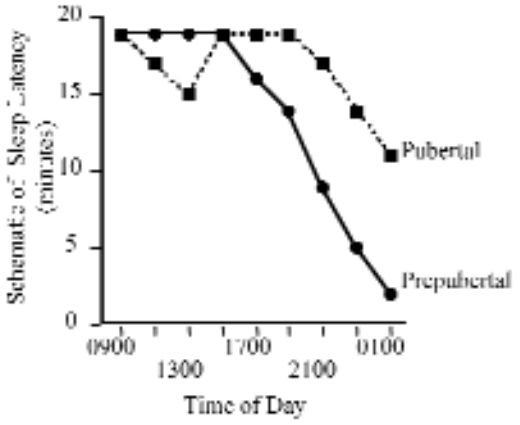

Figure 7—This figure provides a schematic illustration of the multiple sleep latency test findings from the 1980 paper,[5] showing sustained daytime alertness in prepubertal adolescents (solid line) and the pubertal midday trough in alertness (dashed line). We speculate that the pubertal adolescents also sustain alertness later into the night. Times are based upon the original 1980 sleep-wake schedule.

is relevant because these studies show that developmental changes in circadian parameters may occur, though certain conclusions are in dispute. For example, Pittendrigh and Daan[48] showed that the period of the circadian activity rhythm is faster in old versus young animals. This finding was subsequently confirmed in several studies and with regard to sleep patterns as well as activity.[49] Assessment of aging humans, however, have not confirmed an age-related decrease in the period of the circadian activity rhythm.[50] A decline in the amplitude of circadian rhythms with advanced age—with a speculated impact on the sleep-wake system—has also been suggested, though results are mixed.[51-54] Other features of the aging circadian timing system have been shown with somewhat greater consistency. Earlier phase positions in old versus young adult humans have been noted.[55,56] These changes are reflected by earlier temperature phase and earlier bedtimes and rising times with increasing age.[51]

Changes occurring within the circadian timing system also point to a reorganization of biologic systems during adolescent development that are "permissive" for, if not driving, the adolescent delay. Our first piece of evidence for such a change came in 1992 when we had the opportunity to explore the association of puberty and the circadian timing system through a survey performed in conjunction with a children's science magazine (*SuperScience Blue*). Data were collected from 11- and 12-year-old sixth-grade girls and boys in 36 schools from around the United States. The survey included a number of questions about sleep habits, a set of items providing a scale of pubertal development,[57] and a set of child-friendly items to assess circadian phase preference.[58] The analyses of these data attempted to control for psychosocial factors by choosing children from the same academic grade and by controlling for such factors as birth order and type of school. This report concluded that more mature girls were more evening type in their phase preference. Boys showed a similar trend that did not reach statistical significance, probably because fewer boys had achieved more than modest landmarks in pubertal development.[58] Laberge's longitudinal survey study is strong confirmation of an association of puberty and delayed sleep patterns.[41]

We ran a follow-up sleep-lab study to examine puberty and circadian phase with more direct measures.[59] This study controlled for psychosocial factors using an elaborate experimental design involving 10 nights on a fixed sleep-wake schedule (compliance checked with actigraphy, sleep logs, and daily telephone calls), followed by three 18-hour nights in the lab sleeping or resting in bed under less than 1-lux light levels, followed by a constant-routine assessment of phase using half-hourly saliva samples to measure melatonin (onset and offset) and cortisol (peak) secretion. Although these measures were available for only 14 participants, Tanner stage of pubertal development and the phase of melatonin offset were significantly correlated (r = .62; df = 2; p = .02). This association supports the hypothesis that circadian timing shifts significantly during pubertal development, even when not exposed to changes deriving from an altered adolescent psychosocial context.

