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Chronotherapy: Resetting the Circadian Clocks of Patients with Delayed Sleep Phase Insomnia

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Summary: We report here the development of a brief drug-free rescheduling treatment ("chronotherapy") for Delayed Sleep Phase (DSP) insomnia, a syndrome characterized by sleep-onset insomnia with difficulty in morning awakening. We postulated that patients with DSP insomnia had an inadequate capacity to achieve phase advance shifts of the circadian pacemaker which times the sleep-wake cycle. Chronotherapy was therefore designed to reset these patients' biological clocks by the phase delay route. This single 5–6 day treatment was tested in 5 patients with a 4–15 year history of DSP insomnia. All 5 patients reported a lasting resolution of their symptoms substantiated by systematic long-term self-reports and objective polygraphic recording before and after treatment (average follow-up of 260 days; range, 42–910 days). The average sleep onset advanced from 4:50 a.m. before treatment to 12:20 a.m. afterwards, and wake times advanced from 1:00 p.m. to 7:55 a.m. (for both, $p < 0.001$), with no reduction in sleep efficiency. As a result, all 5 patients were able to end their chronic dependence on hypnotic medications. **Key Words:** Sleep scheduling disorders—Chronotherapy—Circadian rhythms—Insomnia.

. . . they lie awake, for perhaps two or three hours, after going to bed, and do not fall into slumber till towards morning. Persons of this description often lie long and are reputed lazy by early risers, although, it is probable, they actually sleep less than these early risers themselves.

Robert Macnish, 1836

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Sleep onset normally occurs within a short time after going to bed (Kleitman, 1963), yet it has long been recognized that certain individuals have considerable trouble falling asleep at night, followed by corresponding difficulty awakening in the morning (Macnish, 1836). Despite their difficulty initiating sleep at the time desired (so-called "sleep-onset insomnia"), such patients do not have difficulty maintaining sleep once initiated and therefore can be distinguished from patients with other forms of insomnia (Dement et al., 1975; Frankel et al., 1976; Regestein, 1976; Weitzman et al., 1979*a*). Even Sir James Sawyer's rather simplistic classification of insomnias in 1912 ("the inability to sleep at all, or long enough, or at a convenient time") recognized such sleep scheduling disorders as a distinct form of insomnia. We now report the development of an effective clinical treatment for sleep-wake disorder patients with the following set of features: (1) reported sleep onsets and wake times intractably later than desired; (2) actual sleep times at nearly the same clock hours daily; and (3) essentially normal all-night polysomnographic recordings except for delayed sleep onset. We have called this entity the Delayed Sleep Phase Syndrome (DSPS) [Category C.2.b., Association of Sleep Disorders Centers Diagnostic Classification of Sleep and Arousal Disorders (ASDC), 1979].

In a 1975 case series of 100 patients complaining of insomnia conducted at the Stanford University Sleep Disorders Center, 10% of the patients were given a diagnosis of "circadian rhythm disruption," most of whom had DSPS (Dement et al., 1975). In a retrospective analysis of a series of 450 insomnia patients at the Montefiore Hospital Sleep-Wake Disorders Center, we found that approximately 7% had the specific diagnosis of DSPS (Weitzman et al., 1979*a*). However, it is probable that the true prevalence of DSPS among insomniacs is even higher. Since sleep (once achieved) is usually maintained without disruption in such individuals, many would probably not consult a sleep clinic or even a physician for diagnosis. Some of them even alter their daytime work schedule to accommodate to their sleep time (e.g., take a 3 p.m.–11 p.m. job) without ever seeking medical treatment. Kleitman (1963) speculated that delayed sleep onset was "undoubtedly the most common" complaint of individuals with insomnia. In fact, in a recent epidemiological study, Bixler et al. (1979) reported that 23.4% of adults complained of "difficulty falling asleep."

Current treatment. Various assumptions about the etiology of this condition shape attitudes regarding treatment. Labeling DSPS patients as extreme "night owls" or "evening types" implies that it is a personality characteristic which is unlikely to change in treatment. The view that psychopathology is the primary cause of all types of insomnia has led some researchers to recommend either psychotherapy (Solomon, 1956; Kales and Kales, 1974) or behavioral conditioning (Turner and Ascher, 1979; Zwart and Lisman, 1979) as treatment. However, the vast majority of practicing physicians react to the complaint of insomnia by prescribing sedative hypnotic drugs to induce sleep (25.6 million prescriptions for benzodiazepines and barbiturates in 1977 alone) (Institute of Medicine, 1979). For example, like most "insomniacs," our DSPS patients typically had been taking hypnotic and/or other drugs (both prescription and nonprescription) regularly for

many years without sustained relief. The Institute of Medicine (1979) has criticized the contemporary widespread use of "sleeping pills" as a nonspecific treatment of chronic insomnia. They questioned the efficacy of such drugs and cited their dangerous interaction with alcohol, the cumulative buildup of toxic metabolites, interference with daytime performance, rebound insomnia leading to drug dependency, and the easy availability of these drugs for suicides. The committee further recognized the fallacy of viewing insomnia as a unitary disorder and emphasized the need for the development of specific modes of treatment for the different types of insomnia.

We have identified DSPS as a specific type of insomnia and have recommended procedures for establishing its diagnosis (Weitzman et al., 1979*a*). We now propose a new model which is based on circadian theory for the primary pathophysiology underlying this disorder. It is our hypothesis that DSP insomnia is due to a specific abnormality of the system which *times* sleep within our 24 hr schedule, rather than a dysfunction of the sleep generating process per se.

Pathophysiology of DSP Insomnia

Patients with DSP insomnia, as the name implies, have a sleep scheduling disorder characterized by an *inappropriate* temporal or phase relationship between their circadian sleep-wake cycle and the periodic environment. Insight into the environmental factors which affect the timing of sleep has been achieved through studies of human beings living in schedule-free environments (i.e., deep within caves isolated from the periodic day/night changes of the environment or in controlled laboratory environments designed to achieve the same results) (Aschoff, 1965; Chouvet et al., 1974; Czeisler, 1978; Wever, 1979; Weitzman et al., 1979*b*). In such "constant conditions," the timing of the sleep-wake cycle in man (corresponding to subjective night and day) continues to be periodic. Similar inherently periodic physiologic functions have been demonstrated in virtually all other eukaryotic organisms studied since the recognition of these endogenous oscillations 250 years ago (Bünning, 1973).

Properties of the Circadian Timing System

In the absence of periodic environmental inputs, the cycle length or the "free-running period length" (τ) of such endogenous oscillations is no longer synchronized or "entrained" to a 24 hr period. Whether τ is greater or less than 24 hr depends on the species; nonetheless, it remains close to 24 hr in all (hence the word circadian to describe the rhythms). In normal human subjects, the average free-running period of the sleep-wake cycle is approximately 25 hr; in other words, in constant conditions our internal biological clock runs a little slower than its mechanical or geophysical counterparts (Fig. 1, days 21–52). Therefore, successful entrainment of human circadian rhythms to the 24 hr day requires that our biological clocks be "reset" (in this case, phase advanced) by an average of 1 hr each day.

