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Excessive Daytime Sleepiness and the Pathophysiology of Narcolepsy-Cataplexy: A Laboratory Perspective

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Summary: The main disabling symptom of narcolepsy-cataplexy is shown to be the unrelenting excessive daytime sleepiness (EDS) based upon controlled studies of socioeconomic effects and the poor response to treatment. Objective performance deficits mainly involve tests of ability to sustain performance on repetitive boring tasks and are reversible by improved alertness. Physiologically, EDS is seen to represent relatively slow waxing and waning of alertness rather than punctate microsleeps. Evidence is provided for complex cerebral evoked potentials (P300, contingent negative variation) being very sensitive EDS measures comparable to the multiple sleep latency test (MSLT). EDS appears to have qualitatively somewhat different forms mainly reflecting pressure for REM sleep (REM sleepiness) or pressure for NREM sleep (NREM sleepiness), which have different effects on cerebral evoked potentials as well as subjective and objective (MSLT) differences. It is argued that in pathophysiological terms narcolepsy may best be considered a disease of state boundary control. **Key Words:** Narcolepsy—Sleepiness—Arousal—Performance—Evoked potentials.

Narcolepsy is usually characterized by extreme excessive daytime sleepiness (EDS), microsleep lapses, memory problems, amnesic automatisms, ocular symptoms (blurring, diplopia, flickering), depression, hallucinosis, and concomitant sleep apnea or periodic movements in sleep, as well as the diagnostic symptom tetrad of more or less irresistible sleep attacks, cataplexy, sleep paralysis, and vivid hypnagogic hallucinations. Numerous issues still not entirely resolved include the following: which symptom is the most disabling, what higher nervous or other neuropsychological functions are most impaired, how such impairment occurs, how major characteristic subjective symptoms can best be measured, and what are the neurophysiological and neurochemical bases of such specific dysfunctions, as well as issues regarding the overall disease itself. This paper will consider these and related issues, which have been of major interest to our center over the past 10 years.

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Which symptom is the most disabling for the patient?

The criteria for the most disabling symptom should include socioeconomic impact, chronicity, intensity, and low response to therapy.

An initial report from our center (1) was later expanded into the first major study of narcolepsy's socioeconomic effects as an international collaborative endeavor involving narcolepsy centers in Canada, Japan, and Czechoslovakia. The study comprised 180 patients with narcolepsy-cataplexy and 180 age- and sex-matched controls; it documented the potentially debilitating nature of this chronic neurological disease (2). Narcolepsy was found to incur multiple, serious problems in occupation, education, recreation, driving, accidents, personality, interpersonal relationships, quality of marriage, sex life, and other areas. Most problems were attributed to EDS rather than to the diagnostic symptoms. Subsequent further analysis of these data (3) indicated that these effects showed few significant differences according to patient geographic origin (60 each from North America, Europe, and Asia), age, sex, age at disease onset, duration of illness, or even presence or absence of treatment. The main psychosocial effects therefore appeared to be an integral part of the disease.

Comparison of narcolepsy-cataplexy to idiopathic central nervous system (CNS) hypersomnia (another neurological disorder with extreme EDS and sleep attacks but without cataplexy, sleep paralysis, or vivid hypnagogic hallucinations) in matched patients found slightly lesser overall levels of socioeconomic effects in narcoleptic patients (4). But narcoleptic patients were significantly more impaired in those situations in which the more abrupt onset of their daytime sleep attacks and cataplexy would have a major impact, e.g., household and smoking accidents, problems with driving, and recreation. Subsequent comparison of narcoleptic patients to matched epileptic patients lacking significant detectable cerebral pathology or major psychiatric problems, but suffering from frequent seizures of primary generalized epilepsy or temporal lobe epilepsy, indicated even greater psychosocial impairment in the narcoleptic patients (5). Both diseases are chronic neurological conditions expressed by intermittent symptoms involving loss of consciousness and motor phenomena. The results strongly suggested that it was the chronic unrelenting EDS of narcoleptic patients between attacks that caused the greater psychosocial impact.

EDS, as well as being the symptom attributed by patients to be the most disabling, is characterized in most patients by an unrelenting chronicity, marked intensity (at least at certain times of the day), and poor response to treatment. Guilleminault and Dement (6), using traditional antinarcoleptic therapy (tricyclic antidepressant and stimulant medications), first reported that EDS was the most refractory symptom for control. This also holds true (7,8) for treatment with nocturnal γ-hydroxybutyrate, as introduced a decade ago for the treatment of narcolepsy-cataplexy by Broughton and Mamelak (9), a phenomenon recently confirmed by Scharf and collaborators (10). The fundamental neurochemical (or other) reasons why EDS, rather than sleep attacks, cataplexy, sleep paralysis, or hypnagogic hallucinations, should be the most refractory major symptom to medication remain obscure.

What are the objective performance deficits of EDS in narcolepsy?

