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RAPID EYE MOVEMENT SLEEP DEPRIVATION EXCESSIVE DAYTIME
SLEEPINESS, AND SLEEP ONSET RAPID EYE MOVEMENT PERIODS
(SOREMPS) IN NARCOLEPTICS AND NORMALS CONTROLS

City University of New York

Ph.D. 1984

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RAPID EYE MOVEMENT SLEEP DEPRIVATION
EXCESSIVE DAYTIME SLEEPINESS,
AND SLEEP ONSET RAPID EYE MOVEMENT PERIODS (SOREMPS)
IN NARCOLEPTICS AND NORMALS CONTROLS

by John Michael Adler

A dissertation submitted to the Graduate Faculty
in Psychology in partial fulfillment of the
requirements for the degree of Doctor of Philosophy,
The City University of New York

1984

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1984

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy

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"My Weariness Amazes Me"

Robert Dylan, from the song
"Mr. Tambourine Man"

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CHAPTER ONE

INTRODUCTION

Allure: A Case

"People have always been fascinated by my condition, asking me questions, watching me, doctors who want to examine me. I've always just wished it would go away and leave me be." This 42 year old black woman, a patient at the Sleep-Wake Disorders Center of Montefiore Hospital and Medical Center in the Bronx, New York, was a narcoleptic subject in this study, and had understood long ago, as a teenager, that something "peculiar" was wrong with her, something that produced strong reactions and generated curiosity in others. Similarly, colleagues, friends, and acquaintances of this author have often, upon discovering the topic of this doctoral dissertation, expressed their belief that something inherently exciting or "fascinating" was imbued in the illness narcolepsy.

One can only speculate regarding the basis for this fascination. Accounts of encephalitic sleepers who awaken after years of repose stir the imagination. Where have they been, and how long a time did it seem to their sleeping minds? The experience of sleep, and especially that of dreaming, is that of a mysterious altered state for most, one where we experience ourselves and the world as fundamentally different. Perhaps the world of the

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narcoleptic appears to others as a life of deep, irresistible dreaming. We are assured, in any event, by these patients that it is not a pleasant dream.

In the instance of this particular woman, the reverberations of narcolepsy within her life have been manifold, and would necessarily lead one, as a point of departure, to her high school days when, unknowingly, she first became symptomatic. From an intelligent, ambitious black, inner city family, within which her sibblings were successfully completing their studies and moving on to higher education and achievement, this patient found that her and her family's expectations for a similar course for herself were gradually and insiduously undermined by the narcoleptic's worst enemy, sleepiness. Her ability to concentrate and perform in high school was impaired, and not surprisingly, this was attributed by others to a variety of undesirable psychic states and attitudes- covert rebelliousness, slothfulness, and intellectual deficiency. No physiological explanation was made available regarding for symptoms, and the patient herself remained unsure as to the cause of her problems.

Gradually, this woman came to feel angry, shameful, and guilty; her sense of self diminished and her relations with peers and family suffered. Eventually, when she developed substantial cataplexy as an adult, facilitating her diagnosis, it came as a relief, a sort of vindicaiton for her tribulations in growing up.

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Yet she remained captive to a disorder that was largely incapacitating, recalcitrant to treatment, and imperious to cure, poorly understood and bizarre in its manifestations, and monumental in its impact on the breadth and scope of her life. For this patient could not drive an automobile, worked sparingly and with great difficulty, in fact could not even experience normal emotions of laughter and anger without risk of cataplectic attack. Most objectionable of all, she felt as though she were living in a fog or trance, the god of Morpheus her constant companion.

As a student of the world of sleep and its perturbations, this author felt intently the intrigue and uniqueness of the disease afflicting those patients with narcolepsy. In particular, its misdiagnosis and iatrogenic sequelae were striking- many patients had been seeking answers for years without satisfaction regarding their condition, and they often, as a result, appeared resentful, confused, and defeated. A variety of compelling reasons existed to investigate this disease further, and some of these are now briefly reviewed.

What is Narcolepsy

A Medical Description

Although uncertainty exists regarding etiology, epidemiology, and

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pathophysiology of narcolepsy, and certain diagnostic issues persist, it is possible to speak of a medical, descriptive consensus for narcolepsy. This is evident in the descriptive definitions of the Diagnostic Classification of Sleep and Arousal Disorders (DCSAD) in 1979 and the First International Symposium on Narcolepsy (1975). The following are the principle areas of description:

1. An illness of no known etiology.
2. A syndrome, that is an illness with a group of commonly associated features, not all of which present simultaneously, some of which may never be present, and none of which, with the exception of excessive daytime sleepiness, is essential. One feature only, cataplexy, is considered virtually pathognomonic, but may not develop for years after onset.
3. An illness of abnormal sleep tendencies, especially:
 - a. REM sleep phenomena, which involve dissociated or dislocated REM elements, such as sleep onset REM periods, a temporal advancement of the initial REM as it relates to sleep architecture; hypnagogic hallucinations, a manifestation of dream-like activity outside of sleep; and the dissociation from REM sleep of tonic muscle inhibitory mechanisms that are manifest in cataplexy and sleep paralysis.
 - b. Abnormal or disturbed nocturnal sleep and architecture, with frequent arousals, stage changes, and abnormal percentages of types of NREM sleep.
 - c. Excessive daytime sleepiness (EDS), usually of an irresistible, inappropriate nature.

The illness is defined in the DCSAD as "a syndrome consisting of EDS and abnormal manifestations of REM sleep. The latter include frequent sleep onset REM periods (SOREMPs), which may be subjectively appreciated as hypnagogic hallucinations, and the

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dissociated REM sleep inhibitory processes, cataplexy and sleep paralysis. The appearance of REM sleep within 10 minutes of sleep onset is considered evidence for narcolepsy."

Epidemiology

The incidence of narcolepsy in the population has been estimated at between 40 (Soloman 1945) to 160 (Honda and Hishakawa 1968) per one hundred thousand. However, an accurate estimate of the numbers of those afflicted with narcolepsy is problematical, and in fact estimates are increasing due to increased public and medical awareness (Scrima 1981).

This is so for a variety of reasons. Many patients present with "idiopathic hypersomnia", or narcolepsy by history, but without either sleep onset REM periods (SOREMPS) on polysomnogram (PSG) or cataplexy as a primary symptom, and therefore classifying these patients is an arduous task. Narcolepsy as a disease remains poorly known and understood by physicians and even some neurologists. Its diagnosis by objective criteria, namely PSG, was a recent development and remains a procedure whose skillful utilization and interpretation is limited to a small number of sleep disorder centers. This illness may, as well, easily present as a psychiatric condition, and within a social context other explanations for the major symptom, excessive daytime sleepiness (EDS), are readily available. Patients often do not

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present at all if cataplexy is absent and EDS is not severe, for denial of daytime sleepiness in the absence of diagnosis and other symptoms is frequent with incipient narcolepsy.

Psychological and Behavioral Aspects

Narcolepsy can be considered to be a highly significant illness for several compelling reasons. It is chronic in nature, notwithstanding exacerbations and remissions that may occur. Its primary symptom, EDS, is frequently disabling, and comprises, in addition to reported sleep attacks or irresistible urges to nap, a rather continuous state of sleepiness and lowered cognitive functioning. A wide variety of activities of daily living become arduous and even impossible for these patients. The illness is not reversible or curable, and its control by pharmacological means is problematical, resulting in management of varying success, unpleasant side effects, and tolerance related decreases in efficacy.

The psychological and behavioral sequelae of narcolepsy are dramatic, and are consequences of several issues: the disabling nature of the symptoms themselves, especially EDS; deleterious developmental and ego psychological consequences secondary to the unpropitious conventional timing of the onset of illness during adolescence; and the lack of diagnostic and medical clarity during this period as to the reasons for the symptomatology.

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The occurrence of substantial EDS during the formative years has a tremendous impact on the narcoleptic's life. Concentration, attention, and interest are all impaired, and learning is hampered. In addition to the general dysphoria that accompanies constant sleepiness, the frustration surrounding difficulties in performance may lead to anger, self blame, and despair. EDS and associated affects routinely inhibit interpersonal development and stress family relations, and as a result the sense of self of these individuals invariably suffers injury, often in a irremediable manner.

These consequences can be ameliorated by prompt, accurate diagnosis, but frequently the condition persists into adulthood until the correct diagnosis is made. Thus the behavioral manifestations of the illness become socially interpreted as negative character attributes involving laziness, avoidance, passive-aggressive behavior, or insipidity. Correct diagnosis notwithstanding, substantial EDS greatly restricts a narcoleptic's ability to work, love, and enjoy recreation. Repetitive tasks and complex or creative work involving concentration are difficult to sustain. Activities such as driving, watching movies or TV, and reading are especially soporific and routinely eschewed. Personal relations are constricted, in addition to their limitation due to sleepiness,

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by the occurrence in the symptom picture of cataplexy, the triggering of which is associated with emotional arousal. The development of affective coarctation and emotional avoidance as coping skills for managing cataplexy is thus common.

Diagnosis

As previously indicated, the areas of epidemiology and diagnosis are interrelated. The issues surrounding accurate diagnosis in narcolepsy serve as a major focus of this study, and the consequences of diagnosis regarding this disorder should not be underestimated. Proper treatment and illness management, psychological attitudes of patients, family, and employees, and issues regarding disability arise in this regard. Although a consensus generally exists regarding the conventions for making the diagnosis of narcolepsy, significant problems and areas of doubt remain.

Two methods, often utilized complementarily, are relied upon to make this diagnosis: diagnosis by history and diagnosis by objective finding, namely a polysomnogram (PSG). The reliance on the diagnosis by history is undermined by several factors. No pathognomonic symptoms exist, although clear cut cataplexy when observed or convincingly described is a reliable indicator of narcolepsy when present in conjunction with the primary symptom, EDS. In fact, Guilleminault has stated that in this case PSG is

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unnecessary (1976), so consistent is the relationship between cataplexy and SOREMP. Unfortunately, only approximately one third of narcoleptic patients will present with cataplexy during the initial phase of the illness which comprises the first several years. Additionally, there is that group of patients who appear to be narcoleptic in many respects who never develop any auxillary symptoms. Thus when auxillary symptoms are not present by history, the diagnosis rests upon the nature of the EDS, a symptom with a variety of possible etiologies. Additionally, sleepiness, as a normal subjective phenomena, is often inaccurately observed and reported. Self reports of EDS do not necessarily reflect objective findings.

Two objective instruments are utilized for making the diagnosis of narcolepsy: A series of naps, the Multiple Sleep Latency Test (MSLT), and all-night PSG recordings. The aim of objective procedures is to ascertain the presence of a SOREMP and the presence of EDS as indicated by abnormally short sleep latencies on nap opportunities during the day.

Both of these procedures are problematical when no history of cataplexy exists. A positive finding may not confirm the diagnosis, since a variety of other possible and not uncommon etiologies for both SOREMP and EDS are known. These include sleep deprivation, drug and alcohol withdrawal, hypersomnia sleep apnea (HSA), and irregular or disturbed sleep schedule, among

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others. A more troublesome problem is that a negative finding for SOREMPs as a criteria for diagnosis may be too rigorous. This is especially so since the majority of cases begin with EDS without cataplexy, the latter clearly being very highly correlated with SOREMPs. Thus a substantial number of narcoleptics do not have SOREMPs on initial PSG recordings, and an unknown number continue to present with idiopathic narcolepsy or hypersomnias without ever developing cataplexy or having a SOREMP on PSG.

Finally, misdiagnosis may occur due to the nature of the primary complaint, sleepiness. Within a social context, especially in conjunction with psychological sequelae and maladaptive coping mechanisms, this complaint is often prone to be misinterpreted by physicians as well as others.

Pathophysiology

A detailed review of the issues involved in the pathophysiology of narcolepsy and EDS will follow at the end of this chapter. No known pathophysiology exists for narcolepsy, and so resistant to understanding has the illness's clinical presentations been that in recent years speculations and experimental research have been minimal. A recent text of sleep disorders mentions narcolepsy only three times. Nonetheless, the pathophysiology of this disorder may prove to be of special interest. If it is found to

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encompass, as believed, faulty mechanisms involved in the timing, flexibility, and control of REM sleep mechanisms, either via hypothecated REM inhibitory arousal or NREM systems, then its understanding may be highly relevant to the study of REM sleep functions and their impairments, and the relationship of REM sleep to neurophysiological well-being.

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NORMAL HUMAN SLEEP AND WAKEFULNESS

Sleep and wakefulness can be conceptualized as dichotomous, cyclical "states" that occur in regular circadian (24 hour) alteration in adults. Interest in their properties and interrelationships is long standing, and more recent attention in the electrophysiological aspects of these states has led to considerable investigation. Whereas conceptually it has been convenient to regard these states as separate with separate neural regulatory mechanisms, their actual dichotomization is, in some respects, artificial. This is apparent in borderline states between sleep and wakefulness, during which it is often difficult, even with EEG monitoring, to determine if someone is "awake" or "asleep". Additionally, individual phenomena that comprise these states may be dissociated into the other state, in most instances either after changes in sleep schedules, experimental manipulations, or in pathological conditions and parasomnias such as sleep walking and sleep talking. The subjective distinction between sleep and wakefulness is also problematical, especially during transitional periods such as sleep onset and during daytime states of relaxation and day dreaming that lead to napping.

Questions about the dichotomization of sleep and waking have existed for some time. These questions were applied in a reconsideration of the conceptualization of sleep itself as a

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unitary state, due primarily to the advances in sleep EEG monitoring in the 1950's after the fortuitous discovery of rapid eye movement (REM) sleep. Early sleep recordings in the 1930's by Berger and others led to the notion of sleep as a homogeneous physiological state of varying quality. Research conducted during this initial period of investigation by Berger, Loomis, Blake, Davis, and Gerard, utilizing EEG techniques, investigated issues of sleep depth and variation. Depth of sleep was felt to be related to synchronicity and slowing of central EEG activity, in conjunction with increased electrical amplitude. Wakefulness was conceptualized as representing the operation of the ascending reticular activating system (ARAS) (Moruzzi and Magoon 1949).

The seminal discovery of REM sleep (Aserinsky and Kleitman 1953) and its association with dreaming (Aserinsky and Kleitman 1955; Dement 1955; Dement and Kleitman 1957) began and intensified interest in sleep as comprising dual states with distinct neuromechanisms, and as psychophysiological states of a qualitatively different nature. These discoveries led to the investigation of the temporal relationships of sleep states, or sleep architecture, and their relation to subjective states.

The new importance accorded sleep architecture stimulated the careful longterm monitoring of nocturnal sleep in humans for the entire sleep period (Dement and Kleitman 1957) and led to more

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refined sleep stage and state quantification, in particular as it applied to the temporal relationships between REM and NREM states (Dement and Wolpert 1958). Of particular importance was the finding that dream recall was associated with REM awakenings at a rate of about 80% (Dement and Kleitman 1957), implying a ostensible unity between REM sleep and dreaming, especially in light of negative findings at that time for dream reports from NREM awakenings as reported in the above three studies, as well as by Wolpert and Trosman (1958).

A variety of startling findings in animals enhanced the two state theory: Recordings of REM sleep in cats (Dement 1958); the discovery of tonic EMG suppression during REM in cats (Jouvet and Michel 1959) and in humans (Berger 1961); and the finding of unusual electrical potentials just prior to and during REM sleep in the cat emanating from the pontine, geniculate, and occipital areas (Jouvet et al 1959; Jouvet and Michel 1960; Brooks and Bizzi 1963). Sawtooth waves in humans were observed by Schwartz (1962) during REM sleep, and certain autonomic physiological parameters were found to undergo changes during REM sleep (Snyder 1969). Hoddes and Dement (1964) noted the absence of the H reflex during REM in humans.

Dement and Mitler (1974) credit Oswald (1962) with initially proposing the dual state model for sleep. This model implied the dichotomous grouping in REM and NREM sleep of qualitatively

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different, non-overlapping phenomena such as REM sleep dreaming, tonic EMG suppression, and rapid eye movements (REMs). However, this view may be said to be far more uncertain and complex today, in part due to greater understanding of the individual phenomena and to the conceptualization of states as conglomerations of individual processes with some common timing element, but not necessarily a common "function". The ability to experimentally separate or dissociate these processes through REM deprivation, pharmacological preparation (Passouant 1974), changes in sleep scheduling (Carskadon and Dement 1975; Weitzman et al 1970; 1974) and environment (Weitzman et al 1979), and their natural occurrence in normals (Salzarulo and Mori 1969) and disorders of sleep and arousal, such as narcolepsy, has necessitated a less simplistic model of sleep processes. Findings indicating the presence of substantial "dreaming" during NREM sleep (Foulkes 1962; Goodenough et al 1959) further undermined the two state theory, especially the association of REM with dreaming. Furthermore, the prevalence of REM sleep in animals gave pause to beliefs about the functional relationship between REM sleep and 'dreaming' as it is experienced by humans. Animals, too, 'needed' REM sleep, for they had rebound in a similar manner to humans, but did not, one would think need dreams.

On the other hand, evidence indicating differing circadian rhythms for REM and NREM sleep based on REM sleep propensity

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during daytime (Webb et al 1966; Endo 1977), persistence of this propensity despite acute changes in sleep schedules or phase shifts (Weitzman et al 1970; Carskadon 1976), and differences in rhythms or period length of NREM and REM-related rhythms in subjects under free-running conditions (Czeisler 1978; Weitzman et al 1979; Weaver 1979) has led to increased support for the dual state theory, as conceptualized as agglomerations of processes largely controlled by independent but mutually influencing endogenous oscillators. Kleitman (1982) has reviewed the evidence, in support of dual state theory, of multiple processes occurring rhythmically and simultaneously, and whose timing is controlled by one oscillator with an approximate ultradian period of 90 minutes. Thus REM sleep and a host of other intermittent physiological events have been found to occur according to a similar 90 minute ultradian rhythm not identifiable with NREM sleep, and having common properties of arousal and possible increased motivational levels.

The use of PSG for quantification of sleep stages was given impetus by early REM deprivation studies that suggested a "need" for REM sleep which was "recovered" in the so-called "rebound" phenomena (Dement 1960; Fisher and Dement 1963; Dement 1965). Epochal scoring of sleep stages and characteristics was developed by Rechtschaffen and Kales in 1968 to further sleep stage quantification methods, especially that of REM sleep. The

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conceptualization of sleep as involving two separate mechanisms aroused interest regarding the separate functions of REM and NREM sleep, their neurophysiological substrates (Dement and Mitler 1974), and the ontogenic (Anders et al 1971; Roffwarg et al 1964) and phylogentic aspects (Snyder 1966).

Several theories of discrete functions for the REM and NREM states were proposed, yet it soon became evident that these states were not unitary in themselves but collections of processes that worked in tandem but that could be separated experimentally (Dement and Mitler 1974). In REM sleep, long lasting, or tonic conditions were identified, such as EMG suppression, reflex suppression, and hyperpolarization of alpha motor neurons (Pompiano 1970), all suggestive of active motoric paralysis in REM sleep. These phenomena could be experimentally dissociated by electrical stimulation (Magoun and Rhines 1946) or pharmacological preparation (George et al 1964) in cats, and appeared related to cataplexy in narcoleptics. General CNS arousal was also identified as a tonic condition of REM sleep.

Phasic, or short lasting REM phenomena were found to include rapid eye movements (Aserinsky and Kleitman 1953), muscle twitches (Balderidge et al 1965), cardiovascular irregularities (Baust and Bohnert 1969), and PGO spikes in the cat (Jouvet and Michel 1959), among others. The electrical activity of PGOs has

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been viewed as emanating from an internal generator that influences a variety of phasic REM phenomena, and is itself inhibited by monoaminergic projections (McCarley 1982). The human correlates of PGO activity have been posited as phasic integrated muscle potentials or PIPS (Rechtschaffen et al 1972) and phasic EMG suppression prior to REM onset (Pivik and Dement 1970). The ability to temporarily dissociate individual processes from their prevailing sleep state is a test of the process' independence (Dement and Mitler 1974). Normal occurrence of dissociated REM phenomena can be seen in REMs, phasic EMG suppression (Dement and Pivik 1970), and PIPs (Rechtschaffen and Chernick 1972) during NREM sleep. REM deprivation has produced tonic NPT during NREM sleep and longer periods of NREM EMG suppression. Waking behavior in conjunction with SWS EEG in dogs was elicited with atropine preparation (Winkler 1952), and PCPA administration in cats has been found to produce waking PGO spikes (Ferguson et al 1969). Current opinion thus views REM and NREM sleep as groupings of processes which tend to occur together and may have interrelated neural mechanisms, some of which are fairly susceptible to disruption and dissociation. Clearly these agglomerations do not represent all or nothing states, either phenomenologically or functionally. Thus someone may be more or less awake, asleep, or in REM depending on the convergence of the normally anticipated sub-processes, and their timing and strength (Kripke 1976).

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Sleep Architecture and Rhythms

Since initial work by Wolpert and Dement (1958), increasing interest has been focused on architectonics. Human sleep has been found to have regular, stable, predictable temporal relationships involving the appearance of sleep stages and types in orderly patterns and quantities throughout the night. This architecture has been found to be fairly stable and universal, even in most dyssomnias. It appears as an alteration of NREM and REM periods, with an initial NREM period lasting about 90 minutes, followed by a short REM period of 10-20 minutes. REM and NREM then continue to alternate throughout the night with between 3-6 cycles, depending on the length of sleep (TST). The percentage of REM sleep becomes progressively larger throughout the night, both within each cycle (Dement and Kleitman 1957), and as a percentage of TST (Williams et al 1964; Agnew and Webb 1969; Verdone 1968). The majority of SWS occurs early in the night and SWS percentage decreases progressively as a percentage of TST. REM sleep percentages of TST in average age adults have been found to be approximately 20%. Orderly changes in NREM sleep stages have been described by Rechtschaffen and Kales (1968).

Several authors have investigated the occurrence and rhythmicity of REM and NREM outside of the nycthemeron. Webb et al (1966) found shorter REM latencies and increased REM percents in early

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morning naps when compared with nocturnal sleep, and Endo (1977) found an opposite trend in late afternoon and evening naps, implying a circadian or 24 hour periodicity to REM sleep propensity. This finding remained fairly constant even when humans were required to maintain a 90 minute sleep-wake schedule (Carskadon and Dement 1975). Thus REM sleep propensity (RSP) as described by Czeisler et al (1978) has been found to vary with time of day and appears to be "an endogenous self-sustaining rhythm" due to its resistance to change following radical phase shifting (Weitzman et al 1970). RSP has been found to vary in close temporal relationship with core body temperature (Moses et al 1975), with highest RSP occurring with initial rise in body temperature in the early morning. The partial independence of REM and NREM circadian rhythms has been cited based on evidence of changes in and dissociation of circadian period length of REM and NREM relationships in experiments with free running, non-entrained normals (Czeisler 1978; Weitzman et al 1979); and changes in the propensity for types of sleep throughout the day based on NREM and REM latencies on naps. The partial dependence of RSP and rhythm on sleep can be seen in the phase advanced entrainment of REM sleep and body temperature by a Zeitgeber of longer period length (Pollak 1981); and in the apparent disturbance of purported REM sleep ultradian rhythms by changes in sleep schedules and deprivation of NREM sleep (Johnson 1980;

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Carskadon 1976).

Current theory posits the existence of two or three separate oscillators that control timing and periodicity for wakefulness, REM and NREM sleep, as well as for body temperature and several endocrine functions. These oscillators are thought to be interdependent in some manner and able to influence each other in unequal reciprocity. Changes in their natural relationship has been experimentally induced and thought to occur in normally occurring phase shifts and, perhaps, in certain pathological conditions such as manic-depressive illness (Wehr et al 1980).

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STUDIES IN THE DEPRIVATION OF REM SLEEP

In reviewing two decades of work in an area that was initially promising, the REM deprivation of humans and animals, it appears that difficult strategic and methodological issues remain unresolved. Intense interest in this area seems to have waned, and early promises remain largely unfulfilled. Dement (1974) has stated, perhaps unwarrantedly, that "we can no longer regard instrumental REM sleep deprivation as a critical manipulation because we know that processes whose simultaneous occurrence define the REM period can occur independently in a REM sleep deprived animal (p.309)."