It is generally accepted that the most important periodic environmental stimulus

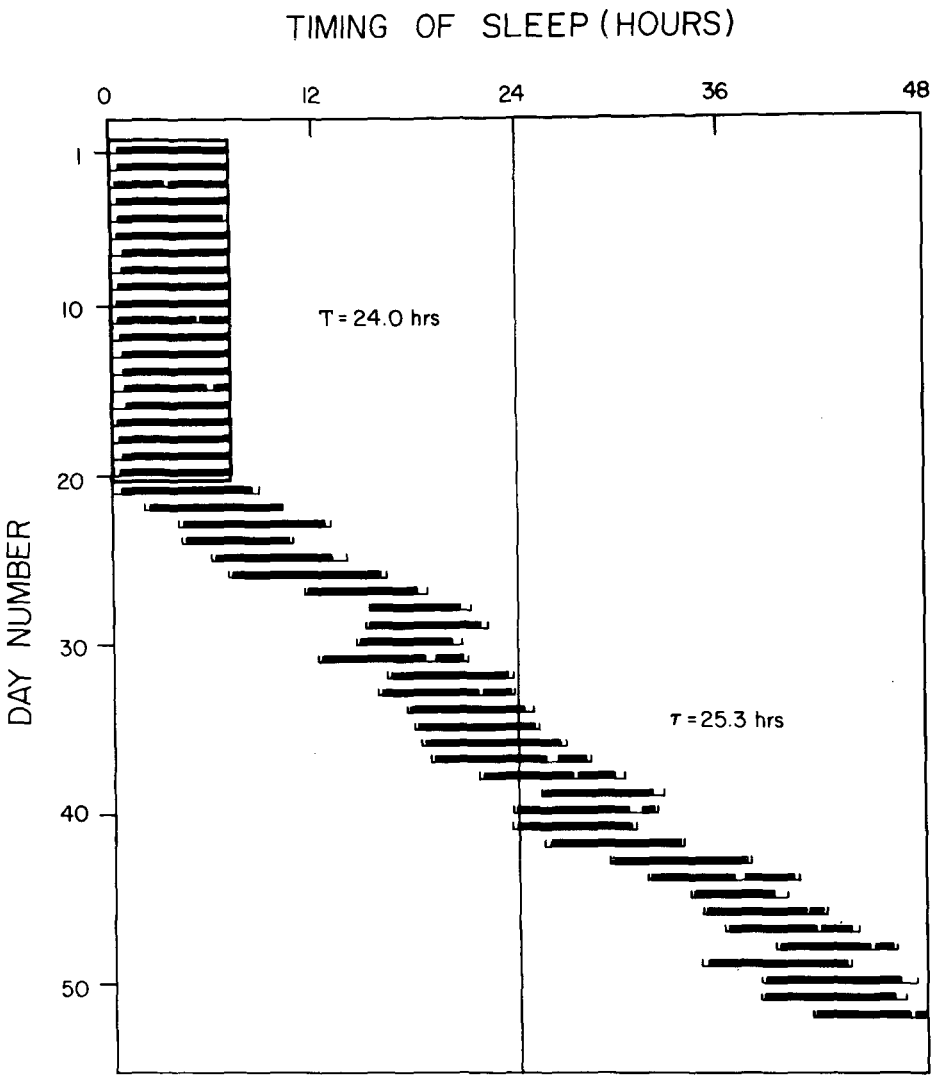


FIG. 1. Entrained and free-running sleep-wake pattern of a normal 22-year-old male subject (DC) living in an environment without the knowledge of time. The horizontal time axis is referenced to the subject's habitual bedtime (hour 0), as recorded in a home sleep-wake diary during the prior week. Successive days are plotted beneath each other. Scheduled sleep/dark intervals (outlined by a black box) were from hour 0 to 7 on days 1–20. Thin horizontal lines indicate time spent *awake* in bed; time asleep (as determined by polysomnographic recording) is indicated by heavy black horizontal bars. After day 20, the exogenous 24 hr schedule was no longer imposed and the subject had a free-running sleep-wake pattern. His free-running period, τ, as determined by linear regression through midsleep times, was 25.3 hr. Thin vertical lines indicate self-selected bedtimes and times of arising.

for entraining circadian rhythms in nearly all nonhuman eukaryotes studied is the daily alternation of light and darkness (Rusak and Zucker, 1975). The effectiveness of a light-dark cycle alone as a synchronizer of human circadian rhythms, however, has only recently been recognized (Czeisler, 1978; Czeisler et al.,

1981). Furthermore, the relative importance of different synchronizers to the human system remains unknown. While the resolution of that question remains of theoretical interest, we have found that the combination of imposing a light-dark cycle and scheduling the time available for sleep and waking was a very effective synchronizer of all measured circadian rhythms (including body temperature, polygraphically recorded sleep-wakefulness, plasma cortisol and somatotropin, urinary constituents, etc.) in all of our 23 subjects and patients. An example of entrainment of the sleep-wake cycle by these stimuli is shown in Fig. 1 (days 1–20).

The recognition of these simple, reproducibly effective entraining stimuli in man now permits application to the human system of the extensive information gathered from studies of other species regarding the formal properties of the entrainment mechanism. DeCoursey reported 20 years ago that identical brief light pulses phase-shifted the free-running activity rhythm of animals living in constant darkness by different amounts and direction depending on when (i.e., at what phase) the stimulus was given (DeCoursey, 1960). By measuring such phase shifts in response to stimuli given at different phases of the circadian cycle, she constructed a phase response curve (PRC). Since that time, such PRCs have been recognized as a universal feature of the mechanism of entrainment to all effective stimuli in a wide variety of species, from unicellular algae to primates (Pittendrigh, 1960; Saunders, 1977; Pierce et al., 1978). Furthermore, PRCs in all species, whether nocturnal or diurnal, share the following general properties (Fig. 2):

1. Phase delay shifts ($-\Delta\phi$) occur when the stimulus is early in the subjective night of the animal.
2. Stimuli late in the subjective night cause phase advance shifts ($+\Delta\phi$).
3. The response system is relatively insensitive (no phase shifts) during most of the subjective day.

These curves describe the capacity of the system to phase advance or phase delay under free-running conditions. Entrainment of circadian rhythms to a 24 hr day (T = 24 hr as in Fig. 1, days 1–20) is accomplished by periodic stimuli which cause a phase shift each day equal in amount to the difference between τ and 24 hr (e.g., 1.3 hr per day in Fig. 1). Entrainment to other day lengths is necessarily limited to a range of values around τ, called the range of entrainment (ROE), which is related to the maximum resetting capacity of the system in each direction as described by the PRC. Since the amplitude and exact shape of the PRC vary between species and among individuals (Daan and Pittendrigh, 1976), the ROE does as well.