If EDS is manifestly the symptom that most frequently causes the very considerable disability of narcolepsy, there is obvious interest in assessing its full neuropsychological impact by objective testing.

Some preliminary data on performance measures were obtained by Billiard (11) and Guilleminault et al. (12) in which statistical comparisons to control subjects were not used and the paradigms were constructed to facilitate drowsiness by employing repetitive and boring tasks repeated several times a day. The first systematic study was that of Valley and

Broughton (13), which used an inverse approach by attempting to minimize drowsiness and to approximate normal working conditions. This was done by morning testing of subjects sitting upright on a hard chair at a desk. Subjects were told not to fall asleep and that they would be awakened if they did fall asleep. The study employed Wilkinson's auditory vigilance test, a serial four-choice reaction time task, the paced auditory serial addition task (PASAT), and the digit span test. The reaction time test has recently been used with multiple daily testings by Godbout and Montplaisir (14).

The most sensitive performance deficit was found to involve prolonged vigilance-type tests. In these tests, narcoleptic patients attained only about one-half the number of signal detections (hits) as did the normal control subjects (13). There were striking moment-to-moment changes in performance as a function of alertness (see the following section for further discussion). In the choice reaction-time test, narcoleptic patients showed significant but less marked differences consisting of longer mean latencies overall and for both correct and incorrect responses, as well as about twice the number of gaps (responses >1 s). These two sensitive tests can be considered repetitious, boring, and unstimulating. Significant impairment on similarly repetitious tasks, the Wilkinson addition task and the digit-symbol substitution test, have been reported by Mitler et al. (15). By comparison, narcoleptic patients performed at normal levels on short challenging tasks involving speed of information processing (PASAT) and attention-concentration-immediate memory (digit span) (13).

Approximately 50% of narcoleptic patients complain of severe memory disturbance, mainly for recent events (2). Indeed, patients often keep extensive lists in order not to forget. This subjective memory disturbance was recently studied by a formal neuropsychological test battery in our laboratories (16). Narcoleptic patients who believed they had a major memory disturbance were chosen. They were tested both while on and off drug treatment by use of eight memory tests chosen to differentiate immediate memory, short-term memory, long-term memory, and recall. Both verbal and nonverbal material, and visual and auditory modes of presentation, were employed. Surprisingly, narcoleptic patients performed as well as control subjects on all tests, both on and off drug treatment. It was concluded (a) that narcoleptic patients challenged by a memory battery in a laboratory situation can rally and remain sufficiently alert to perform at normal levels, and (b) that the memory disturbance experienced is entirely due to drowsiness and does not indicate irreversible organic impairment. Combining results of ourselves and others on tests of performance and higher nervous function, there is currently no evidence whatsoever for any permanent deficit of information processing in narcoleptic patients.

What is the physiological nature of sleepiness and its effects on performance?

Electroencephalographic (EEG) monitoring of motivated, seated narcoleptic patients performing a vigilance task [Valley and Broughton (17)] showed that the physiological dysfunction consists of a rather slow "waxing and waning" of level of alertness through wakefulness, stage 1A (slowing and diffusion of alpha, slow eye movements), and stage 1B sleep (equivalent to stage 1 sleep of Rechtschaffen and Kales) as defined by Gastaut and Broughton (18), and occasionally in stage 2 sleep, thereby confirming earlier EEG reports of others in reclining subjects (19–23). Stages 3 and 4 sleep and REM were absent. There was no evidence for significant numbers of brief punctate "microsleeps," as described by Guilleminault and Dement (23). This might represent differences in the experimental situation, methods of analysis, or other such variables.

During the 1-h vigilance task, narcoleptic patients were awake only 44% of the time as opposed to 99% for controls. "Waxing and waning" was maintained equally throughout