Interest in REM deprivation began after the discovery of stable, cyclical REM periods in humans and animals. Dream reports in humans were found to be associated with REM awakenings at a rate of about 80% (Aserinsky and Kleitman 1953; Dement and Kleitman 1957; Wolpert and Dement 1958). Thus REM sleep appeared to be a separate state that was associated with dreaming, and the initial REM deprivation (RD) experiment in humans was referred to as "dream deprivation" by Dement (1960), indicating his belief at that time in a dreaming-REM isomorphism. The discovery of a variety of physiological phenomena associated with REM sleep, especially unique phasic and tonic events, such as increases in cortical neuronal excitement, added to interest in REM sleep

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function.

The rationale for RD experiments was developed from the biological model of extirpation as a tool for the investigation of function, as described by Dement in his essay on the biological role of REM sleep (1968). It was believed that "regular nightly dreaming served as a safety valve to discharge the accumulated tensions of the day, and that if that discharge were blocked, serious psychological symptoms would occur in wakefulness" (Vogel 1975). Yet it was changes in sleep architecture on the subsequent recovery nights, and not daytime behavioral sequelae, that proved most interesting. These findings regarding REM compensation or rebound in the early RD experiments reinforced the hypothesized belief in a "need" for REM based on its biological ubiquity and notions pertaining to drive discharge and psychological function.

Major early findings pertaining to REM sleep and its deprivation can be summarized: a) it was found to be progressively harder to deprive humans (Dement 1960; Kales et al 1964; Aserinsky et al 1967) and animals (Morden et al 1967) of REM sleep in that it required more frequent awakenings to do so; b) on recovery nights after RD, animals and humans displayed an unusually large percentage and amount of REM sleep which was referred to as a REM "rebound" phenomenon (Dement 1960, 1965; Cohen and Dement

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1966; Kales et al 1964), whereas subjects awakened from NREM sleep as controls did not (Dement 1960; Kales et al 1964); c) that this rebound could last for several nights; could be "saved" or stored by delaying or preventing rebound on initial recovery nights; and that lost REM sleep (partial RD) needed to be "compensated for by means of extra REM sleep" (Cohen and Dement 1966; Dement et al 1966); d) that the amount of REM rebound was proportionately related to the amount of deprivation, and that REM deprivation could be accumulated (Dement et al 1966); e) that REM latency is shortened on recovery nights following RD; f) that eye movement density, or REM density (Ferguson and Dement 1968; Dement et al 1970) and dissociated aspects of REM sleep increase with continuing deprivation in cats Dement, 1974, p. 311); that NREM phasic deprivation in cats results in greater rebound, whereas RD with NREM phasic facilitation decreases rebound (Ferguson et al 1968); g) that behavioral consequences resulting from RD (Dement 1960; Fisher and Dement 1963) were unreplicable and modest; h) that dream content appeared to have some connection with the presence of phasic REM phenomena (psychophysiological parallelism), either in terms of the degree of dreamer participation (Berger and Oswald 1962), bizarreness of content (Schwartz 1981), or the relationship between eye movements and content (Roffwarg et al 1962); and that REM rebound may be delayed in humans by the peremptory occurrence of NREM rebound on the initial recovery night when sleep deprivation

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has occurred (Berger and Oswald, 1962; Webb et al 1964), but not necessarily in animals (Kiyomo et al 1965).

Although RD has been viewed as a theoretically valid approach for investigating the functional significance of REM sleep, issues, however, as to its practical success, the problems of methodological confounds, and the actual findings, remain and can be reviewed with regards to the expectations, methods, and findings in animals and humans. Two reviews of RD literature, Ellman et al (1978) and Vogel (1975) have provided substantial guidance for this section. As Ellman et al suggest, the interest in REM sleep and its functions has generated considerable RD research as a logical method of examination, and "most if not all theoretical views about REM sleep attempt to explain REM deprivation effects" (Ellman et al 1978, p.421).

It should be noted that the study of the effects of RD need not be restricted to experimental selective RD manipulations, although this manner of study is most easily controlled. It is clear that disturbed, restricted and altered sleep schedules, whether naturally occurring or experimental, will result in RD, and that RD states may develop that have a chronic nature. Interest in the issue of chronic REM deprived states was initiated by Dement et al in 1966, where individual differences in rebound were noted, particularly in subjects who displayed

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diminished rebound; and in early studies by Webb of sleep restriction. An understanding of this phenomena is highly relevant to the possible mechanisms involved in sleepiness and narcolepsy.

REM DEPRIVATION RESEARCH IN ANIMALS

Methodological Issues

It has been suggested that the function of REM sleep in animals may be similar to that in humans, a more parsimonious conclusion than one that assumes a different function for human REM sleep, based on models pertaining to dreaming. This is so notwithstanding certain important phylogenetic differences. These include presumed differences in mentation, as well as the timing of REM and NREM sleep as a response to deprivation. Thus in cats sleep deprivation results in immediate partial REM rebound whereas in humans NREM sleep is recovered first, often producing REM levels on the first recovery night following sleep deprivation at or below baseline (Berger and Oswald, 1962). When total sleep time is chronically restricted in animals, REM percent increases (Ferguson and Dement 1967), while in humans REM percent does not increase (Sampson 1965; Webb and Agnew 1965; 1975; Mullaney et al, 1977). Nevertheless, the investigation of REM sleep in animals using RD was regarded as essential especially inasmuch as techniques were available for use with animals that were not applicable to humans. Additionally, the

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ability to circumvent issues pertaining to individual differences was advantageous.

Ellman et al and Vogel both review carefully a number of methodological problems that are crucial to the evaluation of animal RD investigations. These essential questions are do animal RD experiments achieve their basic purported aim, namely are the experimental animals in fact allowed significantly less REM sleep on deprivation nights; and are these studies able to control properly for other influencing factors by the proper use of control animals and conditions, and by utilizing correct methodology. Some of these issues can be enumerated:

1. Animals, unlike human adults, have polyphasic sleep cycles, and therefor require 24 hour PSG monitoring (Ellman et al 1978).
2. It is not possible to rely solely on external, that is hand initiated awakenings from REM due to an animals' tendency to require an inordinate number of awakenings as RD progresses (Morden et al 1967; Vogel 1975; Ellman et al 1978).
3. The absence of continuous PSG monitoring in many of these studies is a serious flaw. Studies have often, without PSG monitoring, utilized REM depriving environments, such as the platform or treadmill, based on assumptions that the loss of muscle tone during REM sleep will prevent its occurrence on a platform, or on a treadmill requiring constant activity. Yet

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without PSG monitoring it is not possible to ascertain the extent of actual RD, the frequency of REM dissociated events, or to control for TST.

Techniques for Animal REM Deprivation

The platform or flower pot method of deprivation is discussed in the RD reviews by Ellman et al and Vogel. A small water-surrounded platform is used to inhibit atonic REM, and a somewhat larger platform is used to allow for REM and SWS while controlling for other environmental influences such as dampness, stress, confinement, etc. Other significant factors associated with platform living in rats and mice are effects of total sleep time (TST) and weight loss. The large platform must allow an animal to obtain significantly more REM sleep than does a small platform, and the small platform must prove efficacious in depriving its inhabitant of REM sleep.

One problem with several studies is the absence of recording for consecutive 24 hour periods. Findings by Mendelson et al (1974) indicate that significant differences in REM percent between large and small platform animals occur only after at least 24 hours of recording, in part due to first night effects of the platform and implanted wires, which can account for attenuated REM sleep in large platform controls (Mouret et al 1969). This effect can be reduced or eliminated by adaptation (Ellman and

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Steiner 1969). Lighting conditions (Fishman and Roffwarg 1974) and animal weight in relation to platform size (Steiner and Ellman 1969) are also factors. Of these issues, continuous PSG monitoring, proper platform size, and either sufficient RD days or adaptation are essential.

The amount of TST for animals in different conditions is an important variable that needs to be carefully controlled and monitored, inasmuch as the procedure involves "selective" RD with NREH sleep intact. The effects of sleep deprivation will confound both the measures of behavior that are being investigated, as well as recovery night findings. Differential sleep deprivation will result in performance confounds, and possible decreases in REM rebound on initial recovery nights due to SWS rebound. Additionally, differential TST between baseline and recovery (R) nights will effect TREMT and REM% for these nights, perhaps creating artificially high rebound phenomena if R TST is greater than BL TST. Both Vogel and Ellman et al agree that TST and stress can be adequately controlled so as not to inherently confound differences between large and small platform animals. These authors conclude that, when properly utilized, the platform method produces dependent measures of RD that are unconfounded.

The use of treadmill for RD is a more questionable procedure due to the effects of partial sleep deprivation in both experimental

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and control animals. Ferguson and Dement (1967) reported that microsleeps occur while cats are on the treadmill, which may contain dissociated REM phenomena. Although both experimental and control animals are partially sleep deprived, results may be confounded by the interaction of RD with partial SD.

The issue of state dependent performance trials as a possible confound is raised by Vogel (1975). When findings are reported for performance, such as learning retention after RD, it is unclear whether changes are due to RD effects on the variable, that is retention, or on the skills required in the performance itself, such as bar pressing and escape. Thus a control group that is REM deprived but tested in a non-deprived state (after recovery) is required. Additionally, even when performance is not confounded by state, the change in a dependent variable may be due to a change in state rather than to RD effects per se. Thus the testing of a variable after RD should have, as an added control, its measurement as occurring in a non-RD state, that is, after recovery (Vogel 1975)>

Findings in Animal Studies

The most consistently reported finding in animals regarding the effects of RD is the occurrence of REM rebound subsequent to significant RD and in conjunction with sufficient recovery nights (Fishbein 1970; Mouret et al 1969; Steiner and Ellman 1972;

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Mendelson et al 1974). In RD studies with cats (Dement 1965; Cohen et al 1967) rebound was found to reach an asymptote of 70% of TST, apparently regardless of the duration of the RD.

Consistent findings for increases in neural excitability with RD have been reported, and include lowered thresholds for waking seizure activity in rats (Cohen and Dement 1965) and cats (Cohen et al 1967). Intercranial self stimulation (ICSS) thresholds are lowered and response rates are increased following RD in rats (Steiner and Ellman 1972). Cortical refractory periods subsequent to auditory stimulation was found to be decreased after RD (Dewson et al 1967).

Learning and retention studies are especially subject to the necessity of proper control, in particular the use of non-platform control groups and controlled performance testing in undrugged states. RD has been suggested to impair acquisition (Stern 1971), retention (Fishbein 1971), or both (Greenberg and Pearlman 1974), and is viewed as an intervention that interferes with processing and consolidating of information. When REM sleep is prevented, these cognitive functions may be disrupted, depending on the temporal relationships of the learning, RD, and subsequent test situations. Greenberg and Pearlman have emphasized the interference by RD with the acquisition of unusual or novel information, its interference with latent learning, and the greater influence of RD on learning when deprivation follows

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learning in close proximity. They have suggested that survival behaviors such as eating are REM independent and not affected by RD. Findings in these studies are problematical due to lack of continuous PSG recording. Both the retention and acquisition of passive avoidance tasks in mice have been studied by Fishbein, who suggested that RD prevented consolidation of new memory traces until recovery REM sleep was allowed. Ellman et al (1978) contend that RD is not a necessary condition for consolidation of a labile memory trace, although it may serve as a facilitator, and that, at the moment, studies in this area are inconclusive.

Studies investigating changes in motivational behaviors and drive state in animals have generally not used continuous PSG recordings, although large platform controls were used in most platform studies. In studies of drive behavior in cats (Dement 1965; 1969) findings indicated that RD led to possible hypersexual and hyperphagic behavior, especially when the cats were previously primed by abstinence. Whereas this effect usually required 18 days to elicit, when a PGO spike depriving technique was utilized, only two days was required. Similar behaviors have been produced using PCPA administration (Dement 1968).

Studies using rats with platform controls indicate that RD facilitates aggressive behavior (Ferguson and Dement 1968 ;

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Morden et al 1968). Dement has stated that "selective REM sleep deprivation has a drive-enhancing effect in terms of observations of intensification of sexual behavior, aggressive behavior, and eating behavior" (1974, p. 310).

An interesting group of findings involve research with the hypothalamic area of the rat, which is attributed to be a motivational area. A relationship between intracranial self stimulation (ICSS) in this area and REM sleep has been found, as reported by Ellman and Steiner. RD was found to 1) lower ICSS thresholds in this area; 2) increases ICSS rates of responding; and ICSS was found to reduce REM rebound by as much as 50% (Steiner and Ellman 1972; Cohen et al 1972). However, this relationship appears temporally limited to times when the REM system is accessible on an ultradian and circadian basis (Spielman, in press). A perhaps related finding was that elicitation of hypothalamic rage reactions have also been found to reduce REM rebound (Putkonen and Putkonen 1971).

The reciprocity of REM sleep, seizures, and hypothalamic stimulation has thus been suggested. Amphetamine and RD both appear to prime the ICSS network, and responses to amphetamine in RD animals are greatly potentiated (Ferguson and Dement 1969). The facilitation of seizures in the cat reduces REM fractionals, and when seizures are elicited in REM deprived cats, rebound is reduced, a finding similar to that of ICSS.

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Ellman and Steiner have suggested that hypothalamic ICSS areas and pontine areas associated with REM phasic events have a reciprocal interaction. Dement and co-researchers have indicated that they believed the essential event involved in REM sleep is phasic discharge, particularly pontine spikes. Ferguson and Dement (1968) have suggested that phasic compensation for RD may occur, accounting for the lack of precise quantitative recovery of lost REM time. In fact, it appears that the amount of REM compensation in cats is directly related to phasic, in particular PGO, discharge (Ferguson et al 1968). When cats are awakened earlier so as to deprive them of NREM PGO's, rebound is markedly increased. RD produced by reserpine results in no rebound, inasmuch as PGOs are freely discharged during the reserpinized state (Dement 1968). When cats on prolonged PCPA administration are REM deprived, they show no rebound, presumably for the same reason (Dement 1968). Finally, awakening procedures that produced RD but facilitated NREM PGO discharge produced significantly smaller rebound (Dement 1968). Thus animal research has produced a model that implies that rebound as it was originally described-increased time spent in REM sleep- may not represent the sole or even primary expression of compensated REM phenomena.

REM Deprivation In Humans

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Introduction

If REM deprivation is conceptualized as a challenge to a given system, the responses to this challenge in humans can be described in several areas, based on their timing, and on their mode of expression. Thus one can speak of sleep and waking effects; same night RD versus recovery night effects; REM versus NREM effects; and one can describe physiological, psychological, and behavioral effects. Furthermore, the relationship between the selective occurrence of these different responses, such as waking versus recovery, may be examined. Finally, the study of RD effects in humans includes examination of individual and group differences as they pertain to responses to the RD challenge and the aforementioned variables.

Responses to RD Based on Timing

Although recovery night responses to RD are the basis for most research, and anticipated waking responses were an initial impetus, RD has been shown to have "same night effects", although these are less well studied. Mentation, eye movement density, cycle length, and probably the number of awakenings required have been found to change within the RD sleep period. Thus findings of individual differences pertaining to recovery nights should include analysis of same night responses to the RD challenge. Sleep architecture has been found to vary on RD nights, so that latency to succeeding REMPs becomes shorter, with shorter

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intervening NREMPs (Pivik and Foulkes, 1966; Fiss and Ellman, 1973). The number of RD awakenings required per REMP increases throughout the night, with most occurring during the last REMP. It is not clear if this is an RD effect per se, or merely a circadian effect, that is, a concomitant of increased REM percent and insistance from early to late night. In order to ascertain this, one would have to compare the number of RD awakenings at the end of the night on an RD night, with a night when RD awakenings were confined to the end of the night.

A similar same night effect has been found on mentation. Reports procured from REM have been reported to be more intense when measured on the Foulkes DF scale on RD nights versus BL nights for certain subjects (Pivik and Foulkes 1966). They report as well an increase in REM density for the fifth REMP on RD nights for certain subjects, when compared with the BL fifth REMP. No findings are reported of effects of RD on same night NREM mentation, an issue that pertains to theories of containment of REM phenomena when its expression is prevented. Dement has described the problems in eliciting mentation reports from REM deprived subjects on recovery, but does not mention this issue regarding same night effects (Dement, 1974, p.311). Dement has, however, reported same night phasic displacement into NREM in animals (1969). Responses to the RD challenge occurring on recovery nights, and in waking states, are discussed in the

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following sections.

Methodological Issues

Vogel (1975) has suggested that the original human RD study (Dement 1960) had an ideal design. In this study, NREM control awakenings were used, having the advantage of allowing subjects to serve as their own controls under crossover conditions (this study was not counterbalanced). Thus effects due to the awakening procedure were controlled for. Adequate baseline nights are necessary due to demonstrated first night effects (Rechtschaffen and Verdane, 1965; Agnew et al 1966; Dement et al 1965) in which REM% and TREMT are reduced and which can thus cause both spuriously high rebound effects and result in RD of control groups. Kales (1969) and Ellman (1969) suggest 3 baseline nights are necessary to stabilize REM sleep. Adequate recovery nights for measuring rebound effects are necessary due to the preferential rebound of SWS on the initial R night (Agnew et al 1967; Berger and Oswald, 1962; Williams et al 1964) and the finding that REM rebound can last up to four nights (Ellman et al 1978). TST for baseline and R nights should be similar, since REM % and TRT tend to increase disproportionately with increased TST, especially in the 2nd half of the night (Verdone 1968). Ellman et al suggest that TST for REM versus NREM awakenings should be constant as well, since the aim is to deprive REM while leaving NREM undisturbed.

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Rechtschaffen and Kales (1968) have described the criteria for the presence of REM sleep which is customarily utilized in RD experiment, that is, the simultaneous occurrence of EMG, EOG, and EEG criteria. REM density measures should be obtained for the study of REM rebound, since RD may increase REM density as a function of deprivation on both RD and RD recovery nights in animals, perhaps instead of increases REM % and REM time (Ferguson and Dement 1968). This finding has not been demonstrated in humans (Antolliolo et al 1981).

The findings that considerable dreaming occurs in NREM sleep (Foulkes 1962), at sleep onset (Foulkes and Vogel 1965), and that something akin to dreaming occurs during relaxed wakefulness (Foulkes and Fleisher 1975) have cast serious doubt on the notion that RD involves dream 'elimination' (Vogel 1975), although some dream deprivation is involved. Whereas it has been possible to differentiate accurately between dream reports from REM and NREM sleep (Monroe et al 1965), the significance of distinguishing between REM and other types of mentation is not clear. What is evident is that qualitative differences in REM vs NREM content as described by Foulkes, and differences in reported dream content and subjective psychic state in phasic vs tonic REM awakenings as reported by Schwartz, indicate that mentation and sleep state and physiology are related in some manner. The finding of REM sleep

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in virtually all mammals (Snyder 1969) and other forms of animal life (Klein et al 1964; Tauber et al 1966) has further eroded the theories equating REM sleep and dreaming.

Another Look at the Rebound Effect

The rebound phenomena has been the keystone of RD investigation. Although RD, especially in animals, has produced behavioral and CNS changes during waking, it was rebound and its associated qualities--proportionate accumulation and rebound, increased pressure for expression, delayed recovery, etc., that stimulated theories of a biological need for REM sleep (in conjunction with ontogenic and phylogenic discoveries and psychoanalytic theories of dreaming). Rebound phenomena have been considered to be the most consistent finding secondary to RD, and are the only primary sequelae to RD in humans.

Yet the very issue of rebound in humans remains unclarified, in regards to psychopathological states, individual differences, narcolepsy, and sleepiness to name several areas. How is one to define a RD state? When adequate recovery is allowed, elevated REM fractionals and/or TREMT will occur when compared with BL. But will it? Even in well controlled lab studies with 10 BL nights, such as Dement et al 1966, individual differences in rebound were striking. The authors suggest that an RD state may persist and no rebound will occur, perhaps resulting in chronic RD states. "Delayed recovery experiments bear on this in that

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the loss of REM sleep on isolated nights of complete or partial insomnia would still be cumulative unless the amounts of REM sleep on other nights were actually above the baseline mean. It is also apparent from this that a RD state could exist and persist in patients, even though essentially normal REM times were being recorded, since a deprivation effect does not appear to be reversed during the occurrence of of an essentially normal REM fraction. If this is so, the question of whether a RD effect is present in patients may depend on a way of measuring RD in humans that does not depend on elevated REM time as a criterion. Thus certain factors may be present in psychotics that would prevent an increase in REM sleep even in the presence of a markedly deprived state" (Dement et al 1966, p.150).

These remarks contain two important points: that certain people may be prevented from recovering lost REM sleep; and that therefore rebound may not be the best measure of the RD state in humans. These points are interdependent in some ways. The former pertains to the literature on individual differences in response to the RD challenge, in terms of rebound phenomena, number of experimental awakenings, changes in sleep architecture on RD and R nights, dissociated REM phenomena, and the relationship of this issue to psychopathological states. Rebound is only one measure of the effects of the RD challenge, and reliance on it as the sole measure may be misleading.

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Studies purporting to show significant individual differences in rebound phenomena in normals (Cartwright et al 1967; Cartwright and Ratzel 1972) are considered inconclusive due to problems in methodology (Ellman et al 1978). However, the Cartwright studies have raised an issue in this regard relevant to the notion of REM leakage or dissociation- that normal individuals with attenuated rebound are "substitutors" rather than "compensators". That is, they make up for lost REM in a fashion other than by subsequent rebound. This attenuated REM rebound was found to correlate in these studies with high onset fantasy (HOF) at sleep onset and similar imaginal mechanisms during waking and as elicited on projective tests. It is interesting that psychopathology within this group seems to correlate with the HOF dimension. Several studies have purported to show reduced or absent rebound in certain schizophrenics, endogenous depressives, and perhaps in narcoleptics, suggesting that the ability to contain and store REM related phenomena may be faulty in these groups, and is susceptible to disruption.

Regarding individual differences, of particular interest are findings pertaining to sleep onset REM periods and rebound, reported by Dement et al (1966), which are reviewed in Dement and Rechtschaffen (1968). Only 1 of 23 subjects in total sleep deprivation studies had a SOREMP, and this subject showed not

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characteristic rebound. All other subjects displayed REM rebound. In a study of 13 subjects with experimental sleep restriction, only 1 subject had a SOREMP, and this subject had 15 additional SOREMPTS over the next 24 days. During the selective RD of 38 subjects, only 2 produced SOREMPS; 1 on the 2nd of 8 RD days; the other on the 5th of 15. Both produced SOREMPS on all subsequent RD days and continued into recovery nights. In a study of chronic sleep deprivation, 1 of 6 subjects produced a SOREMP, and had 2 on subsequent nights. Of the 5 of 78 subjects who had SOREMPS, 3 were "non-rebounders". The authors conclude that once REM becomes ascendant, it continues to dominate sleep architecture in terms of its timing, at least temporarily. Furthermore, that accumulating the need for REM, or REM pressure, rarely leads to SOREMPS in most normals.

Psychological and Behavioral Changes Secondary to REM Deprivation

If one were to imagine the stimulation and interest generated by initial REM and RD findings during the first decade or so of REM sleep history, it is clear that a notion of paramount importance for investigators was the relationship of the function of REM sleep and its physiology to dreaming and its purported psychic functions. Freud had described dream function in terms of unconscious wish fulfillment and preservation of sleep, but what would happen if dreaming was selectively, experimentally

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prevented from occurring? If, in Dement's words (1960), "dream deprivation" was instituted? Merely from asking this question, it is evident that this research was susceptible to a preconceived bias, for it was implicitly assumed that dream deprivation would be psychologically deleterious, if not physically so.

We now know that REM deprivation does not eliminate dreaming. It is generally agreed that REM dreaming is different in some respects from NREM dreaming, onset fantasy, and waking fantasy. Therefore it is not clear whether these other mechanisms can compensate for the blocking of REM mentation, if in fact this is even necessary. (REM sleep is "necessary" only in that it is recovered automatically when lost; there is no direct evidence that the dreaming associated with it is necessary in this same respect, although studies in changes in mentation on recovery nights have shown indication of changes in intensity and timing. Still, this would not logically imply a REM dreaming necessity, but perhaps only its epiphenomenal reflection of "necessary" physiological processes).