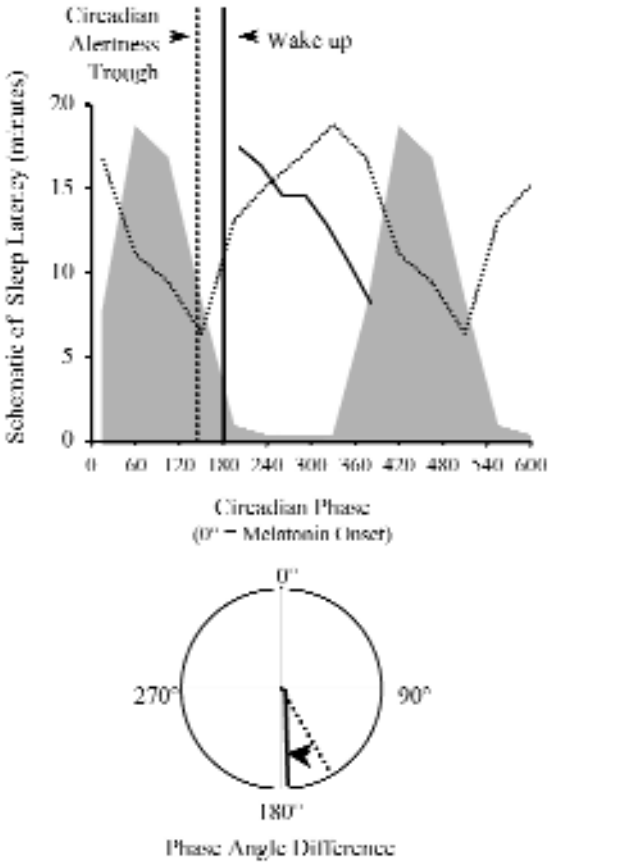

Figure 8—The top panel shows that waking up (solid line) near the trough of the circadian rhythm of alertness (dotted line) produces a small phase angle difference (bottom panel) and moves the homeostatic drive for sleep into an alignment at which it is weakly opposed by the circadian process until late in the circadian day.

The presence of an adolescent or pubertal delay in circadian phase preference—as has been reported in a number of studies[40,41,58,60,61] with quite distinct samples—has important implications for determining how the pubertal change in daytime sleepiness occurs. Whether this observed change represents a true change in the circadian timing system or behavioral masking is uncertain. Recent studies of circadian phase preference in adults, however, provide evidence that circadian phase preference is linked to three distinct underlying circadian parameters: phase angle of entrainment, intrinsic circadian period, and circadian rhythm amplitude. Data from a number of studies in adults indicate that circadian phase preference is linked to the phase angle between habitual (or self-selected) sleep patterns and such markers of the circadian timing system as body temperature and melatonin secretion.[62-66] These studies show a consistent pattern indicating a greater interval (ie, greater phase angle difference) between nocturnal phase markers and habitual sleep offset in those with morning phase preference (M-types) than in those with an evening phase preference (E-types). For example, Baehr et al[65] reported that the minimum of the body-temperature rhythm in young adult volunteers occurred closer to wake up in E-types than in M-types; Liu and colleagues[66] reported that adults who are M-types had a longer interval between the time of melatonin peak and the midpoint of sleep; and Duffy et al[63] reported that the phase angle difference of the minimum of the body temperature rhythm and habitual wake time was longer in M-type than E-type young adults. If behavior alone (ie, sleep and activity patterns) were the factor driving the differences in the clock time of phase markers between M and E types, then one would not expect the phase alignment to differ as a function of circadian phase preference.

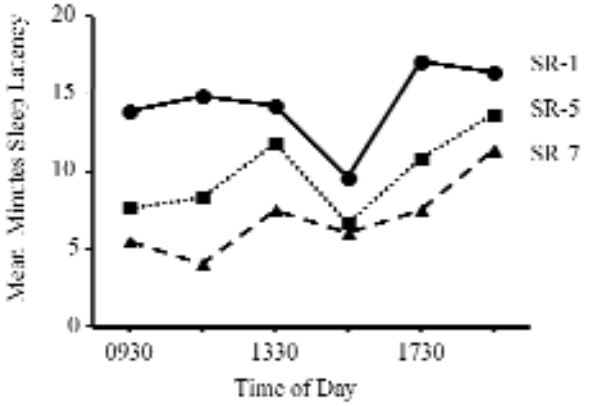

Figure 9—MSLT data from older adolescent/young adult participants in a 7-night study[71] of sleep restriction to 5 hours a night are illustrated for the days following the first, fifth, and seventh nights of sleep restriction.