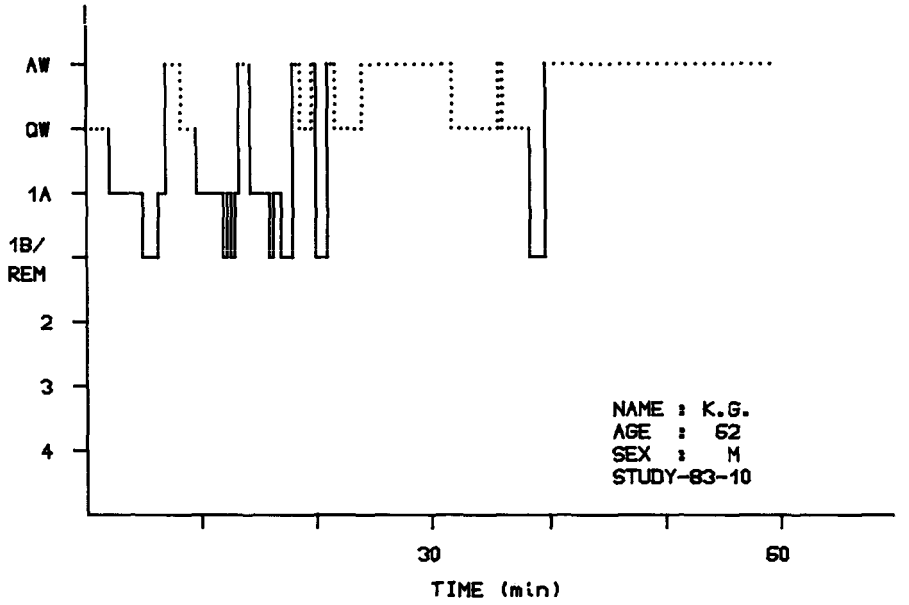

FIG. 1. Histogram of typical waxing and waning of alertness during a 1-h daytime portion of a 24-h ambulant recording in a patient with narcolepsy-cataplexy. Level of alertness shows repeated fluctuations with periods of sustained stage 1B of several minutes duration. AW, active wakefulness; QW, quiet wakefulness; 1A, stage 1A and 1B, stage 1B as defined in Valley and Broughton (17) and Gastaut and Broughton (18).

the test and was expressed as a >10-fold increase in the number of stage shifts per hour in narcoleptic patients compared with control subjects. The main problem in narcoleptic patients is therefore one of an inability to sustain alertness over time. Analysis of the ability of narcoleptic patients to sustain any individual state over time showed that this increased rapidly and in stepwise fashion from wakefulness through stages 1A, 1B, and 2 sleep, wakefulness being the least maintained state (17).

The importance of this "waxing and waning" is further supported by 24-h ambulant recordings in the home environment, which we have been performing regularly in narcoleptic patients since 1975 (7,8,24). As well as documenting sleep attacks and cataplexy, such studies in untreated narcoleptic patients have repeatedly shown waxing and waning of alertness throughout long periods in the daytime. A typical patient histogram for ~1 h of the daytime portion of a 24-h ambulant recording is illustrated in Fig. 1. Such studies also show a propensity to express underlying endogenous biological rhythms, occasionally (especially in very inactive patients) with daytime REM sleep attacks tending to recur at an ultradian 90–120-min period [as described by Passouant et al. (25) and statistically confirmed by Schulz (26)] and almost always (even in quite active subjects) with a major midafternoon nap or sleep attack and an increase in slow wave sleep (SWS) ~12.5 h after nocturnal SWS. The latter appears to express the circasemidian SWS rhythm postulated earlier (27). Apparent microsleeps are sometimes encountered in such recordings; but they are much less characteristic than "waxing and waning" of alertness or episodes of overt sleep.

As mentioned, a tight correlation exists between the moment-to-moment level of alertness and the objective performance on a sensitive vigilance task in narcoleptic patients (17). As narcoleptic patients slipped from wakefulness to stages 1A, 1B, and 2 sleep, the number

of detections decreased dramatically. Hits were immediately halved with progression from wakefulness to the light somnolence of stage 1A sleep (from 38.4 to 14.5%). By stage 1B sleep there were too few responses (only 1 hit) to analyze statistically and in stage 2 sleep there were no responses. Decreased detection rates were associated with fewer responses overall (including false positives). These results emphasize the behavioral importance of subdividing stage 1 of Rechtschaffen and Kales (28) into at least two substages. Other researchers have provided classifications of many further substages of drowsiness [see reference (29)].

There is also intriguing evidence for carryover or "sleep inertia" (drowsiness inertia) effects in the daytime similar to postawakening effects at night (30). When all signals were divided into those preceded by at least 13 s of wakefulness (sustained wakefulness) and those preceded by only 3 s of wakefulness (fragmented wakefulness), it was found that 46.5% of the former were detected (not significantly different from the normal subjects' mean rate of 60.2%) whereas recent drowsiness (fragmented wakefulness) was associated with a substantial drop to only 17.8% of signals detected. Therefore, daytime performance is reduced both by periods of drowsiness and by recent arousal from drowsiness. In short, mental capacities are impaired during both the waxing and waning phases of alertness; and it is only during sustained periods of full arousal that normal ability is attained. On the other hand, like the memory data, the narcoleptic patients' ability to perform a sensitive vigilance task at normal levels during sustained alertness gives rise to optimism that with improved therapy their lives should become much more normal.

Finally, neither the performance data nor the EEG results support a major role for the "lapse-microsleep" hypothesis proposed by others (23). Even in wakefulness, there is a much broader performance deficit than the simple increase in omissions predicted by that hypothesis. In wakefulness and stage 1A these include an increase in false positives (willingness to respond), increase in errors, and a decrease in overall response rate. Moreover, "microsleep" EEG patterns have been essentially absent in such recordings.

Inversely, to what extent do performance demands affect alertness?