However, in the 1960's, in conjunction with initial findings that RD produced psychic changes in humans during waking and perhaps even produced serious deleterious behavioral effects, interest in the connection between dream deprivation and psychopathology increased. The finding that many animal species which

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purportedly do not "dream" in the human or Freudian sense had REM sleep, and that behavioral perturbations occurred in animals as well in RD studies, suggested that REM function, blockade, and rebound had less to do with wishes and thinking than with some basic physiological processes.

Early studies by Dement (1960), Dement and Fisher (1963), and Sampson (1966) report psychological and behavioral changes in humans subsequent to RD, specifically that irritability, anxiety, and poor concentration resulted from prolonged RD (Dement and Fisher 1963), and that certain drive phenomena were enhanced (Sampson 1966). In one study, Dement and Fisher (1963) REM deprived two subjects for two weeks with the aid of amphetamine, and reported serious personality changes with striking psychotic symptomatology. These studies are now considered unsound for several reasons, and the results have not been replicated (Kales et al 1964).

Confounds in these studies due to poor methodology include lack of NREM control awakenings in some studies, absence of even single blind conditions, and unreliable, varied, and poorly reported dependent psychometric measures. In one study the use of amphetamine was confounding, especially inasmuch as it has known deleterious psychological sequelae. Furthermore, the amount of RD versus baseline levels of REM time, REM %, and rebound effects

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were often omitted, and the sample size has been small. These points are made by Vogel (1975), Ellman et al (1978), and by Dement himself (1974), who states he reached the conclusion in 1965 that RD in animals and humans was not harmful. In 1969 Dement stated that these findings were the result of poor methodology and experimenter bias.

Ellman et al review a number of additional RD studies in humans that report positive findings, ones that measured changes in fantasy, perception, and intro- and extroverted measures on projective tests (Clemes and Dement 1967; Cartwright and Ratzel 1972); and those that measured changes in dream mentation (Pivik and Foulkes 1966; Foulkes 1968). From these studies, it is generally agreed that RD is not deleterious, although it may produce some temporary changes in ego and drive relationships as measured by psychological tests. Based on current research, these changes can not be generalized with the same type of certainty as those described for animal RD effects on drive behavior (Dement 1965; Ferguson and Dement 1969).

REM Deprivation and Psychopathology

A related, special interest that developed during the 1960's concerned the relationship between REM sleep and psychopathology. As Fisher, one of the originators of these ideas, stated (1978): "In the first flush of enthusiasm following these experiments, we

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became convinced that REM sleep and its associated dreaming were necessary psychobiological processes, that variations, deficits, or excesses ... could be correlated with mental disorders...and that prolonged suppression would produce psychosis in man. These findings seemed to confirm certain psychoanalytic propositions about the relation of dreaming to psychosis." These concepts were related to the notion that prolonged RD in animals would lead to something analgous to the eruption of dreaming (endogenous hallucinatory stimulation) during waking, a finding sought by Dement and co-workers but not confirmed. In fact, only pharmacological preparation has been able to produce such behavior consistent with this model.

The relationship of REM sleep, its deprivation, and endogenous depression and schizophrenia has been studied by a number of authors. Several factors promoted interest in these illnesses with respect to REM sleep. Depressives demonstrate an attenuation of drive-related or motivated behaviors of a type possibly enhanced by RD in cats (Dement 1965; 1969), such as eating, sexuality, and aggression. Ellman et al refer to these as stimulus bound behaviors (SBB), which appear similar in their rewarding properties to ICSS. Response rates or pressure for both SBB and ICSS may be potentialted by RD in animals, and the elicitation of ICSS or SBBs may compensate for accumulated REM need or pressure in some direct manner.

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Furthermore, findings that certain depressives have shortened REM latencies (Kupfer et al 1972), that antidepressant medications are strong REM suppressants and that those patients who respond favorably to antidepressant medication are the ones whose REM architecture is most notably influenced by antidepressants have suggested an interrelationship between REM sleep and depression.

Regarding schizophrenia, the dream-like, primary process quality of the schizophrenic's cognitions and perceptions, and the regressive quality of ego functioning, implied a penetration by the D-state into waking life. Psychoanalytic theories pointed to the "narcissistic" and wish fulfillment nature of dreaming and its relation to psychosis, inasmuch as both dreaming and psychosis were thought to imply a withdrawal of cathexis from the world. The need for REM sleep based on rebound findings, and "findings" of deleterious sequelae secondary to "dream" deprivation, created impetus to study the effects of REM deprivation in schizophrenics.

REM Deprivation in Schizophrenia

Interest in this area was motivated by beliefs that dreaming and schizophrenic phenomena were related, and that RD would exacerbate symptomatology. The initial finding of absent or diminished REM rebound in acute schizophrenics following RD further enhanced this interest, and was explained as possibly

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"due to the discharge of REM sleep equivalents in the waking state" -other words, the inadequate REM containment hypothesis (Zarcone et al 1975; Azumi et al 1967; Gillin et al 1974). This notion contained several ideas- that attenuated or absent rebound existed because REM equivalents were routinely discharged in other states (waking); or that, perhaps, this was due to the build-up of REM pressure secondary to disturbed nocturnal sleep (DNS) in schizophrenics, and thus schizophrenics were unable to compensate for lost REM with subsequent rebound due to a basic inability to achieve elevated REM fractionals. REM was thus forced into a dissociated position. Of course, since this has not been experimentally produced in "normals" by RD, some constitutional factor might be implied. In any event, it was conjectured that schizophrenia comprised a chronically REM deprived state (Vogel 1974).

Important issues to be evaluated that concern RD studies in schizophrenics are: Possible differences in the amount of REM sleep of schizophrenics versus normals and their ability to store blocked REM and produce rebound effects; the notion, especially relevant to narcolepsy, of the intrusion of REM events into wakefulness; and the inherent relationship, if any, between the illness and these phenomena (Vogel has posited such a relationship in depression). It is important to bear in mind the need for PSG monitoring for all nights, including RD nights, to

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substantiate RD efficacy, and the need to control for TST and DNS (Monroe 1967; Verdone 1968) as it impacts on REM % and total REM time. Clearly, a finding of no rebound that was caused by poor sleep maintenance, especially REM maintenance such as found in obstructive sleep apnea, is quite different from notions pertaining to leaky REM systems.

Vogel and Rechtschaffen (1964) found in normals that daytime administration of amphetamine does not produce REM rebound and concluded that therefore no dissociated waking aspects of REM were expressed in normals that could be stored in a manner similar to nocturnal REM sleep. Only in narcolepsy is there clear evidence that aspects of REM sleep pertaining to atonia and dreaming are sleep-dissociated. Several studies have reported that no exacerbation of symptoms occurs following RD in schizophrenics (Vogel and Traub, 1968; Gillin et al 1974; Azumi et al 1967; de Barros-Ferreira et al 1973), and there is no evidence that "REM sleep intrudes into wakefulness... in a manifest fashion in schizophrenics" (Vogel 1974).

The notion of RD or REM pathology as either an integral part or and etiological factor in schizophrenia and the concept of REM deprivation occurring as secondary to the illness must be distinguished. Although several clinical groups have shown abnormal tendencies regarding REM phenomena, there is no evidence

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that REM pathology is a trait that is in any way casual to schizophrenia. Studies have not found significant differences in REM % or total REM time in schizophrenia versus normals (Vogel and Traub 1968; Azumi et al 1967; Feinberg et al 1965; Zarcone et al 1975), or between different schizophrenic sub-types, and thus no evidence exists that they represent a REM deprived group. In fact, Azumi et al (1967) and Zarcone et al (1975) show unexplained, non-significant increases in REM % on BL for schizophrenics. Findings that REM sleep is proportionately decreased in waxing schizophrenics is confounded by shorter TST in these patients (cf. Vogel's calculations based on Verdone's findings, Vogel 1974).

This point is of interest, for in Dement et al 1966 the notion was posited that since no acute psychopathological effects were evident from 15 days of RD in normals (described by Dement in 1965 in Jouvet), perhaps a model of partial chronic RD was applicable in schizophrenia. These authors suggest that disturbed nocturnal sleep or sleep restriction may lead to RD that is not recovered due to preferential NREM rebound, even when REM fractionals return to "normal". Whereas it seems possible that such a mechanism may account for chronic EDS and perhaps even narcolepsy, no evidence exists to link it with schizophrenia.

Findings of absent or diminished rebound are reported by Gillin et al (1974), Zarcone et al (1975), and Azumi et al (1967). The

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first two studies are reasonably sound methodologically, although Zarcone does not report either total REM time, REM %, or number of awakenings for the RD nights. The Azumi study appears clearly unsound, especially inasmuch as neither normals or controls showed proportional increases in number of RD awakenings throughout the five nights as reported by Dement (1960), thus implying improper or incomplete RD. Differences in rebound in the Zarcone study for the first two recovery nights may be due to significant TST differences between groups, although no differences were found in TST over 5 recovery nights, during which the schizophrenic group had significantly less REM%. Furthermore, data was analyzed for REM density as a source of compensation, and no evidence for increased compensation through changes in REM density were reported to account for differences in rebound. Both Vogel and Ellman agree that a possible explanation for the data is that schizophrenics are "poor sleepers" (Monroe 1967), that frequent interruptions from REM sleep inhibit adequate rebound, especially in a population that may be more subject to sleep disruption secondary to the methodology. Yet it should be added that diminished rebound may be a function of poor sleep irrespective of TST, and that schizophrenics may be chronically REM deprived due to an inability to increase REM % above baseline secondary to DNS.

In summary, the Gillin and Zarcone studies can not be dismissed,

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and the issue of rebound in schizophrenia remains unclear. However, much of the impetus within the sleep community for pursuing the connection between schizophrenia and REM sleep was the result of pharmacological research in animals, especially the PCPA studies in cats. These indicated that REM phasic PGOs could be dissociated to waking states in conjunction with what appeared like hallucinatory behavior through a mechanism thought to involve serotonin depletion. When PGOs occurred in waking cats who were previously REM deprived, rebound did not occur. Chlorpromazine reversed the PCPA-induced behavioral changes in cats. However, as Vogel (1974) and Hobson (1970) suggest, the applicability of these findings to schizophrenics is far from certain. What is of some interest for this study is the reported misdiagnosis of narcoleptics, who more certainly have some form of "REM" pathology, as schizophrenic.

REM Deprivation in Depression

The use of RD in patients with endogenous depression has been considered to be a useful investigative tool and therapeutic modality, although its therapeutics have been found to be brief and inefficient. RD and sleep deprivation (SD) have been found efficacious in temporarily ameliorating certain endogenous depressions (Pflug 1976; Van Den Berg et al 1975; Rudolf and Tolle 1978; Vogel and Traub 1968; Vogel et al 1975; 1977; 1980).

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Several observations, theories, and findings have been consistently suggested as bearing on the above phenomena and have been used to both explain it and develop the rationale for the RD procedure with this group. REM deprivation increases cortical excitability and has been suggested to be directly related in animals to the potentiation of motivated or stimulus bound behaviors (SBB), such as eating, sexuality, aggression, and sleeping (Ellman et al 1978; Dement 1965; 1969; Morden et al 1968; Ferguson and Dement 1969). These behaviors are often disturbed in depression. Additionally, these behaviors can be characterized as pleasurable, rewarding, and reinforcing-animals will perform work to attain them in a manner comparable to the work they will perform to attain ICSS, a hypothecated direct neural reinforcer in certain brain cites (Olds 1956). RD has been found in animals to lower ICSS thresholds and increase ICSS response rates (Steiner and Ellman 1972).

An extrapolation of this to humans, attempted by Ellman et al (1978), might go something like this: RD either primes the reward system in ICSS areas or makes access to it easier (REM pressure or disinhibition models). A high threshold would imply that normally reinforcing activities such as sex would no longer be reinforcing, that is, they would not be motivators for work that aimed at their attainment. Thus relatively high ICSS thresholds in depressives might interfere with their ability to

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gain gratification from previously pleasurable activities. RD would then lower these thresholds or increase access. Naturally, these assumptions should be reconciled with the findings regarding pharmacotherapeutics in depression and their effects of REM sleep.

Powerful REM suppressant drugs are reported to improve depression (Rechtschaffen and Maron 1964; Mendelson et al 1977), and specific antidepressant medications such as tricyclics and MAOIs are especially strong REM suppressants (Hishakawa 1965). The least efficacious antidepressants are said by Vogel to be weaker REM suppressants (Vogel 1975). Patients who respond favorably to antidepressants demonstrate faster REM sleep suppression (Kupfer et al 1975) and following day increases in REM latency as well as greater REM rebound following drug withdrawal (Gillin et al 1978). Patients who fail to improve following RD also fail to improve on imipramine (Vogel et al 1975). Vogel et al (1980) contend that the only known common specific action of antidepressants is REM suppression. Another antidepressant intervention, ECT, is reported to be a strong REM suppressant in animals (Cohen et al 1966). Thus, to continue the speculative model, antidepressants might work by lowering reward thresholds, perhaps indirectly through RD. It would, therefore, be expected that these drugs would lower ICSS thresholds in animals. Although amphetamine has been found to both lower ICSS thresholds

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and increase certain SBBs, the effects of tricyclics in this area are unclear.

Depression has been conceptualized as a perturbation of biological rhythms, specifically as a phase advance of the strong REM oscillator with respect to the weaker oscillator that controls circadian sleep-wake and NREM rhythms (Kripke 1976; Vogel et al 1980; Weitzman et al 1974; Lowey 1982; Kripke 1982). This has been suggested as accounting for the early timing of REM sleep, the inability to suppress cortisol and its possible phase advance, and a possible phase advance of melatonin. However, since early awakenings occur when sleep onset time is normal, a simple phase advance of the sleep cycle is not implied. Furthermore, the phase advance of REM sleep with respect to sleep onset (shortened REM latencies) has been found to be a consequence of RD, thus depressives with short latencies appear to be, in this respect, in a REM deprived state. If so, then motivated behaviors should be enhanced, not inhibited as is the case.

The action of RD in depression is not known. Vogel (1980) has viewed RD as a mechanism for "realigning" abnormal relationships between biological rhythms, although he is not specific as to how this is accomplished. The SD studies, while depriving REM sleep, are confounded by NREM deprivation. Vogel has conducted several

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studies using RD in depression, and has consistently reported transient improvements in certain depressives. He has contended that "REM sleep deprivation is the only effect of antidepressant drugs that, in a double blind crossover study, has been found to improve endogenous depression" (1980).

Vogel has in his studies examined endogenous depressives (1968), depressives versus reactive depressives (1975), and depressives versus normal controls matched for age and insomnia (1980). Interestingly, Vogel has reported some findings similar to those in narcolepsy: That these depressives do not tend to have progressively longer REMPs as the night goes on--that is, late night REM% is relatively reduced; that REM latency is often shortened (Kupfer et al 1972); and that REM sleep is more fragmented.

The 1980 study reported individual differences for depressives based on their baseline sleep, and on sleep architectonic responses to RD as it related to improvement, a finding quite relevant to the present study. Although early and late REM% did not differ between normal and depressive groups, within the depressives, early and late night REM% were inversely correlated and significantly more variable than in normals. Improvement correlated with the ability to store or delay REM rebound on the recovery night until the second half of the night, thus increasing late night REM percent and rendering the architecture

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more normal in its appearance (Vogel et al 1977). Those depressives that did not improve showed an exaggerated early timing of REM sleep and REM percent on recovery. Thus the amount of early and late night REM in depressives are interdependent, and a shift along this continuum, as instituted by the RD challenge, towards late night REM, appears involved in the process of improvement.

Also, increased REM% on recovery nights (REM pressure) correlated with improvement, indirectly replicating the finding that those depressives who do not demonstrate normal REM% increases following drug withdrawal of antidepressants are the non-responders. Interestingly, total REM time (REM rebound) was not correlated with improvement. Vogel et al (1975) also report that those patients who respond to tricyclics are the ones who respond to RD. Taken in conjunction with the Kupfer finding that the ability of tricyclics to delay REM latency predicts response, one might conclude that those individuals with modifiable REM systems or rhythms are the ones who are helped by treatment.

Specifically, Vogel et al suggest that REM sleep inhibition stimulated by RD may account for improvement, and that individual differences exist with respect to this. At first glance, the notion that RD would lead to REM inhibition seems paradoxical, unless one were to regard the RD procedure as a type of

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conditioning of REM timing. Vogel et al suggest that were it not for this initial inhibition of REM sleep in the first REMP by prior RD, all rebound would occur in the first part of the night. Implicitly, since depressives and narcoleptics have greater early REM%, this precocious occurrence would be maladaptive. Thus it is preferable if stored REM can be successfully maintained until its circadian appropriate timing, viz late night sleep. To carry this further, a more pathological failure to store REM and inhibit premature REM rebound could result in daytime phenomena-EDS, cataplexy, and hallucination.

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THE DESCRIPTIVE CHARACTERISTICS OF NARCOLEPTIC SLEEP

Although the association of narcolepsy with a disorder of sleep can be traced to the incipience of the conceptualization and description of the syndrome in 1877 by Westphal, the polysomnographic monitoring of narcoleptic sleep did not aid significantly in developing an understanding of the illness until the 1960's, when, beginning with the seminal papers of Rechtschaffen et al and Takahashi and Jimbo in 1963, the basic electrical properties of narcoleptic sleep were uncovered.

Monitoring of narcoleptic sleep with EEG began with work by Blake et al (1939) and Dynes and Finley (1941). In this pre-REM era, the sleep of narcoleptics presented as essentially normal, with the exception of the finding of what appeared as prolonged stage I sleep at sleep onset. Similiar extended, episodic stage I sleep was observed in EEG recordings of narcoleptics made during daytime (Pond 1952; Daly and Yoss, 1957; Gastaut and Roth, 1957). However, it was Rechtschaffen et al in 1963 who conducted the first significant PSG study of narcoleptics. Their findings encompassed a wide variety characteristics most of which remain currently valid, and will be reviewed in this section.

Total Sleep Time

Total sleep time (TST) for nocturnal and 24 hour periods in narcoleptics is an important statistic, since narcolepsy has

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previously been considered to be a facilitation of sleep. Yet findings indicating increases in TST for either nighttime or 24 hour recordings are not reported, when, under experimental conditions, narcoleptics are compared with normal controls. Richardson et al (1978) reported decreased TST compared with normal controls, which was attributed as secondary to disturbed nocturnal sleep (DNS). Many narcoleptic patients report that they sleep in excess of 10 hours daily; however, in a controlled 24 hour study (Hishakawa et al 1976) where narcoleptics and normals slept in a darkened room until satiation, no differences in TST between groups were found (means for both groups were 12-13 hours). The authors concluded that narcolepsy does not involve a facilitation of sleep in general.

Kales and Kales (1974) also report no differences in 24 hour sleep time in narcolepsy. Dement (1976), however, has pointed out that the controlled conditions of the laboratory alter behavioral patterns substantially and perhaps differentially between groups, and that longer studies are required to resolve this issue. Two 48 hour studies with normal controls do not report TST or sleep efficiency for the study periods (Montplaisir 1976; Billiard 1976). It would appear that the unusual environment in the Hishakawa et al study which involved confinement to a darkened room makes interpretation of these data problematical.

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NREM Sleep

A basic finding has been that sleep tendency as measured by sleep latency is greater in narcoleptics than in normal controls (Montplaisir 1976; Rechtschaffen et al 1963) or other patients with sleep disorders (Van der Hoed et al 1981); with the exception of one group, hypersomnia sleep apnea (HSA) patients (Mitler et al 1982; Dement et al 1978). This finding has been confirmed irrespective of the type of sleep onset involved in the latency for narcoleptics-SOREMP or SONREMP (Richardson et al 1978); and irrespective of time of day, that is, nocturnal PSG or varying daytime naps (Richardson et al 1978).

Percentage of NREM sleep within TST has not been found to differ between narcoleptics and normal controls, although significant differences exist in the percentages of individual sleep stages. SWS, when stages III and IV are combined, has been found to be reduced in narcoleptics during nocturnal sleep by several authors (Rechtschaffen et al 1963; Gastaut et al 1966; Suzuki 1966; Passouant 1968; Montplaisir 1976; Hishakawa et al 1976). This difference is often a non-significant one, and tends to be more prominent for stage IV (Hishakawa et al 1976). Differences in age have accounted for more of the variation in SWS than differences between groups in some studies (Montplaisir 1976).

Increased percentage and amount of stage I in narcolepsy is a

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consistent significant finding in both controlled and uncontrolled studies (Montplaisir 1976; Hishakawa et al 1976; Rechtschaffen et al 1963; Passouant 1968). The percentage and amount of nocturnal stage II has been reported as decreased in narcolepsy (Rechtschaffen et al 1963; Suzuki 1966; Cadhillac 1966; Wakamatsu et al 1974; Hishakawa et al 1976), although this finding was not confirmed by Montplaisir in his controlled study (1976). In summary, nocturnal NREM narcoleptic sleep is comprised of significantly more stage one, with shorter sleep latency, and possibly significantly less stage II and III-IV.

Disturbed Nocturnal Sleep

Narcoleptics with auxillary symptoms (REM or N+ narcoleptics) display significantly disturbed nocturnal sleep (DNS), a finding reported by virtually all investigators. Their sleep is broadly characterized by frequent episodes of nocturnal myoclonus in many patients, frequent and sustained awakenings, brief body movements and arousals, disturbing dreams, large amounts of wakefulness after sleep onset (WASO), decreased sleep efficiency, and increases of light sleep versus SWS.

A high incidence of frightening dreams as reported by narcoleptics was cited (60% of the cases) by Roth and Bruhova (1969), with a similar finding in a controlled study by Montplaisir (1976). An equal percentage of patients reported DNS

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as a major symptom (Montplaisir 1976). Montplaisir further reported that 75% of his sample group believed a good night's rest ameliorated their sleep attacks.

Increased frequency of awakenings, body movements, and WASO have been reported by Rechtschaffen et al (1963), Suzuki (1966), Berti-Ceroni (1968), Hishakawa et al (1976), Richardson et al (1978), de Barros-Ferreira and Lairy (1976), and Montplaisir (1976). In an interesting finding, Hishakawa et al report a mean of 15 $\pm$ 1 arousals in 20 narcoleptics, versus 2 arousals for 4 non-REM narcoleptics and 5 for 10 normals. He thus raises the issue of the presence of DNS in non-REM narcoleptics, although it is unclear how the diagnosis of narcolepsy was made in these patients who had "only sleep attacks". The question of the degree of DNS, and its relationship with, the REM aspects of narcolepsy remains unresolved. With regards to longer periods of wakefulness during nocturnal sleep, frequent long awakenings as reported by Cadhillac (1966) were not confirmed by Monplaisir.

Both Montplaisir and Van der Hoed et al (1981) found insignificant increases in WASO in narcoleptics; both reported significant increases in brief awakenings. Thus it appears that whereas significantly more brief awakenings may occur at night in narcolepsy, sleep efficiency may remain normal, and Van der Hoed reports this in narcoleptics as 88%, within the normal range. Montplaisir has reported that narcoleptics have significantly

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more body movements than normal controls, and that a disproportionate amount of them occur in REM (1976). Thus it remains possible that narcoleptics have, notwithstanding normal total REM time and percent, sufficient REM disruption to produce a "deprived" state. It is in fact evident from findings in this study (Adler) that narcoleptics have similar amounts of REM sleep, but respond to REM interruptions differently than normals. That is, if the initial RD awakening is viewed merely as an interruption, the response of narcoleptics to this is suggestive of an existing deprived state. Whether this can be accounted for based on disturbed REM sleep rather than "less" REM sleep is unclear.

Van der Hoed et al (1981) reported significantly greater frequencies of myoclonic jerks in narcoleptics than in normals or other EDS patients. These occurred in both REM and NREM sleep, and were associated with frequent subsequent brief awakenings. The relationship between disturbed sleep, EDS, and auxillary symptoms will be discussed in the pathophysiology section and the final chapter.