In man, the synchronized circadian system can be entrained to period lengths ranging from about 23 to 27 hr (a ROE centered around the average free-running period length of 25 hr in man) (Wever, 1979). But, as illustrated in Fig. 3, even 2 individuals with the same free-running period could theoretically have different ROEs to a given periodic stimulus if the amplitude of their respective PRCs were different. In fact, evidence that such interindividual differences occur was present in DeCoursey's original report of the PRC (DeCoursey, 1960); the 2 animals shown there had different waveshapes and PRC amplitudes, though their free-running period lengths (reported in DeCoursey, 1959) were indistinguishable.

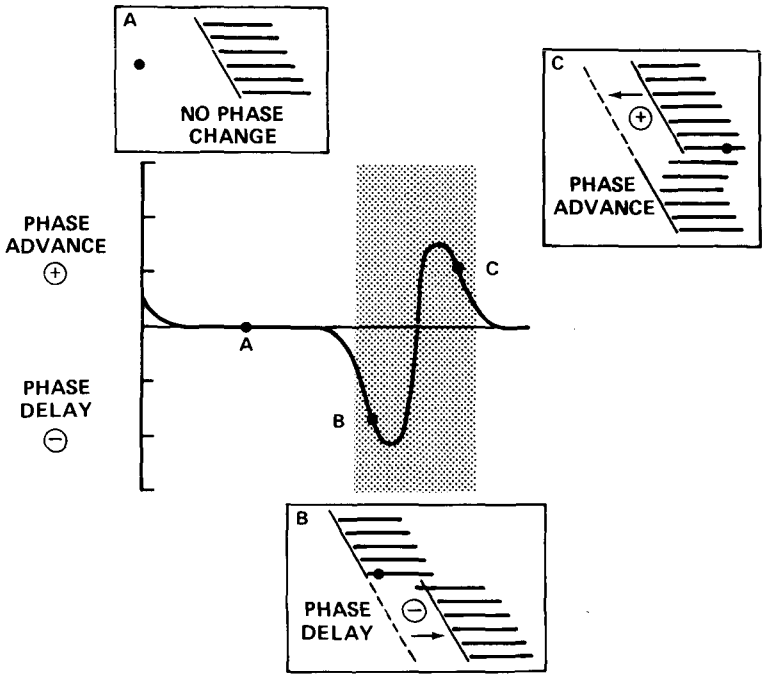


FIG. 2. Schematic illustration of the determination of a phase response curve (PRC). The horizontal black bars within each inset indicate the timing of whatever behavior is normal for that organism during its "subjective night" (i.e., the sleep time in diurnally active animals or the activity time in nocturnal animals). Within each inset, the effect of a single stimulus (e.g., a light pulse in otherwise constant darkness) on a free-running rest-activity pattern is shown. The effects of stimuli (closed circles) presented during the subjective day (A), the early part of the subjective night (B), and late in the subjective night (C) are shown. Note the very different effects which these identical stimuli have at those different phases. Those results are then plotted at corresponding points (labeled A–C) in the central diagram, which is a PRC. The shaded area represents the subjective night of the organism.

Proposed Model of DSP Insomnia

On the basis of the foregoing analysis, we propose the following mechanism for the pathophysiology of DSP insomnia:

1. Since DSPS patients can successfully entrain their sleep-wake times to occur at about the same clock hours daily, their synchronized circadian system must have sufficient resetting capacity to accomplish a phase advance shift equal to the difference between their endogenous free-running period and the 24 hr day/night cycle.

2. However, unlike normal subjects, such patients lack the *additional* phase advancing capacity to shift the daily sleep episode to an earlier clock hour.

3. In addition, other synchronizing cues from the environment, which do not allow their sleep episodes to drift into the afternoon, prevent resynchronization by phase retardation.

Consequently, their sleep is locked into an inappropriate phase position with respect to the daily work-rest schedule required by society. For example, while they are able to sleep without difficulty from 4:00 a.m. to noon, they are re-

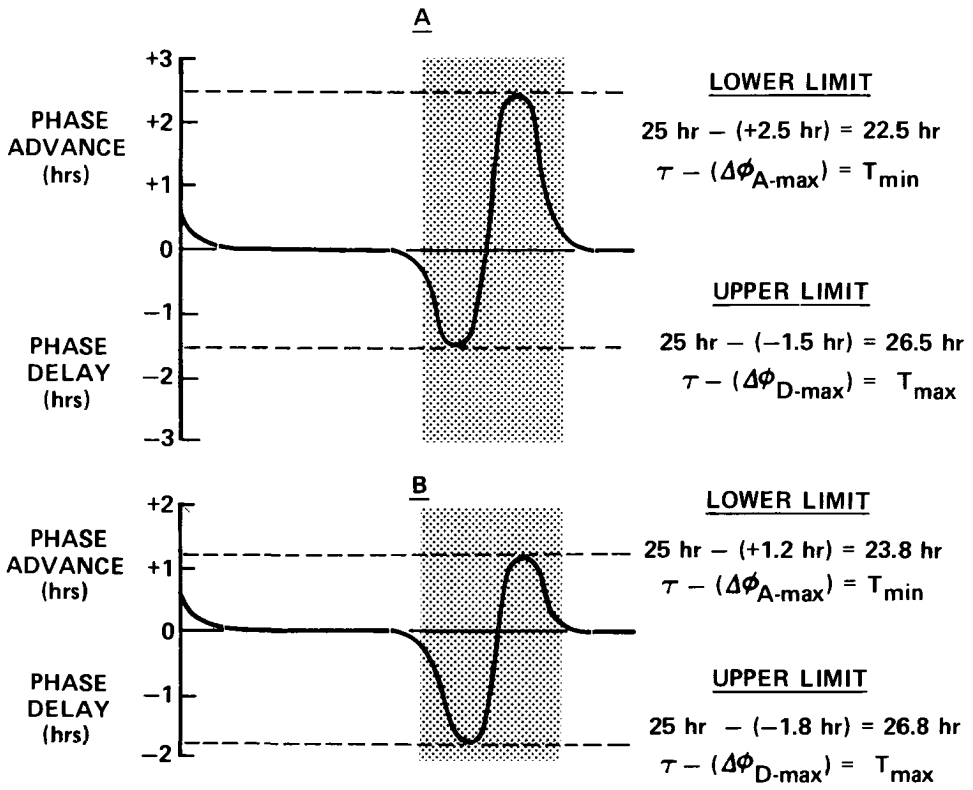


FIG. 3. Hypothetical determination of range of entrainment (ROE) from two phase response curves. PRCs from two individuals with the same τ illustrate in simplified form how interindividual differences in PRC amplitude could affect the lower limit of the ROE, with or without a significant effect on the upper limit. The curves are plotted as in Fig. 2. In the formulae on the right: $\Delta\phi_{A\text{-}max}$ = maximum capacity of the system to phase advance shift each cycle in response to the entraining stimulus; $\Delta\phi_{D\text{-}max}$ = maximum capacity to phase delay shift; T_{max} = longest imposed day length of the entraining stimulus to which the system could be entrained; and T_{min} = shortest imposed day length to which it could be entrained.