Just as drowsiness and sleep negatively affect performance, the performance demands either at work or in formal laboratory situations reciprocally affect alertness. For instance, in narcoleptic patients during the study mentioned above (13), the relatively monotonous 1-h vigilance task contained drowsiness or light sleep in 56.1% of the test duration (stage 1A sleep 28.5%, stage 1B sleep 26.0%, and stage 2 sleep 2.5%; with only 44% wakefulness), whereas there was much less drowsiness and no stage 2 sleep in the more challenging digit span and PASAT tests. Moreover, even within the latter test, there was progressive decrease in drowsiness as subjects went from the less demanding slower series to the more challenging rapid ones. Such studies quantify the ability of narcoleptic patients to suppress drowsiness in order to complete short, challenging, and stressful tasks.

Fighting off drowsiness is, however, apparently not without cost. This was indicated by the fact that although only two episodes of cataplexy occurred during the entire experiment, both were encountered in subjects immediately after the PASAT, the test self-rated by the subjects as requiring the highest objective effort (13). Moreover, these two (of 10) patients had the greatest amount of drowsiness (all stage 1A sleep) during the task indicating that they were the least successful in their struggles to maintain alertness.

While some have suggested that narcoleptic patients function best in a stimulating situation, it would seem (13) that more moderate levels of stimulation plus the ability to schedule breaks or naps would permit better overall levels of performance and feelings of wellbeing.

Is EDS composed of qualitatively different states?

Sleepiness (impaired alertness) has generally been considered a more or less homogeneous state, which varies only in intensity. In 1982 the proposal was made by one of the authors (31) that EDS can in fact be composed of mixtures of at least three qualitatively different dimensions. On the basis of relative involvement of the three basic biological states, these would express (mainly) pressure for NREM sleep, pressure for REM sleep, or impaired waking mechanisms and can be referred to as NREM sleepiness, REM sleepiness, and de-arousal, respectively. It was further proposed that subjective state, performance capabilities, higher nervous functions, biological rhythms, and neurophysiological, neurochemical, and neuroendocrine status might all show differences in such multiple states of sleepiness.

There is now increasingly strong support for such multidimensionality in sleepiness. Aguirre and Broughton (32,33) have performed two 7-min evoked potential (EP) studies immediately prior to five multiple sleep latency tests (MSLT) across the day in both narcoleptic patients and control subjects. The EP studies were (a) P300 paradigm (34) consisting of an auditory vigilance task (detection of somewhat lower frequency tones among a series of regular tones) and (b) the contingent negative variation (CNV) paradigm (35) which consisted of subjects repeatedly waiting to respond by button press to a buzzer that sounded 2 s after a warning tone. All data in narcoleptic patients were separated into those in REM sleepiness and NREM sleepiness, according to the sleep state in the immediately subsequent MSLT nap. It was found that REM sleepiness is both subjectively (Stanford Sleepiness Scales) and objectively (MSLT latencies) greater than NREM sleepiness in narcoleptic patients. The more irresistible nature of sleep attacks in narcolepsy compared with other disorders of excessive sleepiness would appear to be due to this more imperative nature of REM sleep pressure.

Moreover, selective differences in EP measures were found. REM compared with NREM sleepiness showed higher amplitude P2 components, an almost significantly smaller P3 component, and marked suppression of CNV amplitude. Significant intergroup differences between narcoleptic patients and control subjects were also present, indicating the overall usefulness of complex EPs as EDS measures. Using simple auditory EP to clicks, Pressman et al. (36) have also shown differences prior to immediately subsequent REM or NREM sleep in narcoleptic patients.

REM sleepiness (waking pressure for REM sleep) may, of course, be encountered in many situations other than narcolepsy-cataplexy. These include ultra-short (e.g., 20-min) and short (e.g., 3- or 6-h) sleep/wake cycles in normal subjects, other biorhythmic disturbances, endogenous depression, and certain drug withdrawal states. Studies of such conditions are providing increasing evidence that brain state in REM sleepiness is qualitatively different than in NREM sleepiness (e.g., idiopathic CNS hypersomnia and sleep apnea syndromes) or in de-arousal (posttraumatic syndrome and subvigilance syndrome).

The extremely refractory nature of EDS to treatment in narcolepsy-cataplexy may, in fact, be due to persistence of a combination of two or even all three basic sleepiness states across the day. It is known that pressure for both REM sleep and NREM sleep exists in awake narcoleptic patients, and it has been suggested that the disease also contains an inherent subvigilance syndrome with impaired reticulocortical arousal (37). Thus, patients may need simultaneous pharmacological control of REM sleepiness, NREM sleepiness, and de-arousal. It may currently be difficult or impossible to attain the necessary drug-induced neurochemical balance.

What is the most sensitive measure of EDS states?

It is of obvious importance to develop sensitive and reliable measures of EDS in order to quantify this major symptom of narcolepsy, as well as of many other conditions ranging through sleep deprivation, various biorhythmic disturbances, psychiatric conditions, and many other medical diseases. An optimum test would be sensitive, replicable, brief, inexpensive, and portable, and would give insight into brain mechanisms (31). Many approaches, of course, have been developed and, to varying extents, assessed: subjective measures, performance tests, pupillometry, MSLT, maintenance of wakefulness tests, EPs, intensive monitoring, and EEG power spectrum analysis. Such measures may be compared according to either (a) their relative sensitivity to detect EDS or (b) the degree by which they distinguish patients from control subjects.