Montplaisir (1976) reports that daytime napping increases DNS in narcoleptics. In a study where narcoleptics were compared when one group was allowed ad libitum napping and the other no napping, the group that napped had increased stage I, decreased

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stage III-IV, increased frequency of SOREMPs and shorter REM latency, increased number of awakenings and WASO, and increased body movements and REM fragmentation. The probability of a SOREMP in the no nap group was 33% (n=11), as opposed to 67% in the nap group (n=9). This is consistent with findings by researchers who have produced SOREMPs in normals by fragmenting the sleep-wake cycle (Carskadon and Dement 1975; Johnson 1980). Thus a relationship between EDS, napping, DNS, and perhaps SOREMPs is likely in narcolepsy, although the relationship of these factors to the etiology and pathophysiology of the illness is unknown. A similar relationship has been posited for insomnia with daytime sleepiness and nap behavior.

Ambiguous or Dissociated Sleep Stages

Rechtschaffen and Kales (1968) have described sleep stage morphology in terms of the simultaneous presence or exclusion of certain individual sleep-related phenomena reflecting EEG, EMG, and EOG potentials. When heterogeneous mixtures of these phenomena occur, it is often problematical to ascribe with surety the epochs to a particular stage of sleep. The dissociation of sleep stage phenomena to other stages of sleep is a known consequence of disturbed sleep and certain experimental manipulations. Narcoleptics in particular have been found to display large amounts of ambiguous sleep, although this has been reported by de Barros-Ferreira et al (1973) in schizophrenics as

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well.

Several authors have described substantial amounts of stage 1-REM mixed sleep in narcolepsy (Hishakawa et al 1976). This is described as low voltage mixed EEG with elevated EMG and REMs. Hishakawa et al report this as 2% of TST in narcoleptics, significantly more than in the control group. Large amounts of stage I-REM have been experimentally produced by chlomipramine treatment in narcoleptics (Passouant et al 1972).

De Barros-Ferreira and Lairy (1976) discuss intermediate sleep (IS) which occurs as sleep that appears like stage I in EEG, but with frequent periods of atonia without REMs; or as fast LVM with spindles or K-complexes (Ey et al 1975). Another condition found in narcoleptics, SWS with complete atonia, has been reported in normals (Salzarulo and Mori 1969). Finally, the presence of simultaneous SWS with REMs has been observed in narcoleptics treated with imipramine (Passouant 1974). Guillemenault and Dement (1974) express interest in the possibility of increased frequency of REM phenomena penetration in SWS in narcolepsy. The Passouant studies imply that this is a possible mechanism for dealing with REM deprivation as a result of pharmacological blockade in narcolepsy, and that it may represent a chronic mode of expression for dissociated REM. Finally, de Barros-Ferreira and Lairy suggest the inclusion of mixed sleep and awake states

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in the classification of IS, states such as alpha-REM (Broughton and Guzman 1973) and REM with SREMs (Schwartz et al 1973); microsleeps occurring during cataplexy (Guillemenault 1976); and wakefulness during hypnagogic phenomena (Hishakawa 1976).

The de Barros-Ferreira study found increased amounts of ambiguous SWS in narcoleptics, with both tonic and phasic REM intrusions. Interestingly, two patients withdrawing from REM surpressant drugs who demonstrated substantial rebound during PSG, showed increased SWS with atonia as a percent of SWS, but decreased IS-stage 1. However, due to the small number of subjects, the confound of drug withdrawal in two subjects and drug maintanence in three, and the lack of a control group, these findings are very tentative. It is clear that narcoleptics do present, in addition to disturbed nocturnal sleep, with anomalous sleep stages, as well as mixtures of sleep and wakefulness.

REM Sleep in Narcolepsy

Nocturnal SOREMPs

The frequent occurrence of nocturnal SOREMPs in narcoleptic patients with cataplexy was a major discovery by Rechtschaffen et al in 1963. This finding was reported by Takahashi and Jimbo (1963), and confirmed by Passouant et al (1964), Hishakawa and Kaneo (1965), and many others. Rechtschaffen et al noted the absence of this finding in normal controls. The nature of these SOREMPs has been debated. Specifically, it has been questioned

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whether those SOREMPs occurring very proximate to supposed sleep onset are actually instances of sleep paralysis and/or hypnagogic hallucinations occurring with waking consciousness (Hishakawa et al 1968; Hishakawa 1976), as opposed to episodes of REM sleep. This clinical phenomenon was examined in the current study in one instance, and will be reported. Most authors distinguish between SOREMPs and hypogogic REM phenomena (Dement and Rechtschaffen 1968). Ribstein 1976) and Hishakawa (1976) assert that the determining factor is the level of consciousness during the event, and thus the timing of the event in relation to EEG changes is crucial. When REM phenomena coincide with initial EEG changes from wakefulness to LVM, with no intervening NREM sleep, often what is occurring is hypnagogic phenomena, not a SOREMP. Regardless of this point, a consensus exists that narcoleptics produce SOREMPs on nocturnal PSG, and frequently these occur after several minutes of unequivocal NREM sleep. However, these phenomena-SOREMPs and hypnagogic events with REM EEG, are clearly related, and the occurrence of one versus the other may depend on the timing of the event and degree of pressure or disinhibition.

It is well known that narcoleptics with auxillary symptoms, especially cataplexy, have been consistently found to produce SOREMPs on daytime naps (Vogel 1960; Rechtschaffen et al 1963; Passouant et al 1964; Mitler et al 1979), and average about 3 SOREMPs on five MSLT opportunities (Mitler et al 1979).

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The probability of a SOREMP occurring on nocturnal PSG is about 50% in narcolepsy (Montplaisir 1976; Rechtschaffen et al 1963; Hishakawa et al 1976; Passouant and Billiard 1976). Not all narcoleptics with cataplexy produce SOREMPs on PSG, although all do so on MSLT (Guilleminault 1976). Thus several authors have found no significant differences in REM latency on PSG between narcoleptics and normals (Montplaisir 1976; Richardson et al 1978). Narcoleptics will produce both SOREMPs and SONREMPs on PSG regardless of whether they are receiving tricyclic REM suppressant medication (Passouant and Billiard 1976), a surprising finding since tricyclic agents would be expected to inhibit SOREMPs. These compounds have been found to inhibit short REM latencies in certain depressive conditions within 24 hours of administration.

Patients with narcolepsy but without auxillary symptoms rarely produce SOREMPs on nocturnal PSG or daytime naps (Hishakawa and Kaneo 1965; Dement 1966; Hishakawa et al 1976), and have been referred to as having idiopathic narcolepsy. Guilleminault (1976) found 20% of 38 EDS patients without cataplexy produced a SOREMP. However, it is not clear which of these patients had narcolepsy. Some authors, such as the Stanford group, restrict the term "Narcolepsy" to narcolepsy with auxillary symptoms, or REM narcolepsy. Billard refers to two types of narcolepsy (1976), one with REM facilitation and SOREMPs, and one with only

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NREM facilitation. Guillemenault and Faull (1982) refer to CNS idiopathic hypersomnia in those instances where chronic, narcoleptic-like EDS persists but no auxillary symptoms or DNS develop, and SOREMPs are never elicited on MSLT.

The tendency to produce SOREMPs is not age dependent, and elderly narcoleptics have been found to produce SOREMPs (Passouant and Billiard 1976). SOREMP production is substantially influenced by sleeping posture (Hishakawa et al 1968), with recumbancy strongly facilitating its occurrence.

REM Time and REM Percent

The quantity of REM sleep at night and for 24 hours in narcoleptics versus normals and EDS patients without cataplexy is of special significance due to the apparent REM facilitation or pressure characterized by REM narcolepsy as illustrated in its "spillover" into waking behavior. A reasonable initial inference might be that either narcoleptics are chronically REM deprived and manifest uncontained rebound phenomena, or that their need for REM sleep is somehow excessive, and not satisfied within the nichthemeron. These hypotheses have been examined by the investigation of REM sleep amounts in narcolepsy: That is, do narcoleptics have less REM at night (deprivation) or excessive REM, whether at night or over 24 hours (facilitation)? The presence of healthy REM storage and recuperative mechanisms as

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demonstrated in normal rebound phenomena has not been systematically studied.

The fairly consistent finding that narcoleptics show neither increased TREMT or REM% is important. A number of authors have reported this finding. Rechtschaffen et al (1963) were the first to report no differences between normal controls and narcoleptics for nocturnal REM sleep time. Richardson et al (1978), in a controlled study, reported significantly less TREMT at night in the narcoleptic group. Differences in REM% were small, with the narcoleptics producing 17% REM as opposed to 19% for the normal controls. Hishakawa et al (1976) in a study of narcoleptics, EDS patients without cataplexy, and normal controls found no significant differences in REM amounts for either nocturnal sleep or 24 hour monitoring, although the variance in the narcoleptic group was considerably larger. However, this was a sleep satiation study, and thus it is hard to generalize its findings to non-experimental conditions. Montplaisir (1976), in a 24 hour study, also found no significant differences in REM time or percent, and additionally reported that daytime REM sleep amounts did not influence nocturnal REM time or percent.

Thus, it appears that REM sleep in narcoleptics is not excessive, either in TREMT or REM%, for the night or for 24 hours. Neither has it been substantiated that narcoleptics are chronically REM

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deprived—that is, that they have decreased amounts of REM sleep, especially at night. Unfortunately, more sophisticated studies of less apparent REM deprivation effects or REM pathology have not been attempted. These phenomena might not manifest themselves in straightforward REM time or percent.

A number of articles have reported narcoleptic patients with unusually large or small amounts of REM sleep (Suzuki 1966; Mouret et al 1972; Passouant et al 1968; Kendel et al 1973; Passouant and Billiard 1976). This finding is consistent with the greater variance in narcoleptic REM sleep. However, Hishakawa et al (1976) were unable to find any relationship between symptom severity and REM time. A positive finding for this had been reported by Takahashi and Jimbo (1963) and Suzuki (1966). Unfortunately, in these studies control subjects were not used, and increased REM quantities may be secondary to drug withdrawal. Interestingly, the presence of cataplexy in the Hishakawa study accounted for the least of the variance in narcoleptic REM time, a surprising finding since cataplexy is correlated with SOREMPs at 100%. This implies that SOREMPs and REM time and percent may not be related.

Sleep Architecture, Periodicity, and Rhythmicity

Inasmuch as sleep stage percentages and characteristics have not accounted for the sleep disorders of narcolepsy, and in fact can

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not be used to discriminate narcoleptics from normals according to Richardson (1978), interest has focused on the temporal relationship of sleep stages, especially since narcolepsy seems to involve "precocious" as opposed to excessive REM sleep (Dement 1976). Several authors have examined the architecture and periodicity of nocturnal narcoleptic sleep. General findings are that the periodicity of REM/NREM sleep is maintained (Hishakawa et al 1976; Montplaisir 1976), with some exceptions. Narcoleptics appear to have a regular alteration of REM/NREM sleep with an appropriate 90 minute cycle length. When REM sleep is phase advanced with respect to NREM sleep, as in the case of SOREMPs, subsequent normal alternation between REM and NREM is unaffected (Montplaisir 1976).

Narcoleptics appear to demonstrate greater within subject variability regarding the duration of REM cycles than is found in normals or EDS patients. These differences were reported as significant by Hishakawa et al (1976) who measured the index of REM sleep rhythmicity. Montplaisir has found similar findings not reaching significance. All narcoleptics in both of these 48 hours studies were found to maintain a regular alternation of REM/NREM periods.

Montplaisir reported a longer inter-REMP interval between the first and second REM in narcoleptics in conjunction with a decreased tendency, when compared with normals, for REMs to

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become increasingly longer as sleep time increased. In normals, REMP length increases significantly with time. Both authors explained the greater variance for REM cycle length as due to general DNS in narcolepsy.

Sleep architecture in general in narcolepsy has been reported as resembling that of normals. Narcoleptics, like normals, appear to have progressively decreased amounts of stage III-IV sleep as a function of TST (Hishakawa et al 1976), as well as the increase in late versus early REM. However, this increase is proportionately smaller than that found in normals (Montplaisir 1976). Unlike normals, narcoleptics had a tendency for decreased percent of stage II and increased stage I percent with sleep time. Additionally, narcoleptics showed a tendency for REM fragmentation, with episodes of waking or stage I interrupting REMPs frequently (Passouant 1968). This point is discussed elsewhere, and has implications regarding REM pathology.

When a 24 hour circadian sleep-wake rhythm in narcoleptics is examined, what is most evident is the flattening of the 24 hour sleep tendency curve, a tendency commonly associated with elderly normals and some patients with insomnias and secondary EDS (Richardson et al 1982). This flattening is less evident at night, since sleep latency is normal; however, sleep maintenance is abnormally disturbed, primarily with increased brief arousals.

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Sleep tendency during daytime is elevated, and the predominantly bi-phasic circadian sleep rhythm found in normals is not evident in narcoleptics. It remains unclear whether this phenomena can be best accounted for by models of inadequate daytime arousal levels or by those describing a prepotency of sleep mechanisms, either REM or NREM.

REM sleep rhythms for 24 hours in narcoleptics appear similar to that of normals. Progressively reduced REM sleep propensity has been reported from morning to evening. However, although the direction of these measures is the same, narcoleptics have significantly greater REM sleep tendency during daytime than do normals. Additionally, early night RSP is increased in narcolepsy. Core body temperature 23-hour rhythms, which are thought to follow RSP in normals, has been described as disturbed in narcolepsy, in terms of a phase advance of temperature nadir at night by several hours (Mosko et al, 1983).

In summary, narcoleptic sleep is in many ways qualitatively similar to normal sleep. Significant tendencies towards DNS, ambiguous sleep, phase advanced REM sleep, and disproportionate amounts of stage I and IV have been noted. However, with the exception of the tendency for SOREMPs, nocturnal sleep in narcolepsy appears surprisingly normal, given the apparent extreme disturbances of sleep mechanisms, especially REM mechanisms, during wakefulness.

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It thus remains unclear how one can account for the REM and NREM symptomatology of narcolepsy given the apparent similarity in sleep patterns and sleep morphology of narcoleptics with normals.

SLEEPINESS

Sleepiness refers to a normal phenomena or state experienced at some time by everyone. It can be said to represent the junction or intermingling of two presumed neuroprocesses, wakefulness and sleep, and is often manifest in states arising from their perturbation, namely disorders of initiating and maintaining sleep and disorders of excessive somnolence. In these instances a sort of overlapping or infringement of one process into territory customarily allotted to the other occurs, that is in the occurrence of wakefulness during the night and sleepiness or sleep during the day. In normals, sleepiness is present most often secondary to sleep loss, or as a function of time of day, interest, and motivation.

Circadian Tendencies and Sleepiness

Investigation of sleep tendencies during the day and night have led to the proposal of a model for circadian or 24-hour sleep-wake rhythms in the normal adult human. When normal circadian rhythm is maintained, sleep and waking states generally appear as dichotomous and separate. Their infringement upon each other is less obvious, except at normal junctures of bedtime and awakening, although changes in objective alertness as measured by pupilometry, nap sleep latencies, and subjective alertness indicate regular fluctuations in alertness and sleepiness

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throughout the course of the day. These fluctuations have been found to have a normal 24-hour rhythm as well as a period or rhythm of less than 24 hours (ultradian). Thus sleep and alertness are interactional if not reciprocal processes which vary in predominance and relationship continually, with both a 24 hour and ultradian rhythm.

Studies of sleep-wake patterns have been conducted by measuring sleep tendency as represented by sleep latency on naps throughout the day, thus producing a sleep tendency (sleepiness) curve for periods outside the nichthemeron. Additionally, other bodily functions thought to be rhythmic, such as endocrine levels, core body temperature (Czeisler et al 1980), pupil size (Lavie & Schultz, 1980), eating (Oswald 1970), heart rate (Orr et al 1976), and REM/NREM sleep (Kripke 1976) among others have been investigated in order to determine possible circadian and ultradian patterns. Several of these patterns have been found to vary in conjunction with each other in a stable manner.

Relationships between physiological rhythms have been investigated utilizing napping, 24-hour blood sampling and electrophysiological monitoring, and experimental studies using changes in sleep-wake schedules and REM deprivation (Ellman, and Roffwarg, unpub. study). These studies have included 3 hour sleep-wake schedules (Weitzman et al 1974), 90 minute sleep-wake schedules (Carskadon and Dement 1975), 220 minute sleep-wake

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schedules (Moses et al 1975), multiple daytime naps with restricted sleep after total sleep deprivation (Carskadon and Dement 1979) restricted nocturnal sleep (Carskadon and Dement 1981), sleep extension (Carskadon and Dement 1979), ad libitum sleeping in temporal isolation (Czeisler et al 1978), sampling of multiple naps occurring during nocturnal sleep hours (Richardson et al 1982) and MSLT studies during daytime (Richardson et al 1978) among others.

Findings indicate a pronounced 24-hour sleep-wake rhythm measured by sleep tendency (sleep latency), with increased sleep tendency during customary sleep periods. This rhythm has been found to be biphasic, with minimal sleepiness in the mid morning and evening, and maximal sleepiness in early morning (about 5:00), and a second "sleepiness trough" at about 14:00 (Carskadon 1979). Several conclusions are reported. Sleep tendency has been described as a clock time dependent function with a 24-hour rhythm (Mitler 1981; Carskadon 1979). An associated, identifiable 90-120 minute ultradian rhythm for a variety of functions, including REM sleep, has been reported, although no finding for sleep tendency for this schedule has been found (c.f. review by Kleitman, 1983). An increased tendency to fall asleep persists secondary to sleep deprivation regardless of clock time (Carskadon and Dement 1979, 1981). The biphasic character of the 24 hour sleep-wake rhythm is generally "flattened out" as

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individuals age (Carskadon 1979).

The pattern of circadian and ultradian rhythms purportedly represent the interrelationships between several partially independent oscillators controlling physiological rhythms, including, in various combinations, sleep, waking, endocrine, and homeostatic functions. These relationships are complex, and only partially understood. The 24 hour rhythms for body temperature and sleep tendency follow each other closely (Czeisler et al 1980), with the exception that the latter does not reflect the increase in sleep tendency at mid-day (Aschoff 1955; Richardson et al 1982). Thus sleepiness maybe a multi-dimensional phenomena reflecting semi-autonomous physiological processes of alternance, temperature, and REM and NREM sleep. These relationships can be effected by a variety of environmental factors, causing changes in their phase relationships and period length. Sleep schedule changes produce the most evident disruptions. Daytime sleepiness is most clearly related to disturbed nocturnal sleep and sleep deprivation, and is also evident secondary to changes in time zone and radical changes in sleep-wake schedules as a result of shift work (Akerstedt et al 1982).

The most consistent sequelae to sleep deprivation studies has been sleepiness (Webb 1972; Dement and Carskadon 1982) and "the most obvious interactions between sleep and wakefulness other

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than their sequential occurrence in each 24-hour period are the predictable fluctuations of daytime alertness as a function of primarily the amount of nocturnal sleep" (Dement and Carskadon 1982). A variety of other perturbations resulting in altered and disturbed nocturnal sleep have been found to result in daytime sleepiness, including drug and alcohol use, REM deprivation, and sleep disorders resulting in disturbed nocturnal sleep. Sleepiness in general can be viewed as a reversible condition which is affected by subsequent sleep such as napping, as well as by time of day effects which can produce spontaneous reversal. Changes in mood and motivation are also known to effect sleepiness, as may changes in the stimulus level of the environment.

Descriptive Aspects of sleepiness

Normal sleepiness may be viewed as diminished attention (Dement and Carskadon 1982). Descriptively, its measurement may encompass subjective estimate, objective peripheral physiological estimate, objective central measures, and performance measures. Normal sleepiness is characterized by loss of motivation, decrements in attention, learning, interest, concentration, and performance, sensations of heaviness, eye irritation, a decrease in eye movements, yawning and head drop, loss of facial expression, and motoric retardation or listlessness (Pressman 1982; Dement 1976; Dement and Carskadon 1982). Physiological

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indices include EEG changes, especially EEG slowing (Johnson et al 1969), changes in temperature, heart rate (Lacey 1959), GSR (Duffy 1962), auditory evoked potentials (Weitzman and Kreman 1965), and changes in pupil stability and constrictions (Lowenstein et al 1973). Conceptually it has been viewed as an appetitive behavior or physiological drive state similar to hunger and thirst that involves pursuit and satiation (Moruzzi 1969; Spielman unpub. paper), and a phenomena that occurs in response to sleep loss (Carskadon and Dement 1981); and as a reflection of hypoactivity of the reticular activating system (Malmo 1959) which is responsible for tonic neocortical desynchrony.

Measurement of Sleepiness

Kamiya (1961) as described by Carskadon and Dement (1982) has described four measures of sleepiness, which are decreases in best effort, subjective estimate, decreased activity level, and sleep tendency as measured by sleep latency. Accurate measurement of sleepiness has become increasingly significant with the investigation of the disorders of excessive somnolence and their management. Furthermore, it is now believed that different measures of sleepiness especially subjective and objective measures, may not be as highly correlated as was previously thought (Dement et al 1978; Roth et al 1980). These

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authors report patients with hypersomnia sleep apnea who are clearly sleepy yet rate themselves alert, and in a study Dement et al found "no correlation" between subjective sleepiness and sleep latency in this patient group. Roth et al (1980) confirm that sleep apnea patients's estimation of their pathologically sleepy state may be "grossly inaccurate", as suggested by very short sleep latencies yet alert ratings on subjective measures of sleepiness (p.425). (The construct validity and independence of sleepiness, in terms of its "measurement", thus is still open to some debate (Pressman 1982), when one considers both subjective and objective measures. Subjective measures employ self report questionnaires, the most prevalent of which is the Stanford Sleepiness Scale (SSS), (Hoddes et al 1972). This is a 7 point self rating scale that discriminates normal controls from some patients with EDS (Richardson et al 1978; Hoddes et al 1973; Mitler 1981), and correlates with performance measures within a group of sleep deprived normal controls (Hoddes et al 1973).

Dement and Carskadon have suggested that subjective and objective sleepiness are not equivalent phenomena, the latter representing "a physiological tendency to fall asleep which is fairly long-lasting and stable" whereas subjective sleepiness involves shorter lasting changes in the way we feel and is influenced by motivational, emotional, and motoric states, such as pain, excitement, interest, hunger, boredom, etc. (Dement and Carskadon

1982). These factors influence objective sleepiness but not in a direct linear manner. Thus temporary increases in subjective sleepiness do not automatically translate into sleep behavior, and it is not surprising that these measures do not always reflect each other. Notwithstanding these issues, the SSS is the most widely used and studied of subjective measures of sleepiness.

Performance measures of sleepiness (e.g. Wilkerson et al 1966) test the individual's ability to concentrate, attend, problem solve, and manipulate under varying degrees of alertness, and as would be expected reports indicate very substantial impairment of these functions in the presence of sleepiness in both patients with EDS (Dement 1976), and in normals (Kjelberg 1977) after sleep deprivation. Tests of performance and SSS scores have been found to correlate (Hoddes et al 1973). The issue of motivation as a confound for performance measures has been noted by several authors (Dement et al 1978).

The most widely accepted central physiological measure of supposed central sleepiness is pupilometry (Lowenstein et al 1973). Large and stable pupil diameter has been found to be consistent with alertness, and constricted, unstable pupil size (hippus) is associated with sleepiness (Lowenstein and Lowenfield 1963) and pathological sleepiness (Yoss et al 1970). These findings have been verified in narcoleptics (Yoss et al 1969) and

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over the course of the day with repeated measurement, both in normals (Lavie and Schultz 1981) and in narcoleptics (Pressman et al 1982).

Electro-encephalogram (EEG) and auditory evoked responses (AER) have been utilized to measure central sleepiness. Studies of sleepiness using EEG have not been especially fruitful (Johnson et al 1969). AER research began with the correlation of EEG to AER (Williams 1982) and recently has been utilized to measure changes in alertness in normals and narcoleptics (Pressman et al 1982; Broughton 1982).

An objective measure of hypothecated central sleepiness is the multiple Sleep Latency Test (MSLT), which is conceptualized as measuring sleepiness when that is viewed as the tendency to fall asleep when given the opportunity (Carskadon and Dement 1977; Richardson et al 1978; Mitler 1982). Although this test has been found to be quite sensitive to changes in sleepiness in normals secondary to small amounts of sleep loss or to time of day (Carskadon and Dement 1982), it has not been found to be very sensitive to variations in sleepiness in patients with pathological EDS, especially in the narcoleptic and obstructive apneic groups (Roth et al 1980; Hartse et al 1980; Carskadon and Dement 1982). A similar test developed in Detroit, the Maintenance of Wakefulness Test, employs a different instruction

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that asks the subject to "remain awake" under soporific conditions (Hartse et al 1982). This has been found to be more sensitive to changes in sleepiness in these pathological conditions.