peatedly unable to advance the daily sleep episode to an earlier hour, even if their schedule requires them to arise at 6:00–7:00 a.m. Even if they were to achieve their desired phase position by chance (e.g., by long-distance westward jet travel), it is likely that they would not realize that a regular sleep-wake schedule was essential to *maintain* that desired phase position. As a result, they suffer from sleep loss, disturbed sleep, and excessive daytime sleepiness.

Rationale for a New Therapeutic Approach

The therapeutic goal was twofold: (1) allowing patients to *achieve* their desired phase position and (2) instructing the patients as to how to *maintain* it. Furthermore, any treatment had to be aimed at a wide variety of patients with DSPS and not require prior knowledge of any of the properties of their individual circadian pacemakers (e.g., τ and ROE, which could only be determined in temporal isolation).

Chronotherapy: Stage I

Based on our model, we predicted that a series of phase *delay* shifts of environmental synchronizing cues should enable such patients to *achieve* their desired phase position (Czeisler et al., 1979). This is because delay shifts (in contrast to phase advances) are not solely dependent on the phase shifting capacity, but rather proceed in a direction common to the endogenous drift (Fig. 1) of the free-running human sleep-wake cycle. Since the characteristics of the phase delay portion of their PRCs were unknown, it was decided to phase delay very near the expected upper limit of the range of entrainment of the synchronized circadian system in man (Kleitman, 1963; Wever, 1979). The first part of the treatment therefore involved an attempt to entrain the circadian rhythms of the patients to a 27 hr day (longer than their expected τ) by scheduling their sleep/dark and wake/light times 3 hr later each "day." This relatively rapid rate of phase delay was chosen to minimize the chance that the internal phase delay of the endogenous circadian system in response to the change of schedule would exceed the external phase delay shift being imposed. This would have only perpetuated the condition. Conversely, if the capacity of their circadian timing system to phase delay were exceeded on an imposed 27 hr day, the circadian rhythms in these patients would return to their presumably greater than 24 hr free-running period and therefore proceed in the same direction as their imposed rotation around the clock.

Chronotherapy: Stage II

We further predicted that once *achieved,* the desired phase position could be *maintained* if the patients understood their special need to follow a regular sleep-wake schedule. The properties of their circadian pacemakers (τ and PRC) may remain unchanged after treatment. Therefore, there is a danger that if a patient's sleep-wake schedule even temporarily shifted to an inappropriately delayed phase position (e.g., due to late parties on weekends, temporary adaptation to a westward time zone shift, etc.), he might be unable to return to his desired phase position via a simple phase advance. We predicted that such a relapse could be avoided if a patient seriously attempted to maintain a regular sleep-wake schedule at his desired phase.

MATERIALS AND METHODS

Patient Selection

To test this model, the physicians at our sleep disorders centers were asked to refer all their current patients with the diagnosis of DSPS for consideration in an experimental protocol. As part of their clinical diagnostic evaluation in the sleep disorders centers, such patients had been given a general physical and neurological examination; the O&L ("Owl and Lark") questionnaire developed by Horne and Östberg (1976); and psychological evaluation, including standardized tests (e.g., Minnesota Multiphasic Personality Inventory, Beck Personality Inventory, etc.), and an interview. Only patients without any other serious medical conditions or major psychopathology were considered for this treatment protocol.

In addition, in order to ensure that the trial treatment protocol was carried out only on patients with a well-established, serious clinical condition, patients with DSPS had to meet the following additional eligibility criteria for inclusion in this therapeutic trial:

1. Documented clinical history of the symptoms of DSPS (described by Weitzman et al., 1979*a*) for at least 3 years, including a prior consultation with physicians and other attempts at treatment.
2. Preliminary evaluation at a sleep disorders center showing no abnormalities on an all-night polysomnographic recording other than delayed sleep onset.
3. Complaint by patient that the condition was significantly disrupting his or her life (i.e., due to requirements of work, education, social, or family schedule).
4. Commitment to stop all medications (including use of hypnotics) during a 1–2 month evaluation period and to try to maintain a very regular sleep-wake schedule after treatment.
5. Demonstration with a 1–2 month home sleep-wake diary (while drug-free) that sleep episodes actually occurred at least 3 hr later than desired but could be maintained at the same average clock hours daily.

All eligible patients whose final 1–2 month home sleep-wake diaries confirmed the diagnosis of DSPS were asked whether they wished to volunteer for a 20–30 day experimental treatment protocol which required that they live in a laboratory which had limited contact with the external environment. They were told that the study included recording of multiple physiologic functions, including polygraphic sleep recording and continuous core body temperature measurements using a rectal thermistor throughout the time before, during, and after treatment. They were informed that such recordings were for research purposes and were not part of their treatment. Over a 2½ year period, only 4 eligible patients (cases A–D, ages 24–37, 3 men and 1 woman) were willing or able to volunteer for this extensive period of study in the laboratory during the times it was available. In addition, one patient (case E, a 34-year-old woman) was treated in her home under careful daily supervision to determine the preliminary feasibility of performing this treatment on an outpatient basis.[1] Informed consent was obtained from each patient.

Treatment and Evaluation Protocol

Laboratory Studies (Cases A–D)

Throughout all phases of the studies conducted in the laboratory, all room lights were turned out during scheduled bedrest episodes; the patients were asked to lie in bed in the dark if they awakened before being told that it was time to get out of bed (except for urination). Meals were distributed appropriately within each scheduled waking episode, regardless of the length of the waking episode or the clock time the meal occurred. No naps were permitted during scheduled waking episodes; the subjects were monitored continuously using closed-circuit video equipment to ensure wakefulness. Exercise was permitted *ad libitum*. Sleep was

[1] Case A was evaluated and treated at the Stanford University Sleep Disorders Center, whereas cases B–E were studied at the Montefiore Hospital Sleep-Wake Disorders Center.

polygraphically recorded and scored using standard criteria (Rechtschaffen and Kales, 1968). Core body temperature (rectal) was continuously recorded; subjective assessments of alertness were obtained at frequent intervals throughout each waking episode, and urine was collected for electrolyte and endocrine analysis. The results of those measurements will be reported in detail elsewhere.