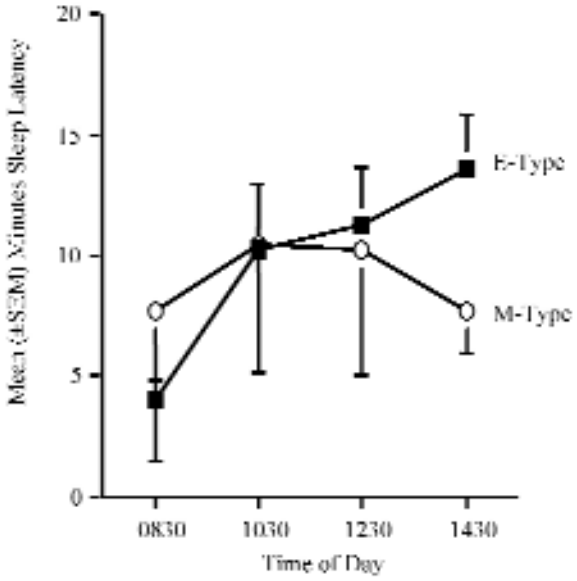

Figure 10—Multiple sleep latency test (MSLT) data from adolescents keeping a self-selected sleep-wake schedule[72]. Drawn from a sample of over 60 participants, these data come from those whose phase preference scores were >1 standard deviation from the group mean. Squares indicate mean MSLT latencies of those with scores indicating greater evening-phase preference (E-Type); open circles indicate mean MSLT latencies of those with scores indicating greater morning-phase preference (M-Type).

Duffy and colleagues[64] have also shown that intrinsic period correlates with circadian phase preference, which could account for these differences in phase angle. In a study of 17 young men in whom the circadian period was assessed using FD, these authors reported a significant negative correlation of circadian-phase-preference score with circadian period. Thus, those with a shorter circadian period were more M-type than were those with a longer intrinsic circadian period. Differences in entrained phase angle as a function of circadian phase preference may arise through the process of entrainment. According to this process, individuals with a longer intrinsic period would require a greater daily phase advance to achieve stable synchrony to a 24-hour cycle. Waking up closer to the minimum of the body-temperature rhythm places rising time at the portion of the phase response curve to light at which a greater phase advance is produced, and thus E-types with a long circadian period are able to phase advance on a daily basis.[64] [Our initial studies of adolescents indicate that intrinsic period is perhaps slightly longer overall in adolescents than in young adults (mean adolescent period = 24.33 hr[35] vs. 24.18 hr in young adults[67]), though our study did not find changes within the adolescent span.]

Baehr and colleagues[65] using ambulatory monitoring of core body temperature in young adult males found that those with more-delayed phases had greater temperature-rhythm amplitudes. This finding is consistent with circadian oscillator theory,[68] which postulates that a stronger rhythm (ie, greater amplitude) entrains to the environment with a lag, thus delaying the rhythm in relation to the environment. One final piece of evidence supporting a biologic basis for circadian-phase preference is the finding that circadian-phase-preference scores in adult humans were correlated with a polymorphism in the human CLOCK gene, thought to be a homologue of circadian regulatory genes identified in other species.[69]

Given these features of the circadian timing system and the known developmental changes of adolescence, we can finally model the processes that converge to produce the observed MSLT pattern in the prepubertal and pubertal adolescents from the 1980 paper.[5] To review: first, we know that less-mature adolescents manifest a more M-type circadian-phase preference than do more-mature adolescents[58]; if we assume the same associations between circadian phase preference and circadian timing in adolescents as in adults, then the phase angle difference between waking up and the circadian phase of minimal alertness will be broad in prepubertal adolescents. Figure 6 shows a schematic diagram depicting this broad phase angle difference and uses the MSLT curves for circadian and sleep-wake homeostatic components to predict the outcome (Figure 7). Note that the broad phase angle difference places wake-up time at a relatively late phase of the clock-dependent alerting cycle. Thus, we speculate that the young well-slept (M-type) adolescent wakes up with a low sleep pressure and minimal sleep tendency due to the nighttime resetting of Process S and the timing of arousal on the rising phase of the alerting cycle. Sleep tendency remains buffered as homeostatic pressure builds across the day, because clock-dependent alerting supports the system through the afternoon. By evening, however, the circadian rhythm that bolsters alertness begins its downward course; from that point on, the sleep-wake homeostatic system and the circadian timing system work together to favor high sleep tendency at an early bedtime (Figure 7).