The MSLT consists of five nap opportunities given to the subject, at two hour intervals beginning at 10:00. Sleep latency is measured and utilized as the measure of sleepiness. This measure has been considered reliable and to have "face validity" (Mittler 1982), that is, someone who is sleepy will fall asleep more quickly. Yet Dement et al (1978) have described patients with pathological sleepiness as represented by short sleep latencies on MSLT who do not report subjective sleepiness, and patients who complain of EDS yet present with long sleep latencies have been reported as well (Richardson et al 1978). This latter group of patients are described as "Subjective DOES Complaint without Objective Finding" in the DCSAD. The individual who falls asleep quickly while watching TV without feeling sleepy does not appear to be the same as someone who wants to remain alert and watch something but is unable to do so despite active resistance, or the same as the person who feels very sleepy but can not fall asleep.

These factors notwithstanding, the MSLT remains a useful and accepted tool for measuring objective sleep tendency and may be said to have construct validity if sleepiness is thought to be a

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state that occurs in response to sleep loss. The MSLT continues to correlate highly with subjective estimate of sleepiness in normals and most patients (Dement et al 1978). Investigation indicates it can carefully measure daytime sleepiness secondary to sleep loss as well as partial sleep deprivation, which has not found to be true of the SSS and performance measures (Carskadon et al 1977).

The MSLT can, as well, reflect circadian fluctuations in temperature as illustrated by comparisons of sleep latency and body temperature curves (Richardson et al 1982); and latencies on a 90 minute sleep-wake schedule (Carskadon and Dement 1975; Carskadon and Dement 1977) are thought to reflect basic sleep-wake rhythms. The interaction of two phenomena- normal circadian rhythms of sleep and alertness (Kleitman 1963; Dement and Carskadon 1975) and sleepiness and alertness secondary to sleep loss (Carskadon and Dement 1979; 1981) is unclear inasmuch as circadian alertness predominates at certain morning hours notwithstanding prior total sleep deprivation and thus alertness appears to be clock time dependent; yet sleepiness after total sleep deprivation will persist regardless of clock time until reversed by recovered sleep (Carskadon and Dement 1979; 1981; Carskadon et al 1981).

The MSLT is a useful tool for investigating the pathological

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occurrence of SOREMPs during daytime naps (Mitler et al 1979) and can discriminate most patients who complain of pathological sleepiness from normals. It is especially successful in discriminating narcoleptics from normal controls, with no overlap in the frequency of SOREMPs (Mitler et al 1979; Mitler 1981). It is less able to distinguish between narcoleptics and other patients groups with EDS, on either the SOREMP or sleep latency criteria. The test remains highly sensitive to sleepiness secondary to sleep loss. False positives on the MSLT can be minimized by assuring, therefore, for the proper maintenance of sleep schedules of subjects prior to testing.

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Pathological Sleepiness and Excessive Daytime Sleepiness (EDS)

Pathological sleepiness as a concept has been differentiated from normal sleepiness in several objective and theoretical ways, although in fact no absolute quantitative or qualitative distinctions exist. Dement, Carskadon, and Richardson, researchers who have devoted substantial energy to the study of sleepiness, describe the pathologically sleepy patient as someone who is "distinguished by a markedly increased chronic susceptibility to falling asleep" (1978). Thus these authors are relying primarily on an objective, quantifiable and behavioral criteria for pathological sleepiness, as it can be measured by daytime sleep latency.

But Dement in particular has noted other more qualitative criteria that are equally essential when describing the syndrome. Inappropriateness of sleepiness and sleep, that is sleep behavior in non-soporific and even life threatening circumstances, can be viewed as a cardinal sign of pathological sleepiness given no prior sleep deprivation. Dement (1976) cites as examples falling asleep during eating, intercourse, strenuous exercise and excitement, or dangerous situations. A patient at City College with narcolepsy who worked as a checkout cashier, described routinely falling asleep while entering sales in the cash register. Another patient has described falling asleep while

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hammering a nail. Instances of this sort, as well as less dramatic ones, are more suspect when they are frequent and persistent. Regarding sleep behavior, the quantity of daytime sleep episodes, their duration, and the occurrence of actual microsleeps, or extremely brief sometimes unnoticed sleep episodes, are determinants of excessive daytime sleepiness (EDS).

Qualitative and Subjective Aspects of Pathological Sleepiness

Pathological sleepiness is global, unlike paralysis, blindness, or hearing loss. In this sense its effect on functioning is unavoidable, ubiquitous, and persistent. It is considered to be the most disabling symptom by those patients who have narcolepsy and sleep apnea. A variety of etiologies are known for EDS (ESD is the technical term for the symptom of excessive sleepiness, and implies that it is pathological). Dement (1976) has described etiologies of EDS from a sample of 200 EDS patients seen at the Stanford Sleep Disorders Center. They were comprised of 63% patients with narcolepsy, 18% with HSA, 5% with both disorders, and 14% with a variety of other etiologies.

Van der Hoed et al (1981), at the same clinic, reports that of those patients seen for sleep disorders, more than one half (58% of 277) present due to EDS. They reported a lower incidence of narcolepsy, only 46%. Interestingly, the number of patients with EDS secondary to psychophysiological and psychiatric disorders

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was much higher, 18%, perhaps due to increased public awareness of treatment for sleep problems.

The nature of the sleepiness in the cases referred to by Van der Hoed and Dement was "excessive" but normal in that it was not related to viral states, compromises to consciousness or known brain damage, yet it was still clearly different from "normal" sleepiness, such as postprandial sleepiness, time appropriate sleepiness, or sleepiness secondary to sleep loss as in the insomnias. In fact, patients with narcolepsy do not attribute their EDS to disturbed nocturnal sleep or sleep deprivation, unlike those patients with EDS secondary to disorders of initiating and maintaining sleep (Dement 1976), and they generally do not report significant time of day effects regarding their sleepiness. Of interest in both studies from the Stanford clinic was the high incidence of non-narcoleptic EDS (37% of all patients), especially the large number with HSA (18%); and the large number of patients with both narcolepsy and HSA (5%). This epidemiology clearly indicates an appropriate separation of EDS from narcolepsy.

Dement (1976) notes that intensity is not a meaningful variable in sleepiness, and believes that sleepiness should be defined by its persistence, duration, and appropriateness (timing), as well as by its consequences and degree of impairment to functioning. A complaint of EDS and impaired functioning must be taken

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seriously, for 90% of such complaints were found to be consistent with an identifiable syndrome (Guillemenault and Dement 1977). The sleepiness for narcoleptics can be described as involving a drowsy, sporific state that lasts throughout the day and requires active resistance in order to maintain wakefulness. Narcoleptics rate their EDS as more severe than do other EDS patients on a 7 point scale (Van der Hoed et al 1981). In fact, the so-called sleep attack is really just a manifestation of this persistent sleepiness that culminates in unintentional sleep (Dement 1976). It may be recalled as an attack with a sudden onset due to the amnestic character of the preceding sustained sleepy state.

Several authors (Guillmenault et al 1975; Dement 1976; Dement et al 1978) have described altered states of consciuosness resulting from persistent drowsiness in narcoleptic patients. After prolonged struggling with sleepiness, the narcoleptic usually experiences a decrease in vigilence and resistance to sleepiness. One observes a decline in alertness, accompanied by gradual loss of awareness of surroundings and actions. A variety of normal ego functions become compromised, including complex problem solving, memory, judgement, and cognitive and motoric manipulation, although more routine responses can be produced in a semi-automatic way (Guillemenalut et al 1975). A variety of abnormal phenomena may present under these conditions, including hyponogogic-like imagery or hallucinations, parathesias, blackout

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and retrograde amnesia, and a general distancing from reality with a corresponding loss of sense of time. Automatic behavior periods may last for hours and not be remembered. Virtually all narcolpetics report such episodes. They might drive for several miles without recollecton, clean the house, or do the laundry, and even converse and make plans without recollection. Such activity is error prone, inefficient, and dangerous. This abnormal behavior syndrome is closely connected with sleepiness, and has a similar circadian pattern, with low frequency in the morning and increasing likelihood in later hours (Dement 1976). Interestingly, similar states have been reported in normals after ingestion of benzodiazepine hypnotics and subsequent sleep.

Subjectively sleepy states have been found to have objective correlates. In a 58 hour study of 20 REM narcoleptics and 12 normal controls (Guillemenault et al 1975), narcoleptic patients were in fact found to produce brief episodes of sleep, or microsleeps, during these periods of "altered states" and decreased performance. These were described by the authors as "short bursts of Stage I NREM or synchronous theta activity". This type of microsleep was seen in all patients and no normals. At times, the microsleeps appeared as microREMPS, with tonic EMG surpression. Dement has concluded (1976) that these brief sleep attacks (sudden unintended naps) are actually the culmination of long periods of drowsiness when resistance to sleep finally

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fails. These naps are recalled as attacks, for often narcoleptics don't remember their prior sleepiness due to retrograde amnesia (Guilleminault and Dement 1977). Additionally, they can usually resist sleep (or sleep attack) when monitored and encouraged to remain awake (Dement 1976).

Objective Findings in Daytime Pathological Sleepiness in Narcolepsy

The frequency of sleep attacks, or unintended sudden napping (Dement 1976) has been reported by Passouant and Billiard (1976) as 4.3/day in 12 untreated narcoleptics, resulting in 3.35 hours of daily laboratory napping. Dement (1976) anecdotally reports a range of 2-6 per day without treatment, although he points out that many microsleeps are not recalled. The amount of sleep obtained during a nap clearly influences the persistence and duration of subsequent narcoleptic sleepiness (Passouant and Billiard 1976), for the number of sleep attacks/naps doubled in their research when total nap time per nap was restricted to 10 minutes.

Several authors have measured pathological sleepiness by utilizing the MSLT (Richardson et al 1978; Mitler et al 1979; van der Hoed et al 1981; Mitler et al 1982; Roth et al 1980), a polysomnographic technique. This and the MWT are now considered to be the standard tools for the measurement of pathological

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sleepiness. The clearest finding has been consistently low values for sleep latency on MSLT for narcoleptics. These studies comprising 100 narcoleptic patients found sleep latency means for the five naps for narcoleptics to be in the 3-4 minute range. Lowered sleep latency during the mid-day "dip" (naps 3 and 4 at 14:00 and 16:00) was also confirmed for narcoleptics, a finding previously reported in normals (Carskadon and Dement 1979; Richardson et al 1978). Normal control mean sleep latency on MSLT has been reported as 12 minutes (Richardson et al 1978) and 10 minutes (Dement et al 1978). Richardson found no data overlap on the 10:00 nap between narcoleptics and normals for sleep latency, and approximately 2 minutes of overlap on other naps, which was within one SD. Nevertheless, the amount of overlap in this measure is small, allowing for fairly accurate discrimination between narcoleptics and normals on the basis of sleep latency.

This is much less evident when comparing normals with other EDS patients. Van der Hoed et al (1981) assert that the discrimination of narcoleptics and other EDS patients (excluding those with HSA) is possible using sleep latency on MSLT, and reported a mean sleep latency for these EDS patients of 9 minutes (N=54). Note, however, that this mean is very similar to the normal control mean, thus making the discrimination between these two groups based on sleep latency impossible. Additionally, over

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40% of those patients with "CNS hypersomnia" and EDS associated with insufficient sleep had latencies under 5 minutes, or within the narcoleptic range. The 5 minute sleep latency criteria for pathological EDS suggested by Richardson was sensitive for 83% of the 46 narcoleptics in the Van der Hoed study, with a 75% specificity for the other EDS patients.

The MSLT is especially unsuitable when relying on sleep latency for discriminating between narcoleptics and HSA patients, especially those with upper airway sleep apnea (Dement et al 1978; Mitler et al 1982). These HSA patients have mean sleep latencies on MSLT virtually identical to those of narcoleptics (Dement et al 1978). Thus sleep latency per se can not discriminate between HSA and narcoleptic patients; between these groups and other EDS patients; and between other EDS patients and normals. It can discriminate fairly successfully between normals and EDS patients with narcolepsy or HSA with secondary EDS.

PSG Characteristics of Daytime Narcoleptic Sleep

Continuous PSG monitoring of narcoleptic sleep during daytime indicates the presence of long periods of "drowsy" Stage I sleep (Daly and Yoss 1957, Berti-Ceroni et al 1968), delayed Stage II during naps, an increase in chin EMG twitches during sleep onset, a paucity of slow rolling eye movements, and the appearance of phasic and tonic sleep dissociations, such as tonic EMG

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surpression during stage I, and REMs without EMG surpression (Hishakawa et al 1976, Dement 1976).

SOREMPs in Daytime Sleep

Most significantly, the study of daytime narcoleptic sleep includes the finding of SOREMPs. This was initially noted by Vogel (1960), and further confirmed by Rechtschaffen et al (1963), in one subject, by Passouant et al (1964), Suzuki (1966), Hishakawa et al (1968), Guilleminault and Dement (1974), and Mitler et al (1979), among others. Several authors have, as well, reported the occurrence of SOREMPs on daytime naps in other groups: in normals, in early morning naps when the presumptive REM circadian rhythm is powerful (Webb et al 1966; Endo et al 1974; Kelly et al 1973; Hayden 1969); in mid-day naps (Endo et al 1981); following prolonged REM deprivation (Dement and Rechtschaffen 1968); following one night of REM deprivation (unpublished study at the SWDC); as secondary to disturbed nocturnal sleep, including nocturnal myoclonus (Weitzman et al 1974); during a 90 minute sleep-wake schedule (Carskadon and Dement 1975;1977) in patients withdrawing from drugs, especially REM surpressing drugs, such as antidepressant medication and amphetamines (Oswald and Thacore 1963); in certain depressed patients; and in patients with HSA (Mitler et al 1982).

The occurrence of SOREMPs in daytime sleep outside of narcolepsy

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is thus well documented. Notwithstanding this, SOREMP occurrence in a non-sleep deprived normal subject is very unusual. The relationship of SOREMPs in narcolepsy to sleepiness is unclear, and will be discussed.

The importance of daytime SOREMPs in narcolepsy has been emphasized as a salient although not pathognomonic sign for several reasons: SOREMPs on nocturnal PSG of narcoleptics are produced inconsistently; an extremely high probability exists in narcoleptics with cataplexy that they will produce a daytime SOREMP on MSLT; only HSA patients amongst other EDS patients produce SOREMPs with any frequency and at a similar rate, including those with EDS secondary to DIMS; finally, "narcoleptics" without auxillary symptoms (N-) rarely produce SOREMPs (Hishakawa and Kaneko 1965; Dement et al 1966); although the relationship of SOREMP to "sleep attack" and sleepiness is now unclear, an apparent basic relationship exists between SOREMP and auxillary symptoms.

Findings regarding these points can be summarized. Nocturnal SOREMPs are produced on approximately 50% of PSG trials by narcoleptics (Hishakawa et al 1976; Roth et al 1969; Coleman et al 1982), yet many narcoleptics do not have nocturnal SOREMPs even after several recordings (unpublished SWDC finding). In fact, mean REM latency on nocturnal PSG for 46 narcoleptics in

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one study was 71 minutes (Hishakawa et al 1981), and Coleman et al found a bi-modal distribution with most narcoleptics in the long latency range (older narcoleptic patients were the ones who tended to have nocturnal SOREMPs, a finding consistent with the ontogenesis of the illness and its symptoms). Virtually 100% of narcoleptics with cataplexy produce SOREMPs on MSLT (Dement 1976; Guilleminault and Dement 1977), and in fact these authors state that "when a history of cataplexy is clear, no sleep recording is necessary for the diagnosis." Guilleminault has reported that 100% of 142 patients with cataplexy had SOREMPs on naps (1976). This fact had led Dement, Rechtschaffen, and Guilleminault to argue that sleep attacks were manifestations of REM sleep (1968, 1974). However, it is now clear that EDS and napping involves NREM sleep as well.

In the Stanford studies, the percentage of patients with EDS but without cataplexy ("EDS-" patients) who had daytime SOREMPs was 21%. Hishakawa et al (1976) found no SOREMPs in "EDS-" patients (n=4) on ad libitum napping. In summary, it appears certain that narcoleptics with cataplexy ("N+" patients) will produce daytime SOREMPs, and that they may represent a distinct pathological entity. Since "N-" patients display similar EDS, it is unclear how the development of SOREMPs with cataplexy in these patients is related to their sleepiness. Other groups will produce SOREMPs as well, and thus it is the history of cataplexy that is

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most instructive.

REM and NREM Daytime Sleep in Narcolepsy

The ratio of SOREMPs on naps, versus naps with sleep onset NREM periods (SONREMPs) and mixed naps with SONREMPs in narcolepsy has been studied, especially in response to the issue of the nature of sleep attacks and EDS (Dement et al 1966; Hishakawa et al 1976; Passouant and Billiard 1976; Billiard 1976; Mitler et al 1979). Passouant and Billiard reported an approximate frequency of SOREMP on ad libitum naps of 50% for both treated and untreated narcoleptics. Mitler et al reported a 74% frequency on MSLT. The higher frequency in Mitler may be due to the sleep time restriction factor on MSLT. However, Billiard (1976) reported that when nap time was restricted to 10 minutes, the relative proportion of SONREMPs increased, and SOREMPs decreased. This might be explained in terms of the sleep dependent theory of REM sleep as described by Johnson. Both he and Hishakawa et al (1976) found the ad libitum SOREMP probability to be in the 80% range. Many factors thus influence the probability of SOREMP on narcoleptic nap, including prior napping, type and amount of prior sleep, as well as body position. It would appear, however, that the probability of SOREMP for narcoleptics is highest on ad libitum daytime napping, a method that allows for what might be an irresistible need for REM sleep. Nap time restriction and pre-scheduling can lead to a higher proportion of NREM onsets, as

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well as to more frequent naps.

The variable relation of REM versus NREM sleep onsets in narcoleptic daytime sleep has been noted with interest, initially by Beti-Ceroni et al (1968) and Passouant et al (1968), who described a competition between NREM and REM systems in narcolepsy as reflected by this variable ratio. This interest was intensified by the relationship of REM onsets to auxillary symptoms, both in correlation, and in their obvious similarities, such as tonic EMG suppression. It is now virtually agreed that all N+ patients have both REM and NREM daytime onsets during naps, including so-called sleep attacks. Some regularity or predictability of SOREMP versus SONREMP appears to exist, based perhaps on ultradian aspects of REM, a basic REM refractory period, and possibly influenced as well by the stage of prior sleep and its amount, although it must be noted that narcoleptics can produce consecutive SOREMPs on MSLT without intervening NREM sleep. This is contrary to the study of normals on a 90' schedule by Carskadon and Dement (1977) who found that normals virtually never had two successive SOREMPs. In one study of narcoleptic napping, under ad libitum conditions, when narcoleptics produced a SOREMP, a second REM period never occurred prior to 60 minutes after the first, which is indicative of the refractory model for REM sleep, and is generally confirmed in narcoleptics in nocturnal PSG findings.(Hisakawa et al 1976).

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It remains unclear in normals whether the refractory period is merely a function of time, or is SWS dependent as well (Johnson 1980). In narcoleptics, it appears to be only time dependent, although a study that prevented any daytime NREM might further clarify this.

Wilson et al (1973) noted that REM occurred on naps either as SOREMP or within the normal 60-120 minute latency, but not at intermediary points, perhaps reflecting a normal REM/NREM oscillation which may begin at either the REM or NREM phase. Although narcoleptics produce SOREMPS on successive naps on MSLT, these are spaced two hours apart. If naps were given at shorter intervals, this finding might be reversed.

Another issue concerning the frequency of SOREMPS is whether the ratio of SOREMPS to SONREMPS is related to severity of auxillary symptoms or EDS (Passouant et al 1968; Hishakawa et al 1976; Billiard 1976). Such a relationship is not confirmed by any reported findings. Thus the meaning of SOREMPS and their frequency is unclear concerning the symptoms of narcolepsy, other than the similarity of REM manifestation. Dement has stated that it is clearly inappropriate to call narcolepsy a disorder of REM sleep due to the NREM aspects of the illness, i.e., SONREMPS in sleep attacks and napping, and due to the unknown pathophysiology of the EDS, a symptom that is present in N- patients as well

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(Dement 1976). As recently as 1974, Guillemenault, Wilson, and Dement considered sleep attacks invariably to represent the "intrusion of REM mechanisms into walking" (Guillemenault and Dement 1974). Thus this view of narcolepsy has changed with recent findings and added reflection.

Recuperative Aspects of REM versus NREM Napping

One response given to the question of why narcoleptics nap is that it is necessary to reverse their sleepiness, that it has a refreshing quality, in a manner similar to a nap for a sleep deprived normal. In this sense narcoleptic EDS has a normal quality (Dement 1976), unlike compromise to consciousness. Since nap onsets include both SOREMPs and SONREMPs, interest has existed as to whether the occurrence of REM sleep per se involved the recovery of wakefulness, especially since the auxillary symptoms seem to imply displaced or uncontained REM phenomena that breakthrough into wakefulness. When sleep attacks were previously thought to be REM sleep attacks, several authors have suggested that those naps were especially refreshing (Yoss and Daly 1960; Rechtschaffen and Dement 1969; Zarcone 1973). In the Billiard study (1976), the recuperative effects of different types of daytime sleep were measured by SSS and performance measures. Effects of REM versus NREM and ad libitum versus restricted napping was assessed. Findings indicated no significant differences in refreshment after differerent types of

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napping in terms of sleep stages, whereas ad libitum napping significantly increased alertness over restricted napping. NREM and mixed naps with SONREMPs showed a trend towards refreshment, whereas SOREMP naps did not! This contradicts the apocryphal belief that brief REM naps are especially refreshing for narcoleptics. Thus the amount of sleep, not the type, seemed most important. This issue warrants further investigation as it relates to the pathophysiology of narcoleptic and EDS, and might be studied by selective REM versus NREM daytime nap deprivation. It also raises the issue of differences in response to napping between N+ versus N- patients.

Circadian Aspects of SOREMPs

It is well known that REM sleep propensity decreases with clock time from early morning to early evening in normals (Endo et al 1981). MSLT studies have not produced significant findings for circadian REM rhythms in narcoleptics during daytime. A trend, however, was found towards increased frequency of SOREMPs on the initial morning nap (Hishakawa et al 1976), in ad libitum napping; and for early naps on MSLT (Mitler et al 1979); as well as an increase in SONREMPs in the afternoon (Billiard 1976). Additionally, shorter non-SOREMP REM latencies were found in the morning and early afternoon than at night time (Hishakawa et al 1976), a finding similar to that with normals. This is

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consistent with postulations concerning the strength of circadian REM-temperature rhythms in morning versus night (Czeisler et al 1980). Finally, the REM/NREM architecture appears to be maintained during daytime naps of narcoleptics, with approximately 90-120 minute inter-REM latency after nap SOREMP (Hishakawa et al 1976).

Practical and Psychological Consequences of EDS in Narcolepsy

The ubiquitous disruption of lifestyles for patients with narcolepsy is remarkable, and is virtually impossible to appreciate for non-affected individuals. Normal people are accustomed to "fighting off" periods of sleepiness, and either recovering spontaneously or subsequent to a nap. We have all experienced intense sleepiness, but not on an indefinite basis.

Narcoleptics, however, can not successfully cope with a lifelong condition where the anticipation of recovery from sleepiness does not exist. The persistent drowsiness results in the loss of motivation and interest, reduced cognitive and ego functioning in virtually all areas, and subsequent impaired performance. Both autonomous ego functions, such as alertness, memory, synthetic and analytic processes, and motoric manipulations; and secondary ego functions of judgment, object relations, and the control of affects and impulses are undermined. Consequently, one sees chronic social difficulty, often beginning with unsatisfactory

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academic performance and impaired learning, inability to succeed and advance at work, reduced and problematical relations with peers, and difficult familial relations. Work performance is impaired for both mechanical, rote tasks that are soporific for the narcoleptic, and for complex tasks that require alertness and judgement. The result of these impairments in function often has a negative impact on socio-economic status.