Subjective assessment of sleepiness in narcoleptic patients has not proved a reliable predictor of any objective measure, including performance deficits (13), MSLT latency (33), a sustained wakefulness test (38), or EP measures (33). Lack of correlation of subjective estimates with MSLT has also been reported for the chronic EDS of sleep apnea (39,40). It is possible that our current subjective scales are insufficiently sensitive. Perhaps more probably, subjective assessment becomes unreliable as a subject adapts to chronic EDS (13,17,39).

Performance measures have the advantage of objectifying actual impairment of abilities. Although vigilance and other repetitive tests can be very sensitive to EDS, motivational effects and, in particular, the ability of sleepy subjects to rally to the test challenge (13,16) obviates much of their utility, at least as they are currently used.

The EP approach was introduced as an EDS measure by our group in 1981 (41) as a rapid replicable measure. The simple auditory evoked potential was found (42) to be even more sensitive than the known most sensitive performance task (Wilkinson's auditory vigilance task). But the variability of the EP measure was considerable, thereby restricting its diagnostic usefulness.

Complex EPs are much more promising. Using data from the study mentioned above (33), we have preliminary results using discriminant analysis of the relative ability of the P300 evoked potential test, compared with MSLT measures, to distinguish patients with narcolepsy-cataplexy from control subjects. The P3 amplitude has been analyzed and compared with MSLT for both stage 1B (or REM) sleep and stage 2 (or REM) sleep latencies, as all three measures showed significant intergroup differences. The EP measure was almost as sensitive as MSLT in successfully separating and classifying patients from control subjects (Table 1). However, neither MSLT nor P3 measures were able to completely distinguish the groups, there being a considerable degree of overlap, confirming the results of Hartse et al. for a maintenance of alertness test (38). That is, when either MSLT or EP criteria were used, there was a proportion of results in patients with narcolepsy-cataplexy indicating as high a level of alertness as in control subjects; inversely, control subjects on some occasions were as sleepy as narcoleptic patients.

Some might consider that the EDS of patients (like narcoleptic patients) who experience more or less imperative daytime sleep attacks is itself qualitatively different from marked sleepiness in normal persons, and that it perhaps should be referred to as "pathological sleepiness." To date, however, there has been no objective evidence for qualitative differences in any sleepiness measure reported. Given the right degree and type of sleep disruption (e.g., ultra-short sleep schedules), at least some normal individuals will show similar degrees of subjective sleepiness, actual sleep, performance deficits, MSLT latencies, and SOREMPs

TABLE 1. *Discriminant analysis of data collapsed across sessions (n = 110 naps, 55 each group)*[a]

P3 amplitude, stage 1B and 2 combined		P3 amplitude	Stage 1B	Stage 2	r^2	p overall
Univariate *F* test	p	<0.0001	<0.0001	<0.0001	0.69	<0.0001
Relative weights		0.32	0.37	0.62		
Misclass (of 55)			Narcoleptic 8 (14.5%)			Control 13 (23.6%)

Individual	r^2	p	Misclass narcoleptic	Misclass control
P3 amplitude	0.38	<0.0001	21 (38.2%)	18 (32.7%)
MSLT stage 1B[b]/REM	0.64	<0.0001	10 (18.2%)	16 (29.1%)
MSLT stage 2/REM	0.62	<0.0001	7 (12.7%)	17 (30.9%)

Stage 1A measures in MSLT did not distinguish groups. r^2 is the squared multiple correlation. Relative weights in combined discriminant analysis are based on standardized discriminant coefficients. Misclass refers to the number of subjects misclassified by discriminant analysis into the other group.

[a]Sleepiness was measured by P3 amplitude and MSLT to both stage 1B* (or REM) and stage 2 (or REM).

[b]Stage 1B of Gastaut and Broughton (18) is equivalent to stage 1 of Rechtschaffen-Kales (28).

as narcoleptic patients. It would, of course, be expected that this would not be the case for other groups of neurological patients with essentially irreversible sleepiness related to permanent organic brain disease.

Is the fundamental pathophysiology of narcolepsy-cataplexy one of REM sleep, all sleep stages, biological rhythms, or perhaps of state boundary control?