Base line. As described above, each patient recorded a 1–2 month home sleep-wake diary, while drug-free. Each day they recorded on preprinted forms the clock hours of the following five events: (1) bedtime; (2) estimated sleep onset; (3) nocturnal awakenings (time and length); (4) wake time; and (5) time out of bed. Each patient was then admitted for 4–7 days of base-line recording/adaptation before the rescheduling regimen was initiated. During the laboratory base-line period, scheduled sleep and wake times were based on the patient's own average schedule during the previous week, as recorded in the home sleep-wake diary.

Phase delay shift (Chronotherapy: stage I). A 27 hr day was imposed by delay-shifting scheduled bedtimes and wake times (relative to clock hour) by 3 hr per bedrest episode until the approximate clock hours desired for the patient's sleep episode were reached. The length of the scheduled bedrest episode was about the same as that during base line; only its scheduled times changed. For example, if the patient's habitual sleep episode before treatment occurred from 6:00 a.m. to 2:00 p.m. but he wished to sleep from 10:00 p.m. to 6:00 a.m., then his scheduled bedtimes were delay shifted to the following successive intervals: 9:00 a.m.–5:00 p.m.; noon–8:00 p.m.; 3:00 p.m.–11:00 p.m.; 6:00 p.m.–2:00 a.m.; and 9:00 p.m.–5:00 a.m. Delay shifting was usually stopped about 1 hr short of the preferred time for going to sleep, to allow for small adjustments following stabilization.

Stabilization. Patients were then maintained on their desired schedule for 5–9 days in the laboratory prior to discharge.

Patient education (Chronotherapy: stage II). After discharge, each patient was instructed to maintain their new sleep-wake schedule on a regular basis, without naps. They were advised that physiologically it should be as easy (or difficult) for them to maintain their new schedule as it had been to maintain their former schedule (e.g., 4:00 a.m.–noon). We suggested that they try, as before, to go to bed at about the same time each night, including weekends, and to remain in bed with the lights out until the regularly scheduled wake time.

Follow-up. Patients were asked to record the same data on their home sleep-wake diary forms as before, for as many weeks as possible after treatment. These records were then compared with their diaries before treatment. At least two follow-up visits with one of the clinical staff were arranged within the first 6 weeks after treatment. This allowed us to evaluate whether the schedule transition from the laboratory to home had been successfully achieved. The patients' subjective assessments of the results of treatment were also recorded at those visits.

One or two months after treatment, 4 of the patients (cases A–C, and E) were restudied in the sleep research laboratory, including at least two all-night polygraphic sleep recordings. Sleep efficiency (percentage of time asleep while in bed at the newly scheduled time) was computed and compared with pretreatment levels.

In this way, the self-reports from the follow-up home sleep-wake diaries were verified in the laboratory.

Home Study (Case E)

As mentioned above, one study (Case E) was conducted at the patient's home. The pretreatment evaluation and treatment schedule were identical to that of patients studied in the laboratory. However, the exact nature of the rescheduling regimen was explained to the patient in detail. A written schedule for each day during the treatment was given to the patient, who lived alone and was able to darken her bedroom during the daytime to accommodate bedrest episodes scheduled at that time. A telephone-answering machine prevented interruptions of her scheduled bedrest episodes by telephone calls.

Daily contact was maintained with one of us (R.M.C.) throughout the treatment to answer questions and advise the patient as to how to deal with unexpected problems. She also visited the laboratory frequently during treatment, and a follow-up study was conducted in the laboratory as described above.

RESULTS

All 5 patients reported a significant and lasting resolution of their symptoms (average follow-up sleep-wake diary records of 37 weeks; range, 6 weeks–2.5 years). As shown in Table 1, the group average of reported sleep onsets before and after chronotherapy advanced from 4:50 a.m. to 12:20 a.m.; wake times from 1:00 p.m. to 7:55 a.m. (for both $p < 0.001$, paired t-test). Total sleep episode duration reported (bedtime to wake time) did not change significantly before and after treatment. Comparison of objective polygraphic recordings before treatment with those 1–2 months after discharge confirmed these self-reports. As expected (Table 2), there were no significant differences between the sleep efficiencies polygraphically recorded before treatment ($\bar{x}$ = 88.6% ± 5.6%) and those obtained either during stabilization ($\bar{x}$ = 93.8% ± 3.3%) or follow-up ($\bar{x}$ = 86.4% ± 4.7%).

To illustrate the treatment protocol, the treatment of one patient (case B) is described in detail. His home sleep-wake diary data before and after treatment and the results of the polygraphic recordings during the laboratory treatment protocol are illustrated in Fig. 4. The data are double plotted in a raster format (for explanation, see Legend). The home sleep-wake diary data from case B before treatment confirmed the diagnosis of DSPS. Note that this patient, a medical student, had reported sleep latencies of several hours per night during the school week (e.g., days 2–6 and 9–13). He arose each weekday morning at 7:00 a.m. with great difficulty in order to attend medical school lectures, reporting that he was very sleepy and groggy at those hours. Cumulative sleep deprivation effects may have reduced the length of time required for him to fall asleep near the end of each week, but his early morning sleepiness persisted. When his daily responsibilities did not necessitate such an early wake time, such as on weekend nights (e.g., days 7–8 or 14–15) or during a vacation (days 19–45), he retired much later and slept

TABLE 1. *Average sleep-wake schedule recorded by patients before and after chronotherapy*

Case		Average bedtime		Estimated sleep onset		Average wake time		Hours in bed per day	Length of follow-up (days)
		Clock hour[a]	Hours shifted	Clock hour	Hours shifted	Clock hour	Hours shifted		
A	Before	3:20 a.m. ± 1:10	+4:05	4:10 a.m. ± 1:20	+4:20	11:45 a.m. ± 0:50	+4:30	8:25	910
	After	11:15 p.m. ± 0:45		11:50 p.m. ± 0:50		7:15 a.m. ± 1:00		8:00	
B	Before	4:10 a.m. ± 0:30	+6:30	4:30 a.m. ± 0:30	+6:15	2:05 p.m. ± 0:40	+7:15	9:55	42
	After	9:40 p.m. ± 0:35		10:15 p.m. ± 0:40		6:50 a.m. ± 0:40		9:10	
C	Before	3:50 a.m. ± 1:16	+5:05	4:00 a.m. ± 1:20	+4:05	11:30 a.m. ± 1:55	+4:50	7:40	56
	After	10:45 p.m. ± 0:25		11:55 p.m. ± 0:50		6:40 a.m. ± 0:45		7:50	
D	Before	4:15 a.m. ± 0:40	+3:50	4:50 a.m. ± 0:40	+3:40	12:35 p.m. ± 0:30	+4:05	8:20	101[b]
	After	12:25 a.m. ± 0:05		1:10 a.m. ± 0:35		8:30 a.m. ± 0:10		8:00	
E	Before	5:40 a.m. ± 1:05	+4:40	6:35 a.m. ± 0:55	+4:15	3:05 p.m. ± 0:45	+4:40	9:25	189
	After	1:00 a.m. ± 0:05		2:20 a.m. ± 0:40		10:25 a.m. ± 0:30		9:20	
Group average									
	Before	4:15 a.m. ± 0:50	+4:50	4:50 a.m. ± 1:05	+4:30	1:00 p.m. ± 1:35	+5:05	8:45	260
	After	11:25 p.m. ± 1:20[c]		12:20 a.m. ± 1:35[c]		7:55 a.m. ± 1:35[c]		8:30	

[a] Mean clock hour ± standard deviation.
[b] Data for days 52–87 were not recorded.
[c] $p < 0.001$, paired t-test.