Limitations for Narcoleptics Secondary to EDS

Broughton and Ghamen (1976) report the following statistics concerning the incidence of work, driving, personality, and interpersonal difficulties in narcolepsy, from responses to questionaire in 46 patients. Impaired job performance was reported by 61%, with 18% having experienced dismissal as a result of EDS. Sleeping when driving that resulted in accidents was reported by 40%. Five percent of these patients have given up driving altogether, whereas most others were taking stimulant medication. Memory was felt to be impaired by 48%.

Schwartz (1972) found that 67% of his sample felt they had undergone undesirable personality changes due to their illness. Depression, suicidal ideation, and mood swings were most frequently reported. A number of male patients reported the development of impotence due to maintenance on tricyclic medication.

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Auxillary Symptomatology

Cataplexy

Perhaps the most striking feature behaviorally of the narcolepsy-cataplexy syndrome is the cataplectic attack. Gelineau (1880) described the relevance of emotions in sleep attacks, Lowenfeld (1902) included the description of cataplexy as part of the syndrome, and Adie (1926) began the usage of the term cataplexy to describe the symptom. Although this symptom has since been carefully investigated, no known pathophysiology exists, although a theory does exist (Scrima, 1981; Pompeiano 1976).

Clinical Description

Cataplexy is described by Mitler (1976) as "flacid paralysis of the flexor and extensor muscles in the presence of EEG wakefulness and awareness of surroundings." Within this framework, great variance exists regarding severity and extent of cataplectic attacks. This spontaneously reversible phenomena ranges from virtual total loss of movement in voluntary muscles, including reflex reactions in voluntary groups, to partial involvement of certain muscle groups, and finally, in the least disabling condition, to brief sensations of weakness in different body areas (Guillemenault 1976).

Eye movements are commonly unaffected during these episodes, although vision may become blurred. The most commonly effected

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muscle groups include neck, jaw and knee areas, and limited attacks display their manifestations in a slack jaw, lolling or sagging head, and weakness in the knees with some involuntary bending of the joints. More severe attacks may lead to complete loss of tone and collapse. Other than injury secondary to the attack, such as a bruise after collapse, no after effects of an attack are recognized (Guilleminault 1974).

Experiences most frequently cited as cataplectic "triggers" include strong emotion, especially anger and laughter, and exertion. In a survey of 130 REM narcoleptics with cataplexy (Guilleminault 1976), emotion was the principle precipitator, with states such as tension, excitement, surprise, and active resistance of sleepiness also cited as substantial contributors. Spontaneous attacks without observable triggers were also frequently noted.

Cataplectic attacks varied greatly in duration, lasting from a few seconds to thirty minutes. The term "attack" has been used to describe these experiences much as in the case of irresistible sleepiness. However, as Dement (1976) has suggested regarding sleep attack onsets, patients usually have premonitory feelings before the onset of cataplexy, and thus attack may not be the most suitable term. The incidence and ontogenesis of cataplexy in narcoleptics is discussed elsewhere. The daily frequency of

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cataplexy has been found to be 1-4 episodes per day for most patients (69% of Guillemenault's group). Five percent each have more than four episodes per day or less than one week.

Cataplexy has been considered pathognomonic of narcolepsy, and generally does not occur until the development of EDS in the illness. The persistence of independent cataplexy is extremely rare and its diagnosis is usually due to improper follow-up, which, if undertaken, would normally result in the discovery of other symptoms in the narcoleptic tetrad.

Many patients are able to successfully inhibit or reduce cataplectic symptoms by avoidance of stress and emotionally arousing experiences, especially those that involve laughter and anger. Unfortunately, coping with cataplexy is merely one of several tasks for the narcoleptic. The skills and behavioral changes involved are discussed in a subsequent section.

Guillemenault, in agreement with Passouant and Billiard (1976) found no relationship between severity of EDS and cataplexy. In a 24 patient PSG study of REM narcoleptics (1976), he found 20% of the cataplectic attacks occurred when the patients reported being sleepy (a score of 5-7 on the SSS). Thirty-three percent of attacks occurred when patients felt fully alert, which undermines the belief that lowered alertness is necessary for cataplectic attack. Attacks in patients who had more than four

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attacks daily tended to last longer. Age and sex were not related to symptom severity or frequency.

PSG Aspects of Cataplexy

Rechtschaffen et al (1963) were the first to connect cataplexy with the EMG suppression that occurs during REM sleep. The PSG study of cataplexy is of interest for a variety of reasons. The relationship between EDS, microsleeps, and the occurrence of cataplexy bears on the idea advanced by Hishakawa (1976) that cataplexy involves decreased alertness leading to REM sleep in conjunction with sleep paralysis. Although Guillemenault reports states of alertness prior to many cataplectic attacks, in PSG recordings he found 90% of the EEGs produced by patients showed short periods of recording that were indistinguishable from REM sleep (in 23 patients with 63 recorded episodes). Hishakawa (1976) states that "reports describing an EEG pattern of the drowsy state during cataplexy probably represent REM sleep with sleep paralysis." This comment is unclear in light of Hishakawa's differentiation of SOREMPS from sleep paralysis and his contention that short latency SOREMPS are often really sleep paralysis with accompanying hallucinations (1976) and wakeful consciousness.

Guillemenault found that a number of these patients (7) in his study proceeded from cataplexy directly into REM sleep, and

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several developed sleep paralysis and auditory and visual hallucinations when episodes lasted several minutes, a finding confirmed by Ribstein (1976). Hishakawa has posited a reverse phenomena (1976), namely that hypnagogic hallucinations produce fear in patients and thus trigger cataplectic attack (Hishakawa and Kaneo, 1965; Hishakawa 1976). Of course the distinction between the occurrence of REM sleep versus hallucinations and sleep paralysis subsequent to cataplexy is a fine one, and even with PSG monitoring it is not easy or often possible to make this distinction with certainty. In fact, when cataplexy is accompanied by a REM-like EEG, then its differentiation from sleep paralysis becomes difficult. In general, cataplexy has been commonly associated with a predominately waking EEG with only brief periods of REM like EEG (Guillemenault 1974; 1976). Whereas sleep paralysis has a predominantly REM-like or stage 1 EEG. Both conditions occur with tonic EMG suppression. Thus the EEG may be useful in distinguishing these states, whereas the criteria of conscious awareness is helpful in differentiating short latency SOREMPS from sleep paralysis.

Guillemenault (1976) found EMG recordings proved consistent with previous clinical description of muscle inhibition. He found no relationship between length of attack and degree of severity or number of muscle groups involved (1974). When limbs were involved, normal jerk reflexes, including the H reflex, were

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abolished or diminished. A drop in H reflex responsiveness several seconds prior to an attack was noted to be a reliable predictor of an impending episode. EEG recordings confirmed that extra-ocular control remained unaffected, as is the case during REM sleep.

Additionally, Guillemenault comments on the powerful correlation between SOREMPs and cataplexy in narcolepsy. One hundred percent of 142 patients that complained of EDS and cataplexy had at least one SOREMP on 24 hour continuous PSG (see diagnosis section), whereas only 21% of EDS only patients had a SOREMP. Although not all patients with EDS and a SOREMP on PSG have cataplexy both Guillemenault and Passouant and Billard indicate that it is almost certain they will eventually develop the symptom.

Hypnagogic Hallucinations

Whereas the association between narcolepsy, cataplexy, and sleepiness was established prior to 1900, hypnagogic hallucinations were not associated with the syndrome until 1927 (Lhermite and Tournay). The symptom can be regarded as transitional in terms of its relations to REM versus wakefulness, normal versus pathological sleep onset, awareness versus altered state, and psychiatric versus neurological condition (Ribstein 1976).

The incidence of hypnagogic hallucinations in narcoleptics has

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been found to be about 50%. The hallucination typically occurs just prior to sleep onset when in a reclining, comfortable position, although odd postural positions may facilitate its occurrence (Hishakawa 1965). Diurnal drowsiness may develop into daytime hallucinations in narcoleptics, as may extended episodes of cataplexy, fatigue, and emotion (Passouant et al 1968; Guillemenault 1976). Sleep paralysis often accompanies the hallucination, rendering it very similar to SOREMPs (Hishakawa et al 1965), although awareness is routinely maintained during these episodes, unlike a true paradoxical "sleep". The hallucinations are typically followed by sleep, especially what appears to be SOREMPs.

Hypnagogic hallucinations are almost invariably visual and colorful, ordinarily monosensory, and tend to vary greatly concerning content, personal involvement, feeling tone, and awareness of surroundings and sense of reality. Most contain images of people or animals in proximate relation to the patient. Somatosensory experiences of rubbing, itching, and other parathesias are common, and reminiscent of the Issakower phenomena. Involvement ranges from indifference and causal observation, with intact awareness of the phenomena, to complete, terrifying absorption. Most frequently hallucinations are experienced as bothersome and threatening. Patients will often take protective measures such as getting a dog or keeping a

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weapon at bedside (Passouant and Billiard 1976) in order to feel more secure, although Ribstein notes (1976) that "what is striking is that patients act in the real world in order to prevent an imaginary phenomena from occurring." Some patients dread retiring in anticipation of an hallucination.

Polysomnographic Aspects

Most authors (Ribstein 1976) view hypnogogic hallucinations as part of the "REM aspect" of narcolepsy, as opposed to the "NREM" elements of EDS and disturbed nocturnal sleep. When occurring with sleep paralysis, this state becomes almost indistinguishable from the SOREMP. Thus Ribstein agrees with Hishakawa that level of consciousness and awareness are the only distinguishing factors between paralysis with hallucinations, and SOREMPs; and that this determination relies on subjective patient report. The hallucination at sleep onset exhibits the drowsiness and interstate transition of descending stage I, with discontinuous contact with the external world, variable presence of alpha and low voltage mixed, dream like imagery, and when occurring with sleep paralysis possesses tonic EMG suppression. Eye movement may occur in either case. Cataplexy frequently presents with a similar EEG, however normal awareness is routinely maintained and drowsiness is not a necessary feature. Some elements of similarity exist, naturally, to the sleep onset mentation as

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described by Vogel (1978), although the terrifying quality and experience of being awake differentiate hypnogogic hallucinations from typical sleep onset mentation.

The occurrence of hypnogogic hallucinations in normals has been investigated (Dement and Kleitman 1957; Foulkes and Vogel 1965), and has been described as a gradual withdrawal of cathexis from the external world with increased imaginal thinking during increasing drowsiness. Their occurrence in stage I is consistent with the view of stage 1 as transitional and related in its nature to REM (similar EEG), wakefulness (some alpha and maintenance of contact with world), and NREM (loss of contact, no EMG suppression). In narcoleptics, an interesting distinction between hallucinations and SOREMPs is the anguish that accompanies the former, indicating that the mechanisms posited to preserve sleep from dream arousal are not yet engaged, (Liddon 1967); and that the "REM" nature of the hallucinations may make them more bizarre and threatening.

Sleep Paralysis

Sleep paralysis, first described by Mitchell in relation to normals (1876), and in narcoleptics by Adie (1926), presents as the inhibition of voluntary muscular-skeletal movements during either hypnogogic and, less commonly, hypnopompic periods. Its postdormital occurrence is far more common than that of

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hallucinations. Within the narcoleptic syndrome, sleep paralysis may develop during a diurnal cataplectic attack, although its differentiation from cataplexy in these instances, even with PSG, is problematical. The occurrence of sleep paralysis is facilitated by a comfortable reclining position, unlike hypnogogic hallucinations, where the opposite appears true (Hishakawa et al 1965).

Sleep paralysis is experienced as paralysis, that is an inability to effect voluntary movement. It is not experienced as an anesthesia. Speech is often impaired, unlike cataplexy where impairment in this area tends to be partial, if at all. As in cataplexy, awareness routinely remains intact. Post episodic recall is unaffected unless the paralysis is accompanied by a hallucination. Initial episodes are generally frightening, whereas eventual acclimation may occur after repeated episodes, and sleep paralysis is generally better tolerated than are hallucinations or cataplexy. Control may be developed by changes in postural position before sleep onset (Hishakawa 1976). Like cataplexy, sleep paralysis ends spontaneously without sequelae.

Although associated with narcolepsy, sleep paralysis is not uncommon in normals, and its incidence may be greater than is known, inasmuch as it is a state which does not necessitate medical attention. Independent sleep paralysis has been found by Goode (1962), Sours (1963), and Hishakawa (1976) at rates of 5%

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or less among patients presenting to sleep clinics. Its incidence and evolution in narcolepsy is described elsewhere. The frequency of sleep paralysis in narcoleptics varies from daily to monthly. Hallucinations have consistently been associated with sleep paralysis in narcoleptics at a rate of 50% (Sours 1963; Hishakawa 1976).

The differentiation of cataplexy and sleep paralysis is made difficult due to similar tonic muscle suppression with intact awareness and the occasional proximal occurrence of both states. However, cataplexy is clearly associated with emotional triggers, unlike sleep paralysis for which no trigger or facilitator is known, other than drowsiness and recumbancy. Sleep paralysis additionally is more closely associated with sleep onset and hallucinations. PSG analysis of these states show generally similar EEG patterns, although sleep paralysis tends to be more likely to show sawtooth waves and eye movements. Independent sleep paralysis is far more common than is independent cataplexy, a rare condition, whereas the incidence of cataplexy in narcolepsy is greater.

Evolution of Narcolepsy

Narcolepsy is an illness without a fixed and consistent pattern of development, although several pronounced tendencies in its evolution are commonly reported. Foremost is the pattern

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concerning the chronological relationship amongst symptom onset and development. Although development of auxillary symptoms tends to be unpredictable, virtually 90% of narcoleptic patients report EDS as the initial observable complaint. This is reported in a longitudinal polygraphic study by Passouant and Billiard (1976) in which they monitored 50 narcoleptic patients with confirmed PSG SOREMPs. Additonal patterns become less reliable as one investigates further.

Symptom Onset and Precipitating Factors

Several authors have attributed the onset of the illness as associated with periods of significant stress and changes in sleep schedules (Kripke 1976; Passouant and Billiard 1976). Fifty percent of a group of 50 narcoleptics studied by Passouant and Billiard clearly had an initial onset of EDS associated with factors such as familial death, severe trauma, marital conflict, and especially sleep schedule disruption, although it must be noted that this was not objectively varified in any cases by PSG and is based on patient report. The possibility of already existing symptoms coming to attention during periods of stress must be considered when no objective findings are available.

Passouant and Billiard noted that patients reported sleep schedule alterations of several varieties: Either situations where life and job alterations led to increased activity that

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affected sleep schedules; changes in work hours, often to evening work; or sudden long periods of inactivity that led to daytime napping habits. Several patients developed the illness after army induction where they were subject to extreme idleness, and a recent SWDC patient suffered a substantial exacerbation of a pre-existing condition subsequent to incarceration and reduced mobility due to an arthritic knee. Surprisingly, only five percent of Passouant and Billiard's patients had onsets associated with medical illness. Naturally, the presence of contributing or triggering factors does not address the issue of preexisting susceptibility, other than to note that clearly most people do not develop narcolepsy under the circumstances described above.

Chronology of Onset

Narcolepsy has demonstrated a considerable range of onset, from 5-45 years old in subjects studied by Passouant. Sixty percent of his subjects developed initial symptoms between 15 and 30 years of age, with six percent below age 6 and eight percent over age forty. Kessler (1976) reports a bimodal distribution of vulnerability, with the highest peak between ages 16-20, and a second peak between 26-30. Sours (1963) also found a bimodal distribution with the second peak between 31-35. There was no relationship between the eventual severity of the disorder and age

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of initial symptom onset, and Cadihac et al (1963) have reported extreme symptoms in a patient who first developed the illness at 42.

Temporal Relation of Symptoms

Symptoms in the tetrad tend to develop independently, often with substantial intervening periods of time. Ninety percent of patients develop EDS initially, either alone or in conjunction with an auxillary symptom. Eight percent were found to develop cataplexy first, a finding of both Passouant and Billiard and Guillemenuat (1976) in 150 patients; in 2% of the group the initial symptom was hypnogogic hallucinations. Guillemenault found 23% of the group developed both EDS and cataplexy simultaneously as the initial symptom. Passouant and Billiard report no instances in their studies of sleep paralysis as the initial solitary symptom, an interesting finding given the reported prevalence of this symptom in normals (Liddon 1967; Dement et al 1972). Cataplexy occurs on the average 5-6 years after the onset of EDS, and at an mean age of 25 (Guillemenault 1976), and is routinely the second or third symptom to develop. The fourth symptom was restricted to sleep paralysis or hypnagogic hallucinations, and on average occurred 9 years after EDS onset (Passouant and Billiard 1976).

Incidence, Persistence, Severity, Treatment,

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and Course of Symptoms

EDS is unique among symptoms of the tetrad in that its persistence is lifelong (Yoss and Daly, 1960; Passouant 1969) with no reported complete spontaneous or therapeutic remissions within a sample of 50 patients reported by Passouant and Billiard (1976). No patients in the present REM deprivation study have experienced total remission of this symptom. EDS is the cardinal symptom of narcolepsy and is invariably present at some time during the illness, and therefore its incidence may be considered to be 100%. Its ultimate presence is required to make the diagnosis. Temporary or permanent exacerbations and partial remissions are not unknown. Zarcone (1973) has reported amelioration occurring in some patients in middle age, and Passouant and Billiard, in their longitudinal study, have gathered both objective PSG and self report data that indicate considerable fluctuations in this symptom to be commonplace.

Thirty of these fifty subjects reported a marked exacerbation of EDS over time. Other symptoms may exacerbate simultaneously, although EDS generally presents with the most significant exacerbation according to the authors. This exacerbation within this group generally occurred about 8-9 years after EDS onset. Few patients in the Passouant and Billiard study reported significant worsening of EDS proximate to its original onset.

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The duration of increased severity of EDS was reported as variable. The authors report but do not substantiate that temperature, seasonal, and weather changes may cause exacerbation. Seven of thirty patients directly attributed EDS exacerbations to life stressors and illness, including surgery, pregnancy, divorce, and familial death. Twelve patients were recorded in this study in a longitudinal design with an average of 5 years between recordings. Three reported and displayed significant EDS exacerbation as measured by napping, with a mean increase of 3 1/2 hours daytime TST. Four showed substantial EDS amelioration with two hours less nap time, whereas five showed no symptom change. The authors conclude that ameliorations and exacerbations of this symptom are frequent. In several patients who displayed severe exacerbations, the course has led to the virtual loss of circadian sleep-wake cycling with upwards of 15 hours TST distributed throughout the 24 hour period.

The management and improvement of EDS with pharmacotherapy has been reported by several authors, including Parkes (1976) and Guilleminault et al (1974). Treatment using types of amphetamine and methylphenidate produce good therapeutic response in about 1/3 of patients, some improvement in 1/3, and little response in the final 1/3 (Parkes, 1976). CNS stimulant treatment in conjunction with tricyclic medications, which are effective in treating the REM auxiliary symptoms, has resulted in some

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patients in management of all symptoms.

The incidence of cataplexy with narcolepsy depends on definition, that is, what is required to make the diagnosis of narcolepsy. Although the eventual manifestation of cataplexy is required by several authors, such as Scrima (1981), the Diagnostic Classification of Sleep and Arousal Disorders does not, as Scrima asserts, "reserve the term of narcolepsy for only those individuals with both the narcolepsy and cataplexy syndrome." Rather, the DCSAD refers to "a history of cataplexy as a characteristic and unique feature of narcolepsy," and implies the possibility of narcolepsy that is based on the irresistibility of sleep attacks and the presence of SOREMPs without cataplexy. Many studies, especially those without PSG confirmation, have used as subjects only those patients with cataplexy, and thus in these studies the incidence is 100%. Yoss and Daly (1960) and Sours (1963) found only 66% of large samples to have cataplexy. However, these were not confirmed REM narcoleptics. Guilleminault et al (1974) found 96% of PSG confirmed narcoleptics had cataplexy, and only 5% of 150 pts in the 1976 study group (8 pts) did not have cataplexy (Guilleminault 1976). These patients may develop the symptom at a later date, indicating that the incidence of cataplexy in confirmed REM narcoleptics is almost 100%. Studies that show substantially lower incidence have probably included patients with EDS with

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other etiologies, or N- patients who not only have not yet developed cataplexy, but are at a pre-SOREMP stage.

No clear pattern of exacerbation and remission for cataplexy exists. Scrima asserts a tendency towards remission in old age, without supporting data (1981). Both he and Guillemenault (1976) indicate that improved emotional control by patients may reduce the frequency and severity of attacks over a period of years. A pattern of unpredictable exacerbation and remission is reported for many patients by Passouant and Billiard (1976) and Guillemenault (1976). Twenty percent of the patients studied by Passouant and Billiard reported a spontaneous remission. Sixteen percent (8 patients) in this group had severe cataplexy at symptom onset, whereas 40% developed severe symptoms later, ususally about 6 years subsequent to cataplexy onset. Severe cataplexy was never developed by 30% of these patients (15 patients), and for 25% of those reviewed by Guillemenault (37 patients). Guillemenault found no relationship between age, sex, and symptom severity, nor between severity of EDS and cataplexy. Remission in 50% of the patients in the Passouant and Billiad study was associated with medication.

The incidence of hypnogogic hallucinations is reported at 50% by Passouant and Billiard (1976), a figure consistent with findings of Dement et al (1966) in 34 patients, and Hishakawa et al (1965) in 75 patients. A tendency towards remissions is reported by

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Ribstein (1976) as patients approach old age, and Passouant and Billiard report remission in 38% of their group. Additionally, 40% of this group displayed remission secondary to medication.

The incidence of sleep paralysis is reported by Passouant and Billiard (1976) as 48% in their study. Hishakawa (1976) found an incidence of 57% (58 patients). Both groups utilized only confirmed REM narcoleptics. Earlier non-PSG studies (Yoss and Daly, 1957; Sours 1963) reported far lower incidence, again undoubtedly due to the inclusion of patients with EDS without cataplexy. A 50% remission with tricyclics was reported by Passouant and Billiard, as well as a 25% spontaneous remission. They found cataplexy to be most responsive to pharmacological treatment, with 80% of patients responding. Sleep paralysis was next in responsivity to treatment, with 50% of patients improving with pharmacotherapy. Hallucinations were less apt to respond to treatment, at a rate of 40%. Reviews of the efficacy of tricyclics in controlling auxillary symptoms (Cadhilac, 1976; Takahashi, 1976) have stressed the potent REM suppressant effects of these agents, and have described superior management of these symptoms when compared with EDS and DNS.

Passouant and Billiard report the incidence of disturbed nocturnal sleep at 80%, as compared with a report by Montplaisir of 95% for REM narcoleptics (19 patients) who complained of

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disturbed sleep (Montplaisir 1976). Sixty percent in the Montplaisir study felt it to be the major symptom of their illness. Neither authors report spontaneous remission of this facet of narcolepsy, nor any relationship between severity of daytime EDS and DNS, although no comparison in either study between nighttime number and length of arousals and daytime sleep time is made. This finding may be considered interesting, inasmuch as these "NREM" aspects of narcolepsy- EDS and disturbed nocturnal sleep- have been considered to be related (Suzuki 1966; Takahashi 1976) in their manifestation of a disturbance of sleep-wake circadian rhythm.

Generally, no parallel course of symptom development in narcolepsy has been uncovered, and often one symptom may develop or exacerbate simultaneously with a remission in another. In fact, only 15% (7 patients) had all four tetrad symptoms simultaneously in the Passouant and Billiard study. The illness may be said to involve chronic sleepiness with the possibility of some moderate, partial remissions. Auxillary symptoms are more subject to remissions and exacerbations, and more responsive to medication.

COPING MECHANISMS

The task of adaptation to persistent, disabling symptoms has been undertaken by narcoleptic patients in a variety of ways. These

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mechanisms are aimed, in particular, at the symptoms of constant sleepiness, irresistible napping, and cataplexy. Although only limited success is reported by many patients in ameliorating these symptoms, substantial changes in life style are reported by patients in an effort to better manage their disease.