There has been some continuing controversy whether or not narcolepsy should be considered to be basically a disease of REM sleep per se. This conceptualization was, in fact, a conclusion of the 1975 Montpellier narcolepsy symposium, although it was not fully supported by all participants, as was implied in the definition at the start of the volume (43). The reasons are that excessive pressure for REM sleep, including SOREMPs, occurs in numerous other situations and, above all, that there has long been evidence for essentially equal degrees of involvement of NREM and REM mechanisms in narcolepsy. In fact, ~50% of sleep attacks in narcolepsy-cataplexy consist of NREM sleep; sleep latencies are abnormally short for both NREM and REM sleep both in night sleep and in MSLT recordings; and the onset of the disease may be characterized by "monosymptomatic narcolepsy" with NREM sleep attacks alone and lacking evidence for abnormal REM pressure before the appearance of cataplexy, REM sleep attacks, and SOREMPs. As early as 1975, Meier-Ewert et al. (44) proposed that, depending upon the relative involvement of the sleep systems, narcolepsy may be classed into NREM, NREM/REM, REM/NREM, and REM forms.

Although they do involve REM mechanisms, the characteristic symptoms of vivid hypnagogic hallucinations (during SOREMPs) and sleep paralysis (dissociated REM sleep) are nondiagnostic, as they are seen in other conditions. These include irregular sleep habits or drug withdrawal states for the former symptom, and isolated or familial forms of sleep paralysis in the latter. Of the REM-based phenomena, only cataplexy is truly diagnostic of the full syndrome. The essential feature of the narcolepsy-cataplexy syndrome is therefore not an abnormality of REM sleep per se but exclusively one of dissociated REM sleep—

specifically that of atonia plus paralysis appearing without other REM components and expressed clinically as cataplectic attacks triggered by emotional stimuli.

It has been suggested that narcolepsy-cataplexy may be fundamentally a disorder of biological rhythms (45). The disease certainly shows some abnormal biorhythmic features. They include loss of a circadian monophasic sleep pattern with appearance of a more even sleep distribution around the 24 h reminiscent of that of the neonate (25), more even distribution of SWS across the thirds of the night and away from the single acrophase in the first third (46), delay and loss of the normal main circadian peak of growth hormone secretion related to SWS in the first hours of sleep (47), phase advance of the in-sleep ultradian REM cycle expressed as SOREMPs reported as early as 1963 (46,48), increased variability of the nocturnal ultradian periodicity of REM sleep (49,50), and appearance of similar ultradian REM periodicity both in ad-lib daytime sleep (26) and in overt sleep attacks (25). To date, however, none of these abnormal biorhythmic aspects of the disease have been shown to be diagnostic or exclusive features of narcolepsy-cataplexy.

We would propose that rather than conceptualizing narcolepsy-cataplexy as an REM sleep disease, an REM/NREM sleep disease, or a biorhythmic disorder, it might be considered more accurately to be fundamentally a disorder of state boundary control. If it is true that the essential feature is the existence of dissociated motor components of REM sleep in the form of cataplexy, it is equally apparent that dissociations of normal state boundaries and recombinations of state subcomponents are seen in myriad expressions of the disease. Indeed, almost all conceivable dissociations of normal state boundaries of wakefulness, NREM sleep, and REM sleep have been reported. It is as though whatever neurochemical "glues" or integrative neurophysiological mechanisms exist for sleep and wake state continuity and for their full reciprocality have somehow become dissolved.

An analysis of all of the dissociations and recombinations of the state subcomponents is clearly beyond the confines of this report. The instances are many and include isolated atonia and paralysis of REM sleep (cataplexy, sleep paralysis), episodes of REM atonia in NREM sleep (49), REM bursts in NREM sleep (51), phasic middle ear membrane activity at sleep onset prior to SOREMPs (52), subjective wakefulness associated with physiological patterns of sleep (53), simultaneous awareness of the environment and of dream imagery as a form of "double consciousness" (54), marked spindles in REM sleep as "ambiguous" or "intermediate" sleep (55), and the loss of a clear circadian separation of wakefulness from sleep (appearance of much wakefulness in nocturnal sleep and of sleep during the normal waking period).

As night sleep in monosymptomatic (NREM) narcolepsy has been reported repeatedly as essentially normal, this remarkable destructuring of state boundaries so characteristic of narcolepsy-cataplexy seems to occur in the disease evolution only with the appearance of dissociated REM sleep as cataplexy (and/or as sleep paralysis). There is evident need for longitudinal studies of narcoleptic patients from the onset of sleep attacks in order to document the progression of this multifaceted sleep/wake state dissolution. This is particularly of interest in that there is some evidence that the genetics of EDS and of cataplexy may be somewhat different.

In sum, the full narcolepsy-cataplexy syndrome may best be conceptualized as a disorder of sleep/wake state boundaries rather than of REM sleep. This would imply the importance, for a better understanding of the disease, of greater research into the genetic, neurochemical, and neurophysiological mechanisms involved in the integration and maintenance of both NREM and REM sleep states and of wakefulness.