TABLE 2. *Average sleep efficiencies polygraphically recorded before and after chronotherapy*

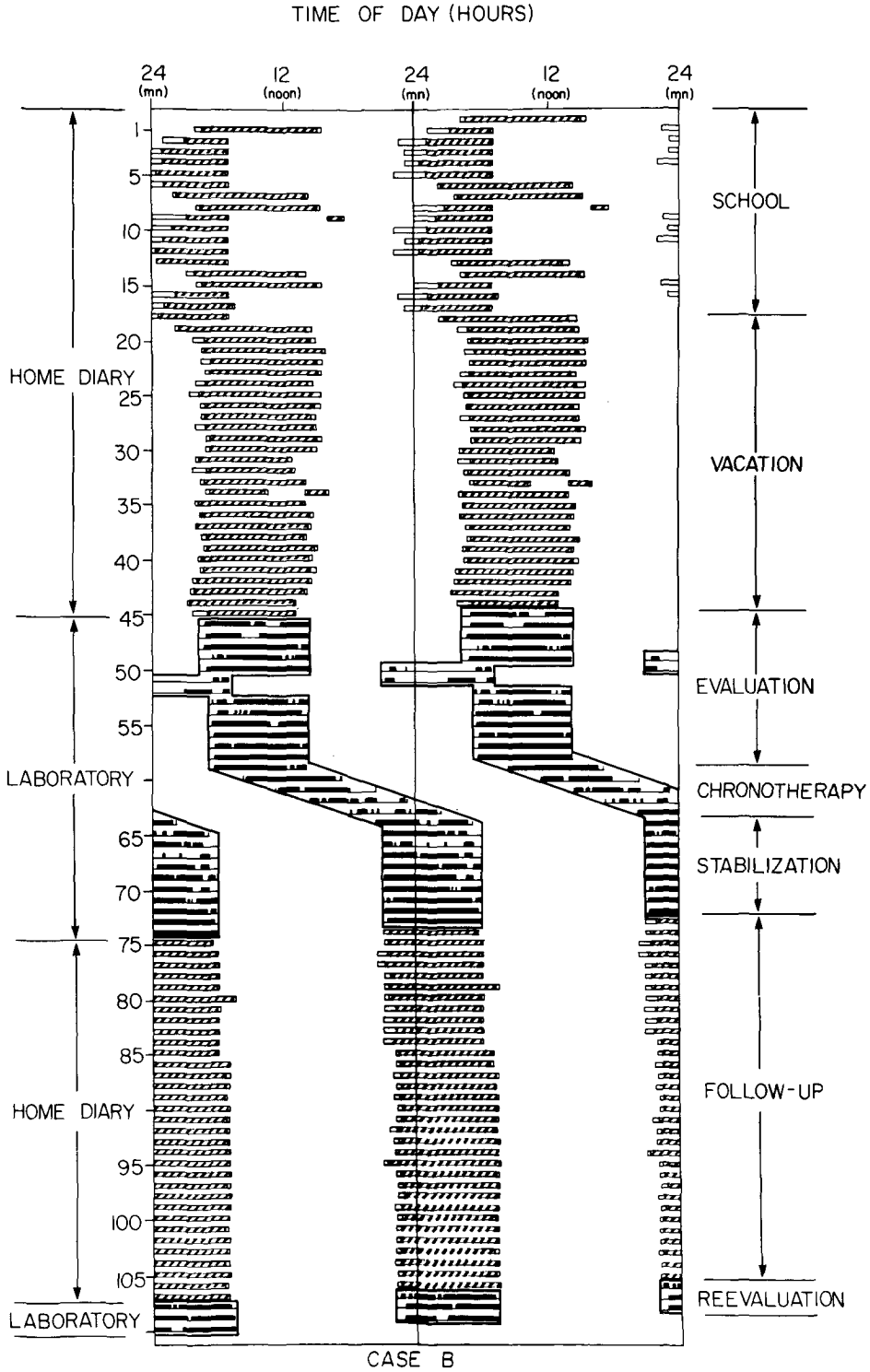
Case	Sleep efficiency[a]		
	Before shift	During stabilization	At follow-up
A	86.7	90.5[b]	89.8
B	84.2	92.1	85.0
C	97.5	94.5	90.5
D	90.5	98.1	—[c]
E	84.3[d]	—	80.4
Group average	88.6	93.8	86.4
±SD	±5.6	±3.3	±4.7

[a] Expressed as percentage of time asleep while in bed.
[b] Due to the patient's schedule, only 2 nights of stabilization were recorded in the laboratory in this case.
[c] No follow-up polygraphic recordings were taken on this patient.
[d] In this patient treated at home, only the evaluation recording performed in the Sleep Disorders Center is available for comparison with the follow-up after treatment.

until early afternoon without the symptoms of sleep-onset insomnia or sleepiness on awakening. The phase position he immediately adopted on those weekends and at the start of his vacation period indicated the severity of his condition. Nevertheless, it is clear from the plot of the last 4 weeks of the sleep–wake diary before treatment that this patient was able to entrain to a 24 hr day, as distinct from patients with a hypernychthemeral sleep-wake cycle (Kokkoris et al., 1978; Weber et al., 1980), one of the conditions which must be considered in the differential diagnosis of DSPS (Dement et al., 1975; ASDC, 1979; Weitzman et al., 1979*a*).

Case B was admitted to the Montefiore Hospital Laboratory of Human Chronophysiology (on day 46 of Fig. 4) for further evaluation and treatment. In this case, we preceded our usual treatment protocol by an additional week of evaluation, including polygraphic verification of the patient's reported difficulty sleeping at the times he desired. Note that when his scheduled sleep episodes were acutely advanced to the times he desired (from 9:00 p.m. to 7:00 a.m. on days 51–52), he spent almost all of both nights awake. His sleep efficiency was only 19.5% on night 51, rising to a mere 41.6% on night 52, notwithstanding the significant level of prior sleep deprivation at that point. This was also despite the fact that he was living in an environment free of time cues, unaware of the time at which we scheduled his activities. Such sleeplessness even under the favorable laboratory conditions of quiet isolation and absolute darkness verifies his reported difficulty sleeping at those desired hours.