In attempting to control EDS, Passouant and Billiard (1976) have reported that within a sample of 50 patients, more than 50% had adopted new living habits to cope with the illness. This included habitual napping at least twice daily (21 patients), 6 patients who had changed career in order to work outdoors, 2 patients who had shifted to nighttime work in combination with daytime work, and 3 patients who had altered their diet. Broughton and Ghamen (1976) report patients who have given up driving, drinking, and smoking, and purposely increased obsessional thinking styles in order to cope with lagging attention, memory, and concentration. Murray (1974) reports patients who deal with drowsiness during driving by leaving all windows open, the radio on full blast, and who bang their head or pinch themselves. A patient in this study reported intentionally bumping a car in front of him during a traffic jam in order to alert himself. Many patients have become aware of the timing of their sleepy periods, and thus arrange to complete all important chores and business during those periods of habitual maximum alertness.

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Coping mechanisms for cataplexy are generally more successful, and many patients have learned to prevent the attacks. The usual method involves avoidance of triggering emotions and circumstances, such as eschewing arguments and humorous situations. Unfortunately, often the result is chronic emotional distancing and interpersonal withdrawal.

Finally, coping with sleep paralysis may be achieved by beginning sleep onset in an uncomfortable position. Hypnagogic hallucinations may be toned down in their frightening aspects for some patients by the acquisition of protections, either a dog, or a weapon.

DIAGNOSIS IN NARCOLEPSY

The purpose of a diagnosis is primarily to allow for and aid in the management and treatment of an illness. A stated aim of this study is to contribute to improvement in the combined sensitivity and specificity of diagnosis for narcolepsy, especially concerning those prodromal cases or instances of diagnostic unclarity. Issues regarding the psychological, behavioral, and medical implications of correct and timely diagnosis are discussed in the introduction to this chapter.

It should be noted that concerning timely diagnosis and treatment, although current therapies for management of EDS are moderately satisfactory and efficacious at best, those treatments for the auxillary symptoms of narcolepsy provide substantial relief and remission. Some narcoleptics find pharmacotherapy for EDS to be substantially helpful as well, especially when intervention allows for the maintenance of a career. Thus proper and prompt diagnosis, from the medical perspective, is important, particularly when one is considering chronic maintenance on analeptic medication.

In those instances when a state of absent or misdiagnosis exists, especially when in place of correct diagnosis a psychopathological etiology is promulgated, here one clearly sees a potentially deleterious effect for the narcoleptic patient.

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Statistics are not available for misdiagnosis of this sort, although a number of case reports in the literature describe the misdiagnosis of schizophrenia within the narcoleptic patient group.

There is, as well, the issue raised by Zarcone and Fuchs (1976) that a number of authors, far from "misdiagnosing" narcolepsy as a psychogenic disorder, view the illness in general as stemming from a psychopathological or psychophysiological etiology (c.f. Zarcone and Fuchs for a review of these papers). Although this is a separate issue pertaining to the pathophysiology and etiology of narcolepsy, it is clearly related to the instance of misdiagnosis, for the syndrome of narcolepsy- sleepiness, hallucinations, and paralytic and soporific "attacks" - have the appearance of psychically motivated phenomena. This is further confounded by the exacerbation or development of other psychological symptomatology secondary to the illness itself (Zarcone and Fuchs 1976).

Shapiro and Spitz have described the problems in the differential diagnosis of narcolepsy and schizophrenia, and related a case wherein a patient was considered psychotic based on her report of vivid hypnogogic hallucinations (1976). "The experience of listening to a narcoleptic patient describe vivid hypnogogic hallucinationaion is striking, since he may recount his

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interactions with people and objects in much the same way a psychotic patient describes hallucinated experiences." Zarcone and Fuchs describe several cases of misdiagnosis of narcolepsy as schizophrenic disorders, in one instance due to depression secondary to the narcolepsy, and in a second due to the abuse of analeptic medication prescribed for the narcolepsy.

Zarcone (1973) has noted similarities between narcolepsy and schizophrenia, such as age of onset, genetic contributions, terrifying hallucination, and the absence of known lesions or pathophysiology. Additionally, drugs influencing the availability of neurotransmitters are used to ameliorate the symptoms. During sleep states, narcoleptic cognitive functioning can appear loose and disorganized (Dement 1976). Reported findings that narcoleptics (Spielman) and schizophrenics (Zarcone et al 1975) show attenuated REM rebound after RD are also noted. However, Zarcone and Fuchs in a study of 130 narcoleptic patients at the Stanford S.D.C. did not find any significant increase in schizophrenia or psychotic states when compared with the general population. Only five patients were found to be psychotic, all secondary to drug use. In a study of 20 narcolepsy-cataplexy patients, Roy (1976) found only one to present with any significant thought disorder. Although a substantial number of psychiatric conditions were present, it was unclear if these were secondary to the narcolepsy. A further discussion of narcolepsy

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and psychopathology is to be found in the pathophysiology section.

The issue of absent or no diagnosis is not directly related to the task of this study. However, due to the type of symptoms involved in the illness, especially EDS when present alone, it should be reiterated that this complaint is ignored or minimized by relatives and physicians due to the ready availability of socio-psychological explanations; and the complaint is resisted by the patient for similar reasons. Pincus and Tucker have stated that "these patients often fall asleep under boring social circumstances conducive to sleep. This is often misunderstood and the patients are considered lazy, impolite, neurotic, and worse" (1974). In fact, EDS secondary to HSA is more likely to come to the attention of a physician with alacrity than that of EDS secondary to narcolepsy (Dement et al 1978).

As stated in the purpose and aims, current methods for the differential diagnosis of narcolepsy have several limitations. The convention for using the occurrence of SOREMPs for diagnostic confirmations has not been systematically studied (Spielman, unpublished paper). Therefore, a summary of the different diagnostic possibilities is useful.

The Case of the Narcoleptic with Unequivocal History and a Positive PSG Finding

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The diagnosis of narcolepsy is made by the positive history of symptoms, particularly cataplexy in conjunction with EDS, and confirmed by the finding of SOREMP on nocturnal PSG or on at least two of five nap opportunities on MSLT (Mitler et al 1979). Guillemenault and Dement (1977) suggest that the PSG/MSLT is unnecessary given an unequivocal history of cataplexy with EDS. However, when chronic analeptic maintenance is contemplated, confirmation is desirable. Mitler (1982) reports that in these cases, 95% meet criteria of two SOREMPs on MSLT, although "some narcoleptics will produce false negative results" (5%). Thus the sensitivity of this measure- its ability to correctly identify a case when the illness is present- is virtually 100% when EDS and cataplexy are present, and here a positive finding on MSLT assures the diagnosis. Unfortunately, it still remains in these cases to rule out other complications, especially HSA which frequently occurs in association with narcolepsy (Dement 1976; Guillemenault and Dement 1977) in males. Thus nocturnal PSG is recommended as well to in order to rule out HSA. Unfortunately, this test by itself is frequently insufficient for diagnosing narcolepsy, since the likelihood of SOREMP on nocturnal PSG is less than 50%.

The case of the narcolepsy-cataplexy patient is the most straightforward possibility. The available tests at present are not especially useful in equivocal cases. This is due to the

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fact that a) a negative finding for SOREMP on PSG or MSLT is essentially uninformative when EDS is present, since narcoleptics, EDS patients, and normals all commonly have NREM sleep onsets. No finding concerning SOREMPs rules out narcolepsy when a history and finding of EDS is present; and b) a positive finding for SOREMP in conjunction with an equivocal history does not result in diagnostic certainty. Only when a negative finding for EDS on MSLT exists can narcolepsy may be ruled out.

The Narcoleptic Patient with a Negative finding for SOREMP on MSLT

It must be remembered that SOREMPS are very highly correlated with cataplexy (almost 100%), more so than with the clinical diagnosis of narcolepsy (Dement 1976). However, since it is well known that cataplexy customarily develops subsequent to EDS and narcoleptic onset (mean time differential is 7 years--Passouant and Billiard 1976; also Sours 1963; Guilleminault 1976), many patients in the early phase of the illness do not present with cataplexy, SOREMPS, or any other "REM" symptomatology. Thus if it is desirous to correctly diagnose these patients as narcoleptics, the SOREMP test then becomes too rigorous a measure and results in poor sensitivity with regards to this population--that is, the test will frequently not confirm the illness in narcoleptics without cataplexy. Hishakawa et al (1976) thus

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found no nocturnal SOREMPs on two PSGs for four narcoleptics without auxillary symptoms. These patients are therefore often relegated to a diagnostic limbo such as idiopathic hypersomnia or independent narcolepsy (Spielman in unpublished paper).

The Non-narcoleptic EDS Patient with Negative PSG Finding for SOREMP

Similarly, in this instance, the aim of the diagnostic test would be to correctly rule out the diagnosis of narcolepsy in those cases that do not have it. However, the SOREMP test by itself is unable to differentiate between EDS patients with other etiologies and narcoleptics with only EDS, unless an unequivocal history is present. Since the sensitivity for the SOREMP test is low in the narcoleptic patients without cataplexy, a negative PSG for this EDS patient does not rule out the diagnosis of narcolepsy. This is so since negative PSG findings for SOREMPs are common for both groups. Mitler (1982) contends the MSLT can differentiate between narcoleptics and other EDS patients, but it is not clear if he includes among narcoleptics those patients without cataplexy.

When SOREMPs are used as a criteria, the specificity for this test is fairly high, with the exception of patients with obstructive HSA, who often produce SOREMPs on naps. The test does not label many EDS patients incorrectly as narcoleptic,

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although occasionally a false positive may occur. However, it must be remembered that the confidence that one places in this specificity is restricted by the low sensitivity of the SOREMP test - narcoleptics without SOREMPs may also be diagnosed as non-narcoleptic. Thus although the non-narcoleptic EDS patient is correctly identified by this criteria as non-narcoleptic, it is not possible to identify this patient merely from a negative finding. When EDS is utilized as a criteria, i.e. short MSLT latencies, many EDS patients as well all narcoleptics without cataplexy would receive a narcoleptic diagnosis, creating high sensitivity and low specificity. Most patients with obstructive HSA would be included in this grouping (Dement et al 1978). Thus at present, in EDS cases without cataplexy, diagnostic confidence is limited in instances where either positive or negative findings for SOREMP occur.

The Patient with Equivocal History and Positive SOREMP Finding

A final problem involves an inherent specificity difficulty for the SOREMP criteria- etiologies other than narcolepsy-cataplexy can produce SOREMP on PSG, thus given a case of a non-narcoleptic, the possibility exists that the SOREMP criteria will fail to identify these cases. Furthermore, as previously mentioned. diagnostic confidence in a positive finding with an equivocal history is poor, and can not confirm the diagnosis of narcolepsy.

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SOREMPs on naps may be found in patients with HSA (Kurtz et al 1971; Hartse et al 1980, 1982; Mitler et al 1982; Guillemenault et al 1976; Carskadon 1976); during the withdrawal from REM surpressant drugs (Hartmann 1979; Oswald and Thacore 1963); and in certain depressive syndromes (Durllich et al 1978). SOREMPs are found in normals during morning hours (Webb et al 1966; Hayden 1969; Endo et al 1974); and following partial REM and sleep deprivation, altered sleep-wake schedules and enforced ultradian sleep schedules, phase shifts, and free running conditions (Rechtschaffen and Dement 1968; Chernick and Mendels 1974; Carskadon and Dement 1975; Weitzman et al 1974; 1979). Thus the occurrence of a SOREMP on PSG or MSLT is far from pathognomonic of narcolepsy.

In conclusion, the SOREMP test is most useful with regards to its high sensitivity for narcoleptics with cataplexy, and high specificity in normals without any affective or sleep disorders. However, specificity becomes much poorer when considering a general sleep disorders population, as does sensitivity when considering incipient narcolepsy or EDS. Naturally, it is in these instances where the test should be most useful. Finally, diagnostic confidence is generally poor unless a positive finding coheres with a history of cataplexy.

Significance

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Although the appearance of SOREMPs within 15 minutes of sleep on 2 daytime MSLT naps or on nocturnal PSG is utilized to confirm the diagnosis of narcolepsy (Dement et al 1966; Mitler et al 1979), to my knowledge no systematic study of sensitivity, specificity, and diagnostic confidence for this test within a general sleep disorders population has been published. As mentioned, with the exception of the population of individuals with history of cataplexy, the sensitivity and specificity, as well as the diagnostic confidence, of this test remains unclear. Since non-narcoleptics, normals, and narcoleptics frequently have NREM sleep onsets, the lack of information as to how much a negative finding for SOREMP decreases the probability of narcolepsy is undesirable.

To demonstrate this, statistics developed at the SWDC for January 1975 through March 1979 may be useful. In a population of 218 EDS patients without obstructive sleep apnea, 71 were found to have a SOREMP upon initial PSG. A number of those patients with a negative finding (46%) had a second PSG, and some (27%) had four or more PSGs, resulting in 88 confirmed cases. Thus 17 patients had the diagnosis of narcolepsy confirmed by subsequent testing. Therefore the sensitivity for the SOREMP procedure for this group was $71/88$ or $.81$. However, of the remaining 130 patients, 42 had narcoleptic histories that were especially compelling, and were

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managed by staff as presumptive narcoleptics. If this group is considered to be part of the narcolepsy without cataplexy group, then the SOREMP test's sensitivity becomes $71/136=.52$. A low sensitivity of this order means that a negative finding can not rule out the diagnosis. Although sensitivity can be presumed to be higher for SOREMPs on MSLT, it is believed that this problem still persists, especially inasmuch as the inclusion of only 42 presumptive cases is probably conservative.

Additionally, utilizing MSLT criteria for SOREMPs may prove less specific. Although no measures for specificity have been reported in sleep disorders populations, the occurrence of SOREMPs in patients of other etiologies is widely reported, especially in patients with obstructive sleep apnea, where frequently DNS and arousals are associated with REM sleep resulting in chronic REM deprivation. Diagnostic confusion is especially possible⁷ in this group, inasmuch as HSA and narcolepsy in males frequently occur together (Guilleminault and Dement 1977; Dement et al 1978). A recent obstructive HSA patient at the SWDC had 5 SOREMPs on MSLT on two occasions, for both pre and open tracheostomy conditions. Yet this patient had no history of any of the auxillary symptoms of narcolepsy. Thus it was impossible to either confirm or rule out this diagnosis at the time. Although EDS is known to improve several weeks subsequent to tracheostomy in many patients, no study has been made on changes

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in SOREMP production for this group.

One difficulty in ascertaining the sensitivity, specificity and diagnostic confidence of the SOREMP in the literature is its application to different populations. Thus Roth et al (1969) can report a sensitivity of 50% for a single PSG, where as Wilson et al (1973) and Mitler et al (1979) can report sensitivities for MSLT of almost 100% in groups limited to narcoleptics with cataplexy. Most studies of HSA patients utilizing MSLT (Dement et al 1978; Roth et al 1982) do not report SOREMP data. Mitler et al recently reported SOREMP data for narcoleptics and HSA patients without narcolepsy for the Maintenance of Wakefulness Test (MWT), a measure similar to MSLT that produces lowered SOREMP frequencies in narcoleptics ($X=3.8$ for MSLT, 2.7 for MWT during five naps). HSA patients had a mean of 1.4 SOREMPs on MWT. Mitler does not report this statistic for the HSA group for MSLT, but presumably, if one extrapolates, it would reach the 2 SOREMP criteria for narcolepsy. They conclude that "this underscores the importance of evaluating patients for sleep apnea before daytime testing...failure to rule out sleep apnea could lead to erroneous and/or incomplete diagnosis of narcolepsy." Thus Mitler's earlier statement (1982) that the MSLT could differentiate between narcoleptics and other EDS patients appears to be qualified.

Pathophysiology

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Most remarkable is the absence of any accepted explanatory models for narcolepsy-cataplexy. Infact, so refractory to satisfactory understanding has this syndrome been found to be, that little research and even less speculation has occurred in recent years, since the International Symposium in 1975 and the publication of the text on narcolepsy in 1976.

Two principle models have been advanced regarding the illness. One model is based primarily on the orderly, circadian interdependence and relationship of types of sleep and sleep and wakefulness, which are felt to be disrupted in narcolepsy. Several factors have led to this notion. Disturbed nocturnal sleep is common in narcolepsy, and has been found to precede other manifestations of the disease in many patients (Dement and Rechtschaffen 1968). Although those authors who have dichotomized narcolepsy into its REM versus NREM aspects have considered DNS and EDS to be NREM manifestatsions, it is clear that DNS is related to the occurence of SOREMPs, as well as EDS. In HSA patients, the disturbance of nocturnal REM sleep by apneic arousal leads to SOREMPs during daytime, as well as EDS. When normal sleep is fragmented by imposed shortened sleep-wake cycles, SOREMPs are frequent, irrespective of sleep or REM deprivation. Napping during daytime, and irregular and modified sleep schedules have also been found to produce SOREMPs. In

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fact, it is clear that when a sleep onset occurs during a high REM sleep propensity point in the circadian rhythm, a SOREMP is not that unlikely. What is not clear is why this has become a chronic trait in narcoleptics.

One issue is whether the narcoleptic phenomena is a manifestation of a sort of chronic REM deprivation, for whatever reason, or of an alteration in rhythm relationships that allow for the mistimed expression of REM processes. Kripke (9176) has suggested that narcolepsy resembles infantile ultradian rhythm expression, wherein sleep, REM, and wakefulness is polyphasic, with stronger or less inhibited ultradian components. Thus ultradian REM rhythms are masked in normals by fully developed wakefulness system and a strong monophasic circadian sleep-wake cycle.

Dement has commented that narcoleptics do not appear REM deprived since they have normal, consistent amounts of REM sleep. REM nocturnal fractionals are in the normal range, as are 24-hour amounts of REM. Additionally, interREMP intervals and REMP length appear to be fairly normal. Yet the narcoleptic's response to RD- the unusually large number of awakenings required- might be interpreted as representative of REM deprived states, inasmuch as it is known that REM deprivation leads to increased REM awakenings on subsequent RD nights. The question then arises, with relevant reference to the RD literature for

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depression and schizophrenia, of whether it is possible to be chronically REM deprived without exhibiting the normal response to such deprivation, that is, rebound; and whether chronic REM deprivation can exist even when TREMT and REM percent appear normal. This issue has been raised not only for recognized pathophysiological states, but regarding individual differences in normals, by Cartwright in several articles. The question remains as to whether the ability to adjust to challenges to the REM system and its expression in a normal adaptive manner is a trait which is disturbed in some people.

In this regard, it should be noted that healthy responses to REM deprivation involves the ability to store REM sleep, that is to inhibit it, until a phase appropriate opportunity to express it occurs, at which point it is recovered. Thus Vogel has pointed out (1980) that when normals are REM deprived, they inhibit rebound until the latter part of the recovery night; they do not respond by having SOREMPs. The response of SOREMP to RD is not a normal, and presumably adaptive, mechanism. Finally, normals respond to REM interruption on the same night with adaptive flexibility. In the Fiss and Ellman study, it was clear that normals were able to alter their period length and REMP frequency as a response to a REM challenge. In narcolepsy, this flexibility appears to be lost, in terms of the inability to postpone REM sleep until the appropriate latter part of the

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nichthemeron, and in fact Spielman has found in a pilot study that several narcoleptics did not show normal rebound to deprivation. It remains unclear, of course, why REM sleep occurs in its preponderance during the latter part of the night, and why sleep onset is customarily a NREM onset.

One difficulty with the chronic REM sleep deprivation model of narcolepsy is that RD does not seem to increase the symptom severity, nor does it lead to auxiliary symptoms in other populations. It might be expected that if narcoleptics are unable to store REM sleep, and thus respond to REM fragmentation by dissociated REM expression during daytime, then these factors should increase with RD. Additionally, animal and human models of narcolepsy based on experimental or naturally occurring RD would imply that narcoleptic symptoms could be produced by suppression of normal REM expression. However, this has not been found to be the case (Mitler 1976).

The model of disturbed circadian rhythms, while explaining the occurrence of EDS and SOREMPs, requires the addition of a pathophysiological factor to explain auxiliary symptoms. It is the belief of this author that narcolepsy involves a trait defect affecting the REM system, that might be explained by a second model, that of competing neural systems of wakefulness, NREM, and REM sleep. It is believed that either or both the waking and

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NREM systems serve to inhibit the expression of REM at inappropriate times. Several authors, Pompeiano in particular, have described the interaction of a bulbospinal motor inhibitory pathway responsible for tonic REM atonia and cataplexy, with several arousing systems and REM inhibitory systems. Pompeiano has postulated the inhibition by the adrenergic locus coeruleus of tonic postsynaptic spinal motoneuron inhibition during REM and cataplexy; and the inhibition by the serotonergic dorsal raphe of phasic presynaptic spinal motoneuron inhibition which is associated with REM phasic events such as PGOs (1976). What is of interest here is the idea that both waking adrenergic and NREM serotonergic areas are thought to play a role in REM inhibition and containment. A model must therefore account for the notion of a weakened NREM system if this is postulated, and still explain NREM EDS.

The supposition that NREM systems were weak and allowed for REM expression at sleep onset has been suggested. However, the presence of EDS in the early phase of the illness before auxillary symptoms and SOREMPs develop; the occurrence of REM phenomena during daytime, when the NREM is weak in general and would not be expected to exert REM inhibition; and recent findings that narcoleptics do not tend to go into REM sleep following NREM awakenings, tend to mitigate against this theory.

The explanation of a weakened arousal system is perhaps more

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explanatory. It could be argued that nocturnal SOREMPs occur because arousal is low, and not due to weak NREM system. A weakened arousal system would then allow for NREM daytime sleepiness as well. Auxillary narcoleptic phenomena may be explained with this model as well. If it requires more awakenings and arousals to disengage narcoleptics from REM sleep, this also is consistent. However, it is of interest that drugs that bolster the arousal system ameliorate EDS, whereas it is the REM surpressant drugs that elevate auxillary symptoms. Another possibillity is a potentiation of the REM system, but not in manner as described by the hydraulic or pressure model. Thus it is not increased REM pressure leading to increased REM events that is involved, but rather a prepotent REM ultradian rhythm whose normal surpression is lacking.

Significance

From this brief review it is evident that current models are partially explanatory at best. This study is viewed as the first of several that will attempt to test the relative strength of NREM, REM, and arousal regarding REM expression in narcolepsy, as well as evaluate the relationship of REM sleep to EDS. Furthermore, the use of the RD challenge in terms of developing a diagnostic instrument will be investigated.

Pilot REM Deprivation Studies in Narcolepsy

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It is proposed that an RD measure may be more sensitive than the current SOREMP test for narcolepsy in the early phase of the illness (pre-cataplexy), and for those "so-called narcoleptics" who, according to Guillemenault, are not found to have cataplexy. To reiterate, virtually all "REM narcoleptics", that is narcoleptics with SOREMPs, have cataplexy as well, and vice versa (Guillemenault 1976). Thus, by implication, narcoleptics without cataplexy will not produce a SOREMP, or at best only very occasionally. In four studies of narcoleptics, Ach with over one hundred patients (Daniels 1934; Yoss and Daly, 1960; Roth 1957; Sours 1963), one-third of the narcoleptics did not present with cataplexy, and therefore, with SOREMPs. This would translate into a sensitivity for the SOREMP test of about .66.

The RD measure may as well aid in correctly ruling out narcolepsy by manifesting increased specificity versus the SOREMP test. In order to determine these two measures the test must be applied to known index cases of narcolepsy and known normal controls. Naturally, these measures will appear artificially high in a study where the population does not include the most equivocal of cases, and thus such a study is useful in determining the validity, not the usefulness, of the measure.

In a preliminary study using four male narcoleptics (Spielman et al 1977), and in the present study of narcoleptics and controls,

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equivocal cases were not examined. It was initially preferred to confirm the RD measure as able to discriminate between known narcoleptics with cataplexy and SOREMPs and normals without EDS. A further application in a subsequent study will examine this measure's usefulness in discriminating narcoleptics from other EDS patients and from narcoleptics without cataplexy and SOREMPs. Should this latter N- group appear narcoleptic on the RD measure, this would result in greater diagnostic confidence for the test.