REFERENCES

1. Broughton R, Ghanem Q. The impact of compound narcolepsy on the life of the patient. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976:201–20.
2. Broughton R, Ghanem Q, Hishikawa Y, Sugita Y, Nevsimalova S, Roth B. Life effects of narcolepsy in 180 patients from North America, Asia and Europe compared to matched controls. *Can J Neurol Sci* 1981;8:299–304.
3. Broughton R, Ghanem Q, Hishikawa Y, Sugita Y, Nevsimalova S, Roth B. Life effects of narcolepsy: relationships to geographic origin (North American, Asian or European) and to other patient and illness variables. *Can J Neurol Sci* 1983;10:100–4.
4. Broughton R, Nevsimalova S, Roth B. The socio-economic effects of idiopathic hypersomnia—comparisons with controls and with compound narcoleptics. In: Popoviciu L, Asgian B, Badiu G, eds. *Sleep 1978*. Basel: Karger, 1980:229–33.
5. Broughton R, Guberman A, Roberts J. Comparison of the psychosocial effects of epilepsy and narcolepsy/cataplexy: a controlled study. *Epilepsia* 1984;25:423–33.
6. Guilleminault C, Dement WC. Pathologies of excessive daytime sleepiness. In: Weitzman E, ed. *Advances in sleep research*. New York: Spectrum, 1974;3:345–90.
7. Broughton R, Mamelak M. The treatment of narcolepsy-cataplexy with nocturnal gamma-hydroxybutyrate. *Can J Neurol Sci* 1979;6:1–6.
8. Broughton R, Mamelak M. Effects of gamma-hydroxybutyrate on sleep/waking patterns in narcolepsy-cataplexy. *Can J Neurol Sci* 1980;7:23–31.
9. Broughton R, Mamelak M. Gamma-hydroxybutyrate in the treatment of compound narcolepsy. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976:659–66.
10. Scharf MB, Brown D, Woods M, Brown L, Hirschowitz J. The effects and effectiveness of γ-hydroxybutyrate in patients with narcolepsy. *J Clin Psychiatr* 1985;46:222–5.
11. Billiard M. Competition between the two types of sleep, and the recuperative function of REM versus NREM sleep in narcoleptics. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976:77–96.
12. Guilleminault C, Billiard M, Montplaisir J, Dement WC. Altered states of consciousness in disorders of daytime sleepiness. *J Neurol Sci* 1975;26:377–93.
13. Valley V, Broughton R. Daytime performance deficits and physiological vigilance in untreated patients with narcolepsy-cataplexy compared to controls. *Rev EEG Neurophysiol* (Paris) 1981;11:133–9.
14. Godbout R, Montplaisir J. All-day performance variations in normal and narcoleptic subjects with and without naps. Presented at Second International Symposium on Narcolepsy. Stanford, California, July 6–7, 1985.
15. Mitler M, Gujavarty KS, Sampson MG, Browman CP. Multiple daytime nap approaches to evaluating the sleepy patient. *Sleep* 1982;5(suppl 2):119–27.
16. Aguirre M, Broughton R, Stuss D. Does memory impairment exist in narcolepsy-cataplexy? *J Clin Exp Neuropsychol* 1985;7:14–24.
17. Valley V, Broughton R. The physiological (EEG) nature of drowsiness and its relation to performance deficits in narcoleptics. *Electroencephalogr Clin Neurophysiol* 1983;55:243–51.
18. Gastaut H, Broughton R. A clinical and polygraphic study of episodic phenomena during sleep. *Rec Adv Biol Psychiatr* 1965;7:197–221.
19. Pond DA. Narcolepsy: a brief critical review of eight cases. *J Ment Sci* 1952;98:595–604.
20. Gastaut H, Roth B. A propos des manifestations électroencéphalographiques de 150 cas de narcolepsie avec ou sous cataplexie. *Rev Neurol (Paris)* 1957;97:388–93.
21. Daly DD, Yoss RE. The electroencephalogram in narcolepsy. *Electroencephalogr Clin Neurophysiol* 1957;9:109–20.
22. Roth B. L'EEG dans la narcolepsie-cataplexie. *Electroencephalogr Clin Neurophysiol* 1964;16:170–90.
23. Guilleminault C, Dement WC. Amnesia and disorders of excessive sleepiness. In: Drucker Colin RR, McGaugh JL, eds. *Neurobiology of sleep and memory*. New York: Academic Press, 1977:439–56.
24. Healey T, Maru J, Broughton R. A 4-channel portable recording system. *Sleep Res* 1975;4:254.
25. Passouant P, Halberg F, Genicot R, Popoviciu L, Baldy-Moulinier M. La periodicité des accès narcoleptiques et le rhythme ultradien du sommeil rapide. *Rev Neurol (Paris)* 1969;121:155–64.
26. Schulz H. Ultradian rhythms in the nychthermeron in narcoleptic patients and normal subjects. In: Schulz H, Lavie P. *Ultradian rhythms in physiology and behavior*. Stuttgart: Fischer Verlag, 1985:165–85.
27. Broughton R. Biorhythmic variations in consciousness and psychological functions. *Can Psychol Rev* 1985;16:217–30.
28. Rechtschaffen A, Kales A, eds. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Washington: U.S. Government Printing Office, 1968.
29. Roth B. L'activité de sommeil dans l'EEG comme indicateur d'une insuffisance chronique de l'état de vigilance. *Electroencephalgr Clin Neurophysiol* 1957;(suppl 7):309–11.