After that evaluation trial, the patient's bedrest episodes were scheduled at their usual hours for 7 more base-line nights (days 53–59), after which (days 60–65) he was delay shifted according to the standard protocol (Chronotherapy: Stage I). It is of special interest to note that during this imposition of a 27 hr day, the patient's actual sleep became more and more interrupted toward the latter half of each bedrest episode. This is in marked contrast to the sleep records from the subject



illustrated in Fig. 1 (days 21–52), who continued to maintain consolidated sleep episodes while free-running on a 25.3 hr day. These increasing periods of final awakening in case B indicate that the imposed day length of 27 hr (T = 27 hr) was beyond the upper limit of the ROE of his sleep-wake cycle (see Fig. 3). Fortunately, as we suggested earlier (in the Rationale), in such a circumstance the circadian rhythms of the patient should begin to free-run with a greater than 24 hr period. This indeed appears to have happened during stabilization (days 66–74), when the period of consolidated sleep extended a bit later into each scheduled sleep episode on successive nights, being nearly complete by the last three. These results highlight the importance of close adherence to the schedule during stabilization even if the patient encounters sleeplessness, since the rhythms are still in the process of reentrainment. A more detailed examination of the polygraphic data collected from these patients will be presented elsewhere (Czeisler et al., in preparation).

Before discharge home on day 75, the patient was counseled regarding the principles of sleep hygiene (Chronotherapy: Stage II). He was told that once he firmly established the routine, he could delay his bedtime by one more hour, to the time he indicated was best for him. During the 6 weeks of data recording after treatment (days 75–107), he was able to maintain that new schedule at home without any difficulty. Reported sleep latencies were comparable with those seen during the vacation period when the patient had been sleeping from about 6:00 a.m. to 3:00 p.m.

His home sleep-wake diary records were compared with the results of polygraphic recordings 6 weeks after treatment in 3 nights of laboratory reevaluation (days 107–110). As shown in Fig. 4, sleep-onset latencies and sleep efficiencies during the follow-up reevaluation recorded from 10:00 p.m. to 7:30 a.m. were comparable with those recorded from 6:00 a.m. to 3:00 p.m. before treatment. These were similar to the results obtained from the other 4 patients treated (Table 2). Such maintenance of normal sleep efficiencies while on the new schedule is in marked contrast with the average sleep efficiency of 30.6% recorded in this case on nights 51–52, when he was acutely advance shifted to his desired schedule rather than delay shifted according to the chronotherapy protocol (Fig. 4).

Finally, the patient reported that for the first time in years he felt sleepy when it was time to go to bed and had no more difficulty arising at 7:00 a.m. than he used to have waking at 2:00–3:00 p.m. One of the most valuable aspects of the treatment for this patient was his realization that he *could* fall asleep and wake up at normal hours without difficulty. We had explained to him that his new schedule

FIG. 4. Chronotherapy protocol in a patient with Delayed Sleep Phase insomnia. Data from the home sleep-wake diaries and those sleep episodes polygraphically recorded in the laboratory before and after treatment are double plotted in a raster format. Successive days are plotted beneath each other, with the day number indicated on the vertical axis, as well as side by side to aid visualization. Thus, each successive horizontal line has data from day 1 + day 2, then day 2 + day 3, etc., with data from each day plotted twice. Times spent in bed reportedly awake (open bar) and asleep (hatched bar) are plotted from the home sleep-wake diary. Polygraphically scored sleep data recorded in the laboratory are plotted as in Fig. 1. Double plotting illustrates that the therapeutically effective phase delay shifts imposed on day 60–65 lead, via a different route, to the same phase position (clock hours of sleep) that the patient had unsuccessfully attempted to reach by an acute phase advance on days 2–6, 9–13, 16–18, or 51–52. See text for detailed description.

might be disrupted by the haphazard night-call duty required during his clinical years in medical school (it later was). Nonetheless, he knew that if that happened, he would be able to return to a normal schedule once he finished his night-duty requirements using the phase delay technique (which he also later did at home). Thus, the treatment ended his fear of chronic insomnia which had been forcing him to depend increasingly on the hypnotic drugs he had been taking almost nightly for years beforehand.

Each of our subjects relayed personal anecdotes about the effects the schedule change had on their personal and occupational lives. Evidence that the effect of the treatment can be long-lasting is provided by our first patient (case A), treated in August 1976 at the Stanford University Sleep Disorders Center. His follow-up home sleep-wake diary since that time (much too long for illustration here) demonstrates that he has maintained his 11:00 p.m.–7:00 a.m. sleep-wake schedule without difficulty (Table 1). He reports that he now "feels about the same at 10:00 p.m. as he used to feel at 3:00 a.m. before treatment."

In summary, home sleep-wake diaries from all 5 subjects demonstrate that their sleep episodes were successfully rescheduled to the times desired in all cases (Table 1). This was confirmed by follow-up sleep recordings 1–2 months after discharge (Table 2). Furthermore, as a result of this treatment, all 5 patients were able to permanently discontinue use of hypnotic medication.

DISCUSSION

We have reported here that chronotherapy, a drug-free treatment of DSP insomnia, can allow patients to successfully shift the timing of their sleep from inappropriate hours to those that fit optimally with their work/social needs. This single 5–6 day treatment resolved the chronic insomnia of a group of patients who had tried a variety of unsuccessful treatments over the prior 4–15 years. These results were substantiated both by systematic long-term self-reports and objective polygraphic recordings before and after treatment.

Implications for Pathogenesis of DSPS. The successful results of this phase *delay* regimen in rescheduling the sleep-wake cycle of patients with DSPS, who had tried for years to do so by phase advances, support our hypothesis of a diminished capacity to *achieve* phase advance shifts due to an abnormal ROE in DSP insomnia (Czeisler et al., 1979). Mismatches between the intrinsic free-running period of the pacemaker, τ, and the internal phase advance shifting capacity could be due to either (1) a reduction in the amplitude of the advance portion of the PRC with no abnormality of τ; or (2) an increase of τ, probably on a genetic basis (Konopka and Benzer, 1971), unaccompanied by a corresponding increase in the phase advance shifting capacity. Either abnormality would explain the diminished ROE in these patients. It is unknown whether a prior history of recurrent advance and delay shifts could contribute to a diminished capacity of the system to advance shift. However, recent evidence (J. Elliott, personal communication) indicates that PRC amplitude can actually be affected by prior conditions. It is therefore conceivable that recurrent phase shifts may contribute to the condition of DSPS. The maintenance of a very regular schedule after treatment may

therefore improve the response characteristics of the circadian timing system in some patients. This question merits further investigation.