As adolescent development unfolds, the circadian phase preference shifts towards an E-type preference. Again, under the assumption that phase preference in adolescents is similar in its biologic basis to that of adults, the phase angle difference between waking up and minimal circadian alertness becomes narrow. As Figure 8 illustrates, this shift ultimately may bring the wake-up time very close to the sleepiest circadian phase. Nevertheless, the well-slept adolescent manifests a strong level of morning alertness due to the resetting of Process S by the night's sleep. Midday sleepiness reflects the new alignment of the day's increasing homeostatic sleep pressure and clock-dependent alerting: according to the model, the narrow phase angle difference results in a timing of the two functions such that sleep pressure accumulates before clock-dependent alerting achieves adequate strength to offset sleepiness. Subsequently, sleep tendency decreases as the older adolescent experiences the growing strength of the circadian alerting cycle, which can sustain alertness into the late evening hours. Keep in mind as well that more mature adolescents may also benefit from a reduced intensity of Process S (reduced SWS).[5] The schematic in Figure 7 summarizes the outcome of these predictions as they would manifest in sleep tendency measured by MSLT.

In the final section of this paper, we would like to highlight why this model does not apply to many adolescents in the "real world." The problem, of course, is that many adolescents in the real world are not well slept; instead, many suffer from a chronic sleep debt. Carskadon and Wolfson[44] reported, for example, that the median school-night total sleep time reported by a large sample of high-school students (aged 14 to 18 years) is 7.5 hours, considerably less than the time allotted for sleep at the Stanford Summer Sleep Camp. When adolescents are not well slept, their sleepiness pattern looks very different from our 1980 data. For example, one of our studies[70] examined a group of 25 mid-adolescents (aged 14 to 16 years) who were sleeping on their usual sleep schedules, including waking up in time to start school at 7:20 AM. Actigraphy confirmed average school-night bedtimes of about 11:40 PM and rising times

of 6:00 AM. When MSLT tests were performed, these young people showed a pattern of sleep latencies that averaged 5.5 minutes at 8:30 AM and rose to 11.3 minutes at 2:30 PM. This pattern was virtually the mirror image of the monotonic decline of sleep latencies shown in Figure 2.

A partial explanation for this anomalous pattern of sleep latencies derives from data acquired in another of the Stanford Summer Sleep Camp studies performed by Carskadon, Dement, and their colleagues.[71] This study involved restricting nocturnal sleep to 5 hours for 7 nights in a group of 10 older adolescents/young adults (aged 17 to 22 years). Figure 9 depicts the progressive change in MSLT patterns as sleep loss accumulated following 1 night (SR-1), 5 nights (SR-5), and 7 nights (SR-7) of sleep restriction. Although late afternoon and evening sleep latencies for SR-7 were not as long as on baseline, the most significant change in sleep tendency occurred for the morning tests, presumably because Process S was not fully reset by the nocturnal sleep episode and the circadian phase was close to the trough of alertness. The rise of sleep latencies later in the day reflects clock-dependent alerting. Carskadon and colleagues did not measure circadian phase preference in these participants. Because few college students are likely to be M-type, however, the alignment of their usual schedules to their circadian cycle was likely to have had a relatively narrow phase angle difference, as seen in Figure 7.

We predict that E-type pubertal adolescents with chronic insufficient sleep will be most likely to manifest this pattern of very high morning sleep tendency and late-day (relative) alertness as chronic sleep restriction interacts with these processes. We have recently examined a small set of pilot MSLT data from adolescents studied while living on their own self-selected school-year sleep-wake schedule, selecting the participants with the most extreme scores on a measure of circadian phase preference.[72] We predicted that in these chronically sleep-restricted adolescents, the more–M-types—presuming a broader phase angle difference between wake-up and circadian-alertness trough and incomplete resetting of Process S—would have some reduction of morning sleep latencies and an early decline of sleep latency. We also predicted that the more–E-types—presuming a narrower phase angle difference and incomplete resetting of Process S—would have very low morning sleep latencies and that sleep latencies would lengthen across the day. Figure 10 illustrates the findings from the pilot study, which seem to fit the predicted pattern.

In summary, we now have a good sense of the regulatory processes that account for the interesting pubertal change in sleepiness reported in 1980. Maturational changes that affect the alignment of circadian and sleep-wake processes appear to underlie the reorganization of diurnal sleep tendency. The pathway from pubertal maturation to phase angle realignment is not clear, and the possibility that feedback of behavioral factors ultimately is responsible for this reorganization has not been ruled out. In terms of the practical realities of adolescents' lives, this combination of forces is particularly devastating for adjusting easily to the demands of early-morning school starting times.

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