30. Broughton R. Slow wave sleep awakenings in normals and pathology: a brief review. In: Koella WP, Ruther E, Schulz H, eds. *Sleep '84*. Stuttgart: Fischer Verlag, 1985:115–6.
31. Broughton R. Performance and evoked potential measures of various states of daytime sleepiness. *Sleep* 1982;5(suppl 2):135–46.
32. Aguirre M, Broughton R. Objective and subjective measures of (REM and NREM) sleepiness in narcolepsy-cataplexy. *Sleep Res* 1984;13:128.
33. Broughton R, Aguirre M. Evidence for qualitatively different types of excessive daytime sleepiness. In: Koella WP, Ruther E, Schulz H, eds. *Sleep '84*. Stuttgart: Fischer Verlag, 1985:86–7.
34. Picton TW, Campbell KB, Baribeau-Braun J, Proulx GB. The neurophysiology of human attention: a tutorial review. In: Requin J, ed. *Attention and performance VII*. Hillsdale, New Jersey: Lawrence-Erlbaum, 1978:429–67.
35. Walter WB, Cooper R, Aldridge VJ, McCallum WC, Winter AL. Contingent negative variation: an electrical sign of sensorimotor association and expectancy in the human brain. *Nature* 1964;203–4.
36. Pressman MR, Spielman AJ, Pollock CP, Weitzman E. Long-latency auditory evoked responses during sleep deprivation and in narcolepsy. *Sleep* 1982;5(suppl 2):147–56.
37. Broughton R. Discussion. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976:667.
38. Hartse KM, Roth T, Zorick FJ. Daytime sleepiness and daytime wakefulness: the effect of instruction. *Sleep* 1982;5(suppl 2):107–18.
39. Dement WC, Carskadon MA, Richarson G. Excessive daytime sleepiness in the sleep apnea syndrome. In: Guilleminault C, Dement WC, eds. *Sleep apnea syndromes*. New York: Alan R. Liss, 1978:23–46.
40. Roth T, Hartse K, Zorick F, Coneway W. Multiple naps and the evaluation of daytime sleep in patients with upper airway sleep apnea. *Sleep* 1980;3:425–39.
41. Broughton R, Low R, Valley V, da Costa B, Liddiard S. Auditory evoked potentials compared to EEG and performance measures in the assessment of impaired vigilance in narcolepsy-cataplexy. *Sleep Res* 1981;10:184.
42. Broughton R, Low R, Valley V, da Costa B, Liddiard S. Auditory evoked potentials compared to performance measures and EEG in assessing daytime sleepiness in narcolepsy-cataplexy. *Electroencephalogr Clin Neurophysiol* 1982;54:579–82.
43. Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976.
44. Meier-Ewert K, Schopfer B, Ruther E. Drei narkoleptische Syndrome. *Nervenarzt* 1975;46:624–35.
45. Kripke D. Biological rhythm disturbance might cause narcolepsy. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976:475–84.
46. Rechtschaffen A, Wolpert EA, Dement WC, Mitchell SA, Fisher C. Nocturnal sleep of narcoleptics. *Electroencephalgr Clin Neurophysiol* 1963;15:599–609.
47. Higuchi T, Takahashi Y, Takahashi K, Niimi Y, Miyasita A. Twenty-four hour secretory patterns of growth hormone, prolactin and cortisol in narcolepsy. *J Clin Endocrinol Metab* 1979;49:197–204.
48. Hisikawa Y, Tabushi K, Ueyama M, Hariguchi S, Fujiki A, Kaneko Z. Electroencalographic study in narcolepsy: especially concerning the symptoms of cataplexy, sleep paralysis, and hypnagogic hallucinations. *Proc Jap EEG Soc (Tokyo)* 1963;52–5.
49. Montplaisir J. Disturbed nocturnal sleep. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976:43–56.
50. Hishikawa Y, Wakematsu H, Furuya E, et al. Sleep satiation in narcoleptic patients. *Electroencephalogr Clin Neurophysiol* 1976;41:1–18.
51. Guilleminault C, Reynal D, Takahashi S, Carskadon M, Dement W. Evaluation of short-term and long-term treatment of narcolepsy syndrome with chlomiprimine hydrochloride. *Acta Neurol Scand* 1976;54:71–87.
52. Lamstein SM, Spielman AJ, Weitzman E, Pollack C, Roffwarg P. The recording of middle ear activity in narcolepsy. *Sleep Res* 1977;6:175.
53. Vogel G. Mentation reported from naps of narcoleptics. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976:161–8.
54. Broughton R. Human consciousness and sleep/waking rhythms: a review and some neuropsychological considerations. *J Clin Neuropsychol* 1982;4:193–218.
55. Barros-Ferreira M, Lairy GC. Ambiguous sleep in narcolepsy. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976:57–75.