Of equal importance, the ability of our patients to *maintain* their new, previously unattainable schedules for months to years following this simple treatment demonstrates that neither abnormal personality characteristics (Blake and Corcoran, 1972) nor psychopathology (both of which remained untreated after this treatment) could be of primary importance in the pathophysiology of this sleep scheduling disorder.

Support for the important role we have given the scheduling of the sleep-wake cycle in the entrainment of the other circadian rhythms in man comes from theoretical studies recently reported by Kronauer et al. (1981), who conclude (on the basis of the results of a mathematical model) that entrainment impinges on the human circadian system via the actual timing of the sleep-wake cycle. This is probably why acute shifts of the sleep-wake schedule (such as caused by jet travel, shift work, weekend parties, etc.) can be so disruptive to the circadian timing system. Minors and Waterhouse (1981) even reported an attempt to experimentally determine the minimum amount of regularity in the scheduling of the sleep-wake cycle required for successful entrainment of other rhythms to a 24 hr day. Elegant experiments by the late John Mills and his co-workers (1978) demonstrated that the measured circadian rhythms in nearly all normal subjects whose scheduled sleep-wake and light-dark cycles were *advanced* by 8 hr actually *delay* shifted 16 hr around the clock before resynchronizing. This is exactly the result expected in those individuals whose capacity to phase advance has been exceeded. Further, after a 12 hr phase shift, they found that 90% of the partial adaptations proceeded by the phase *delay* route. Those results suggest to us that some normal individuals, without a PRC abnormality, might develop DSPS when forced to attempt an acute 6–8 hr phase advance (e.g., shift workers). Like Mills' normal subjects, some would be unable to achieve the shift by the phase advance route. However, unlike his subjects, who were living on a very strictly imposed schedule in temporal isolation, individuals living in society would also inadvertently prevent complete resynchronization via the phase delay route by "sleeping late" on leisure days (as in Fig. 4, days 1–20). Those episodes of late sleep might prevent their endogenous rhythms from drifting later and later around the clock, thereby effectively trapping the rhythms in a chronically inappropriate phase position (near its position before the imposed phase advance).

Alternate treatments. In contrast to the entrainment which results from the regular scheduling of bedrest episodes as discussed above, the regular nightly use of hypnotics to induce sleep does not appear to be an effective entraining agent for the human circadian timing system. Such nightly use of drugs reported to us by our patients had not enabled them to achieve their desired phase position, despite years of habitual use. Whether this failure was due to an inadequacy of drug-induced sleep as an entraining agent, the inability of hypnotics to consistently produce sleep, or some other side effect of the drugs themselves is not known.

While pharmacotherapy is clearly not an effective treatment for DSP insomnia, other rescheduling regimens could be designed on the basis of our pathophysiological model of the disease outlined above. Patients could be in-

structed to rigidly adhere to their desired, fixed bedtimes and wake times regardless of whether they slept during that period. They could then be assured that (like Mills' normal subjects discussed above), they would eventually adapt to the new schedule. However, it would be unlikely that most such patients would be able to adhere to the schedule during the prolonged period required (probably greater than 2 weeks) without very intense supervision. Even with such supervision, many would be unable to tolerate the discomfort resulting from sleep deprivation and internal dissociation (similar to the jet lag syndrome).

Another approach might be to gradually phase advance shift the patients (e.g., by 15 min/day—essentially an attempt at entrainment to a 23.75 hr day). Unfortunately, the closer it was to 24 hr (and hence more likely to succeed), the longer it would take. Furthermore, any new schedule with a period less than 24 hr presumably would be beyond the ROE of a certain percentage of these patients, who would therefore become worse. Nonetheless, such approaches remain a viable alternative if the total amount of shift required is not great (less than 3 hr), and if the patient is willing to try a treatment requiring discipline which might not be effective. Unfortunately, at the present time there is no way to predict which patients would respond to these alternate chronotherapeutic maneuvers. The treatment protocol we chose was designed to be effective for the broadest spectrum of patients possible, including those with chronic poor sleep hygiene who might be misdiagnosed as having DSP insomnia. The only assumption made was that the free-running sleep-wake cycle period length was greater than 24 hr in DSPS patients, as is true of nearly all humans studied to date in constant conditions (Wever, 1979).

The fact that this treatment was equally effective on the patient treated under our close supervision at home (case E) as with those treated in the laboratory indicates its potential usefulness on an outpatient basis in certain cases. However, it must be emphasized that this rescheduling regimen is difficult for patients living in society to carry out. Scheduling conflicts might make it impossible for such patients to achieve the exactly scheduled sleep times necessary for a proper outcome. Only highly committed patients whose living situations would allow them to reliably carry out the schedule should be considered for home therapy. Daily contact with the therapist during the period of successive delay shifts is especially important. Patients should be cautioned that if they start but do not finish the protocol or carry it out incorrectly, they may be left in a worse condition (i.e., a more inappropriate phase position) than before.

Four hundred years ago, in 1584, Thomas Coghan emphasized to his students the importance of the time at which sleep occurred: ". . . in sleeping and waking, wee must folowe the course of nature, that is, wake in the day, and sleepe in the night. . . . Nothing is more hurtfull than studying in the night." At the start of this century, Sir James Sawyer (1912) also stressed the need for regular and fixed bedtimes and wake times to "cultivate . . . the periodic recurrence of sleep." Current research results further emphasize the role of biological rhythms in the control of sleep and sleep processes (Weitzman et al., 1980). For example, we and others have shown that both the length and structure of sleep depend on the phase relationship of sleep onset to the endogenous circadian system under both free-

running (Czeisler et al., 1980*a*,*b*) and entrained (Åkerstedt and Gillberg, 1981) conditions. Yet such findings have not been accompanied by proper deference within our society to the exigencies of those physiological processes. Despite the repetition of the essential principles of "sleep hygiene" by several authors (Sawyer, 1912; Worster-Drought, 1927; Poucel, 1934; Regestein, 1976), the importance of regularity in the timing of sleep is still not generally appreciated (Institute of Medicine, 1979). Instead, the unnatural challenges imposed on those physiological timing systems (e.g., shift work, jet travel, etc.) increase in degree and prevalence in our society; we may therefore expect a concomitant increase in the incidence of scheduling disorders of the circadian sleep-wake cycle.

Prior research on biological rhythms has provided the basis for an effective nondrug treatment of DSP insomnia. Chronotherapy eliminated the sleep-wake complaint in these patients who had suffered from a chronic, partially disabling sleep disorder. This emphasizes the importance of recognizing the distinctions between the different types of insomnia and developing specific therapies aimed at treating their underlying causes. The success of this counter-intuitive rescheduling regimen in resetting the biological clocks of these patients demonstrates the potential power of applying the principles of circadian rhythm physiology to the rational diagnosis and treatment of selected sleep disorders.

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