It remains unclear whether the RD measure will prove more specific than the SOREMP test. It is anticipated that the RD measure will aid in correctly ruling out patients who have had SOREMPs secondary to phase shifts and depression, but it is unclear whether the measure will be specific for patients who are presumed to be REM deprived, such as obstructive HSA and drug withdrawal patients. Finally, it should be noted that sensitivity and specificity are interactional, and may be artificially set to meet certain aims. Thus in a life threatening illness where pharmacotherapy is indicated, correctly identifying those who have the illness is essential, perhaps at the expense of a number of false positive findings. Conversely, in an instance where an illness is not life threatening but its treatment is invasive or risky, an aim of a measure might be to correctly rule out the illness with certainty, at the expense of overlooking some cases. In the case of narcolepsy, increasing

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the specificity of the measure seems most desirable, so that a negative finding could be used with confidence to rule out the diagnosis. Thus a high criterion for the number of RD awakenings would be set. As a consequence, some patients with narcolepsy may not have their diagnosis confirmed.

A further consideration is that the specificity and sensitivity of a diagnostic test are influenced by the spectrum or range of illness, viz, in narcolepsy, when equivocal cases are used, sensitivity and specificity decrease (Ranschoff and Feinstein 1978; Serby et al 1981). Finally, Cascells et al (1978) have described the confusion in the interpretation of diagnostic findings in physicians with regards to predictive value or confidence, which refers to a test finding, and sensitivity and specificity, which refers to a case. The former refers to the likelihood of the condition given the positive finding, whereas the latter refers to the likelihood of getting the correct finding on a procedure given the existence of the condition.

In narcolepsy, the predictive value of a finding for diagnostic tests has not been examined, which is interesting given the great expense of polysomnography. The predictive value is not equal to the sensitivity or specificity. For the SOREMP test, this relationship is illustrated below. As an example, let us look at 20 sample cases containing 15 narcoleptics, only some of whom have cataplexy, and 5 EDS patients of other etiology. Findings

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for SOREMPs on MSLT for these patients were distributed as follows: 10 positive findings (8 narcoleptics, 2 EDS patients) and 10 negative findings (7 narcoleptics, 3 EDS patients). Thus the sensitivity of the test would be $8/15$ (53%); the specificity would be $3/5$ (60%); the diagnostic confidence given a positive finding is $8/10$ (80%); the diagnostic confidence given a negative finding is $3/10$ (30%). Although these are hypothetical numbers, this scenario is not improbable.

The pilot study of RD awakenings in narcoleptics by Spielman et al (1977) utilized 4 male narcoleptics with confirmed cataplexy and recorded SOREMPs. Similar criteria was used in this study as in the present study--the discontinuance of medications at least two weeks prior to the study and the absence of other sleep pathology. Subjects had 1 baseline night, 1-4 RD nights, and several recovery nights. Findings indicated that abnormally large numbers of awakenings were required to deprive subjects of REM sleep on the first night (mean=32.5 awakenings). Awakenings tended to cluster around REMPs, with one long REMP at the end of the night. When awakenings occurred, subjects tended to return to REM sleep quickly, rather than proceed to NREM sleep. The number of awakenings /hour sleep was significantly elevated when compared with data for normals as provided by David Foulkes.

Of further interest is a study by Nan'no et al (1970) that

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studied sleep paralysis in 8 normals and 8 narcoleptics. When narcoleptics were awakened from REM sleep during the first two REMPs, they returned to REM sleep within five minutes in 25 out of 32 instances. In only two instances following 42 awakenings from REM did normals do this. Both of these studies imply an inherent difficulty in disengaging REM sleep mechanisms when aroused in narcoleptics.

CHAPTER TWO

METHODOLOGY

Subjects

Two groups of subjects participated in this study, confirmed narcoleptics and normal controls. A third group of subjects, comprised of patients with reported hypersomnia without auxillary narcoleptic symptoms, participated to varying extents in the following protocol; however, this group of five subjects was found to be heterogeneous and further investigation and analysis of this data was discontinued.

The narcoleptic group was comprised of thirteen patients from the Sleep-Wake Disorders Center of Montefiore Medical Center, Bronx, New York. All research for this study was conducted at this facility. Within this group, there were 10 female narcoleptics and 3 males, with an age range of 32-57, and a mean age of 41. All narcoleptic patients had prior PSG or MSLT recordings on which the presence of either a nocturnal SOREMP or at least 2 MSLT SOREMPS had been verified. Subjects were disqualified if they were found to have hypersomnia sleep apnea, for which all narcoleptics were screened. One subject was disqualified for this reason. All narcoleptics had histories of significant pathological daytime sleepiness and unequivocal cataplexy, and had received from Sleep-Wake a diagnosis of Narcolepsy (DOES

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B.6), as described by the Diagnostic Classification of Sleep and Arousal Disorders (Roffwarg 1980).

The normal control group consisted of 4 male and 7 female subjects with an age range of 33-60, and a mean age of 39. All normal controls were interviewed and screened for sleep-wake complaints. Subject self-report and examination of sleep logs by the experimenter indicated no sleep or waking disorders within this group. Normal control subjects were group matched for age with the narcoleptics.

A certified clinical polysomnographer (Association of Sleep Disorders Center), A.J. Spielman, Ph.D., reviewed case records and interviewed all narcoleptic patients, in order to ensure that they conformed to the subject requirements of the study. All narcoleptics were selected from the narcoleptic case population of the Center. Normal subjects were recruited by advertisement and through staff at the Center, and were screened by the experimenter and Dr. Spielman.

Subject Information

All prospective subjects were informed in writing that the purpose of the study was to aid in understanding the sleep of normal persons and narcoleptics on a night when their sleep was disrupted by awakenings. Subjects were shown their sleeping quarters prior to the study, and the techniques of sleep

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physiology monitoring were explained. An in-depth description of the experimental protocol was verbally transmitted, in which the plan for two days of recording brief naps, and two nocturnal recordings was explained. Subjects were informed that their bedtime hours would be restricted to their average habitual sleep hours in the weeks prior to the study, as indicated by a sleep log that participants were requested to keep for two weeks prior to the study. Subjects were asked to maintain a regular sleep-wake schedule in the weeks prior to the procedure, and to refrain from excessive consumption of alcohol or caffeinated beverages. These procedures were outlined in a form mailed to subjects prior to participation.

All participants were informed of the drug-free conditions of the study, and told that they would be disqualified if levels of prohibited drugs were detected in urinalysis. Patients and subjects taking medication prior to the study would discontinue tricyclic antidepressants or MAIO inhibitors four weeks prior to participation, and analeptics, anxiolytics, sedative-hypnotics, or other non-essential pharmacological agents were to be discontinued at least two weeks prior to the initial recording. All subjects complied with this restriction. Subjects who customarily consumed large quantities of coffee or alcohol were asked to cut down, or else were excluded from the study.

Subjects were informed that they would be able to sleep

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undisturbed on the initial night, and that they could expect to be awakened from sleep an unspecified number of times on the second night. Subjects, especially narcoleptics, were told that no therapeutic benefit from this study could be anticipated, and that in fact they might feel some excessive sleepiness for a day or so subsequent to the procedure. Subjects were told that no deleterious effects from the procedure were anticipated.

Subjects were required to sign an informed consent and were assured of confidentiality regarding their participation. All subjects were told that it was advisable that they either return to the Center or phone in order to be informed of the findings concerning their participation in the study. Either Dr. Spielman or Mr. Adler would then describe to them the basic characteristics of their sleep at night, the degree, if any, of their daytime sleepiness, and their individual response to the awakening procedure.

Plan of Study

The basic plan for the study consisted of an adaptation night, during which screening, when necessary, was performed for sleep apnea; a REM deprivation night on the subsequent night; and a post-MSLT on the day following the RD night. Additionally, a second MSLT (pre-MSLT), administered at least 7 days prior to or subsequent to the PSG nights, was performed. All subjects

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participated in the two PSG nights, and 9 normal controls and 11 narcoleptics participated in all four recordings. Procedures for these recordings are described in detail in this chapter.

Subjects were told to maintain a daily record of their sleep-wake habits for two weeks prior to the study, as well as during its course, utilizing a sleep log developed by the SWDC. The sleep log provided for daily information as to bed time (lights out); estimated sleep latency and final arousal for the night; intervening awakenings and lights on periods; daytime napping and daytime sleepiness; estimated TST for the 24 hour period; and number of nocturnal arousals. The timing and duration of the experimental sleep period was determined by averaging nocturnal lights out and on times from the subject's log for the period on the log prior to the experimental PSG. In several cases where subjects either failed to keep a log or did so inadequately, the experimental times were determined by interview on the evening prior to the initial PSG. The averaged lights out and on time were utilized for both nights of PSG recording, and subjects were not permitted to arise or retire except at those times unless it was unavoidable. In those instances where unavoidable discrepancies occurred, efforts were made to compensate for these factors.

All subjects were drug free as per above, and a urine screening

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exam was administered to all subjects on the initial PSG night. Positive findings for medications mentioned previously would result in either postponement or disqualification; however, there were no instances where this eventuality occurred, although in the instance of one normal subject who had recently discontinued substantial coffee consumption, the experimental PSG procedure was repeated at a later date.

The Multiple Sleep Latency Test (MSLT)

Both the pre and post MSLTs were conducted in identical fashion, and generally conformed to the description of the test in Mitler (1982) with some exceptions. All naps occurred in the sleep monitoring rooms of the SWDC under standard PSG conditions (lights out, door closed, etc.). Subjects were allowed five brief naps at 10:00, 12:00, 14:00, 16:00, and 18:00 hours. Prior to lights out, subjects were instructed to try to fall asleep. Subjects were allowed to accumulate a maximum of ten minutes of total sleep time (TST) during a single nap, and all naps were discontinued after twenty minutes of recording time, provided that a subject was awake at the twentieth minute. Should a subject accumulate ten minutes of TST prior to the occurrence of twenty minutes of recording time (TRgT), the nap was discontinued. If a subject was asleep at the twentieth minute, he was allowed to remain asleep until either he awoke or ten minutes of sleep was accumulated, whichever occurred first.

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MSLT polysomnographs consisted of recordings from EMG, EOG, and two EEG locations, C-3 and O-2. Prior to and following each nap, subjects were required to complete a subjective questionnaire of sleepiness, the Stanford Sleepiness Scale (SSS) (Hoddes et al 1973), as well as to answer written questions regarding activities within the last two hours, such as caffeine consumption and napping. Subjects were permitted, between naps, to relax, read, watch t.v., eat, and leave the SWDC premises, but were not allowed to lie down, fall asleep, or consume caffeinated beverages. Those subjects at risk for falling asleep were observed continually.

Nocturnal Polysomnographs

All subjects participated in two consecutive nights of polysomnographic recording, an initial adaptation night, and a second REM deprivation night. On adaptation and RD nights, subjects were required to complete a pre and post bedtime questionnaire, which ascertained their subjective estimates of the quality of the night's sleep. Specifically, subjects were required to predict sleep latency, TST, and sleep quality prior to the night's sleep, and to estimate these factors after its conclusions.

Subjects were allowed to get up if required to go to the bathroom

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during a recording, but were not permitted to arise prior to the predetermined hour.

PSG recording techniques for adaptation and RD nights were identical, with the exception of additional adaptation night leads when required in order to rule out other disorders. PSG electrode arrays consisted of C3, C4, and O2 positions referenced to A1-A2; left and right supramentalis in bipolar reference to assess EMG; left and right outer canthi in both monopolar and bipolar recordings, to measure horizontal eye movements; and a superior orbital lead referenced to the contralateral outer canthus to measure vertical eye movements. Recordings were made at a speed of 15 mm/second with an epoch length of 20 seconds. Sensitivity for EEG and EOG recordings were 10 mm equaled 50 microvolts.

Subjects slept in one of three recording rooms on the premises of the SWDC in conditions of darkness and relative quiet. On the adaptation night, sleep was not interrupted, and subjects were monitored continuously and awakened at the preordained hour in the morning. Following the adaptation night, subjects were free to return home or leave for work.

On the RD night, subjects were awakened on every occasion that REM sleep occurred, under the following circumstances. The occurrence of REM sleep was defined as the simultaneous

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occurrence of 3 criteria for REM sleep (Rechtschaffen and Kales 1968): EMG that is relatively reduced when compared with its level during other sleep stages; low voltage mixed central EEG, with no sustained alpha; and at least one artifact-free conjugate horizontal rapid eye movement. This criteria was applied conservatively in order to be certain that all awakenings unequivocally occurred from REM sleep. Thus often some short periods of REM sleep accrued in the absence of a substantial horizontal eye movement. On those occasions when subjects had mixed or intermediate sleep as describe by de Barros-Ferriera and Lairy (1976), such as REMS and low voltage mixed frequency EEG in the presence of elevated EMG, awakenings were not made. This phenomena occurred with far greater predominance in the narcoleptic group. However, since this would presumably have reduced the number of experimental awakenings in this group vis-a-vis the normal controls, this was not considered to be a serious methodological confound. Awakenings were made immediately following the presence of criteria except for the initial awakening, which was postponed for two epochs in order to unequivocally ascertain REM latency.

When an awakening was made, the technician rapidly entered the room and told the subject to wake up. A conversation was then maintained with the subject for three minutes, at which point they were told that they could return to sleep. Often, dream

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mentation reports were elicited in order to ascertain in a non-systematic fashion if the subject was dreaming. In those instances when the subject had difficulty in maintaining alertness for three minutes, the technician would shout at the subject, shake them, and turn on the lights when necessary.

At the conclusion of the RD night, subjects were allowed to have breakfast and one cup of coffee. They then returned to the premises in time to participate in the post-MSLT procedure beginning at 10:00.

Primary Data Collection, Analysis, and Rationale

Sleep Statistics

All sleep recordings were scored for sleep stages by epoch according to standard criteria (Rechtschaffen and Kales 1968). Records were scored by the principle investigator (80%) and by the chief polysomnographic technician of the SWDC (20%). Nearly complete scoring concordance was obtained by a comparison of four jointly scored records. All epochal sleep stage data was entered into and analyzed by a DEC PDP computer, which calculated virtually all primary and secondary statistics for the study. Primary sleep statistics were generated by the SWDC standard PSG and MSLT programs, in conjunction with additional programs for REM deprivation and REM periods developed by the principle investigator and the computer programmer for the SWDC.

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Conventions for these programs are described below.

MSLT recordings were scored for the following sleep statistics:

Sleep Latency (SL): defined as 3 consecutive epochs of stage I or 1 epoch of any other sleep stage, for the MSLT only. A similar modification for the scoring of sleep latency for daytime naps has been suggested by Carskadon and Dement (1979) and Roth et al (1980). This convention is utilized since the tendency to fall asleep is the variable of concern.

REM Latency(RL): latency from sleep onset to the first epoch of REM.

Total Sleep Time (TST): the sum of all sleep time.

Total REM Time (TREMT): the sum of all epochs of REM.

Total Recording Time (TRgT): total length of a PSG recording.

Lights Out (LO) and LightsOn(LOn): actual hour of lights off and lights on.

Nocturnal PSG recordings were additionally scored for the following:

Total Stage Time in minutes spent in different sleep stages-stage I, II, REM, and combined III-IV(TSTI, TSTII, TSTIII-IV, TREMT).

Total Wake Time during recording (TWT).

Total Wake Time After Sleep Onset (WASO).

Total Number of Awakenings after sleep onset for the adaptation night, defined as the occurrence of at least one epoch of awake (#awakAD).

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Total Number of Five Minute Awakenings for the adaptation night (#5'awakAD).

The criteria for REM latency was unchanged. For nocturnal PSGs, the criteria for sleep latency (SL) was the first epoch of sleep followed by five minutes of consolidated sleep occurring from any stage. However, certain special conditions obtained on the RD night. The SL(RD) was defined as SL (as above); or the first epoch of sleep from any stage contiguous with an experimental RD awakening (EA); or an EA, which ever occurred first.

The number of experimental awakenings on the RD night (#EA) was calculated by the computer, and a special stage of sleep, stage VIII, was scored for epochs that were part of a 3 minute EA. The #EAs per hour of TST (#EAs/HS) was calculated, as was the mean duration of EAs for each subject (TVIIIT/#EA), which represents the average time subjects were kept awake by the experimenter during experimental awakenings. This was calculated as the total time in stage VIII divided by the #EAs. Finally, the #EAs per hour of TRgT(RD) was calculated (#EA/TRgT). In an effort to see how rapidly subjects returned to sleep following an EA, the mean SL following EAs was calculated (XEASL). The SL following each EA was defined as the latency to the first epoch of sleep when it was followed by 3 epochs of consolidated sleep from any stage; or another EA, which ever occurred first. This mean was calculated as the sum of all EASLs/#EAs.

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REM Period (REMP) Statistics

The analysis of sleep archetectonics was viewed as highly significant based on theories of possible pathophysiology in narcolepsy, as well as interest in the effects of the experimental REM awakening procedure on normal REM/NREM and sleep-wake rhythms. Although the task of defining REMPs by epochal scoring for the AD night was fairly straightforward, this was not the case for the RD night, where anomalies in REMP length and interval were anticipated due to the experimental interruption of the REM periods and concomitant accumulation of REM pressure. (cf Fiss and Ellman 1972).

Of particular interest for this night was the ability of normals and narcoleptics to maintain basic REM/NREM archetectonic relationships within the course of the RD night, and how this ability was related to daytime sleepiness, the ability to store REM when interrupted, the number of awakenings required for RD, and the ability to disengage REM when aroused from sleep. Additionally, findings concerning differences in REMP length and variability in narcoleptics from normals by Montplasil (1976) could be evaluated on the adaptation night.

Rechtschaffen and Kales (1968) provide no rules for the scoring of sleep from the point of view of its greater archetectural

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gestalt—that is, they do not define such elements as REM or sleep latency, neither do they address themselves to the issue of REMPs in a manner other than epochal. Hartmann (1968) noted the difficulties in defining REMP onset and offset, and proposed a 15' rule, that is, that REM epochs are part of one REMP unless 15' of combined wake and/or SWS intervened. Feinberg (1974) suggested a similar convention, whereas Williams et al (1974) suggested a much more stringent 2' rule for any continuous non-REM interruption. Most authors described a REM cycle as the period from REMP onset to subsequent REMP onset. Recently, Webb and Dreblow (1982) studied the effects of combining rules on REMP frequency and length in young and aged normals. No differences were found between no rule, a 5' rule, and a 15' rule except for the aged men, who when scored by the no rule criteria had twice as many REMPs of considerably shorter length and cycle than the younger subjects (mean number REMPs was 9.3 versus 4.5). By using a combining rule, the REM/NREM relationships of these older male subjects appeared fairly normal. Several older men, who had over 20 REMPs with no rule, had 4 or 5 with a 15' rule. Clearly, the application of such a combining rule seemed preferable if one wished to analyze the cyclicity of these subject's sleep, and "demonstrates that these episodes are temporally organized in time and approximate the established temporal organization of REM" (Webb and Dreblow 1982).

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Like narcoleptics and, presumably, all subjects on RD nights, the older men had more fragmented REM sleep that could result in different architecture, depending on scoring criteria. Thus the application of a REMP combining rule for this study seemed advisable. Interestingly, studies such as Vogel et al(1980), which used a 15' rule, have reported the effects on REMP parameters for recovery nights due to prior RD but have not analyzed REMP data for the RD night, when sleep is most disrupted. Thus it is not only of interest how frequently a subject must be awakened to accomplish RD, but what effects the RD has on architecture on the RD night.

In this and a subsequent companion study, the propensity to have SOREMPs versus SONREMPs following EAs from REM and NREM is examined, a statistic possibly related to the issue of maintenance of a state of sleep after its disruption.

In order to assess this and other REMP related statistics, the following conventions were used and calculated by computer:

REMPs were defined and analyzed by two conventions, a 10' rule and a 15' rule. The 15' rule is identical to that of Webb and Vogel-REMP offset is defined as the last page of REM followed by 15' of anything else but REM. However, it has been proposed that sleep cycling and REM occurrence is a sleep dependent rhythm, that is, that the occurrence of the 90' cycle depends on

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intervening NREM sleep (Johnson et al 1980), and that the REM refractory time is not independent of intervening amounts of NREM sleep. Thus on the RD night, it was unclear if the 15' rule, when it reflected only wakefulness, could properly distinguish between the same and a subsequent REMP, especially since additional wake time on this night is to be expected. It was therefor decided to utilize a sleep dependent REMP convention as well. Thus REMPs were additionally defined by a 10' rule: A REMP ended when the last page of REM was followed by 10' of nonconsecutive NREM sleep. All REMP data was analyzed by both rules.

REMP onset was defined as either the first page of stage V or the occurrence of an EA, whichever came first. REMP offset was defined as the last page of stage V or the first page of an EA

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followed by either a) 15' of continuous NREM and/or awake or 2) 10' of consecutive NREM sleep.

REMP intervals or cycles were defined as the time between the first page of a REMP and the first page of subsequent REMP.

REMP length was defined as the number of pages between the start and end of a particular REMP.

REMP number was calculated as the number of separate REMPs for the night.

InterREMP sleep efficiency and TST were calculated in order to assess how much NREM sleep occurred between REMPs—that is, did REM occur after 90' regardless of how much sleep intervened.

SOREMP frequency following EAs was calculated as the percentage of instances when an EA was followed by a SOREMP. A SOREMP was defined as REM sleep occurring within 15' following sleep onset.

REMP EA density was calculated as the number of EAs divided by the TREMP (sum of all minutes of REMPs).

Mean EA RL was calculated as the number of pages of NREM following an EA until the next EA occurred within the same REMP. This squeezed out all the awake time between awakenings within a REMP, giving a truer picture of EA density and the rapidity with which subjects returned to REM after an EA. The former statistic, REMP EA density, may be confounded by the inclusion of the 3' enforced awake time following each EA, thus making the narcoleptic REMPs appear artificially longer; and by sleep

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latencies following "lights out". A mean EA REM latency for each subject was calculated. Latencies from the last EA of a REMP to the first EA of the next REMP were not included in this statistic.

EAs per REMP was calculated for the first REMP, the last REMP, and the greatest number of EAs for any single REMP.

Secondary Statistics

Basic secondary statistics included calculating averages for a variety of data for individual subjects, such as average REMP length for adaptation and REMP nights, or average sleep latency for naps. Several special cases obtained. When calculating average sleep latency for MSLT naps, a nap for which no sleep occurred was scored as having a 20' SL.

Statistical tests for differences and correlations utilized three measures: T Tests assessing differences between groups, correlated T tests assessing changes within groups, and Pearson correlations. Means, ranges, standard deviations, and significance of differences between means for the two subject groups, normals and narcoleptics, were calculated for all relevant data, and are reported in results, using the T Test for differences between sample means for independent, unequal groups. Thus differences in amount and stages of sleep, number of EAs, number of REMPs, etc were analyzed. Additionally, differences

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between group means for averaged individual subject data was similarly analyzed, such as the average REMP length for groups. A correlated T Test was used to analyze within subject differences between adaptation and RD nights for each group; between pre and post MSLTs; and between pre and post nap subjective states.

Pearson correlation was used to assess the strength of relationship between different variables within groups. Thus a variety of variables, such as adaptation night RL, REM%, TREMT, changes to stage I, and percent stage III-IV were evaluated as predictors of #EAs. Certain pre MSLT data was analyzed as predictors of #EAs such as sleepiness as measured by mean MSLT SL, and #EAs were analyzed as a predictor of post MSLT data. Findings are reported in the results section.

Reliability of EA Data

In order to independently assess the correctness of EAs, an independent scorer was asked to blindly evaluate awakening data. This was done in the following manner. Six records were randomly selected, three from narcoleptic subjects, and three from normal controls. All actual experimental awakenings from the RD nights from these records were separated. An equal number of sections of record from the same records were selected. They were chosen from sections of awake, stage I, II, III, and REM sleep that did

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not meet awakening criteria. The scorer was then asked to determine whether the sections he was presented met the criteria for an experimental awakening. The scorer was shown a portion of the record, and asked to judge whether it was appropriate for an awakening based on the awakening criteria for EOG, EMG, and EEG. He was asked to indicate in writing either "yes" or "no", and whether he was "fairly certain" or "fairly uncertain" about his determination. This procedure was followed for all six RD records. The scorer was first allowed to review the adaptation night record for a particular subject in order to familiarize himself with that subject's EEG. Sections from records were shown to the scorer one subject at a time.

Reliability comparisons were then made between the scorer's judgements and the actual EAs. Reliability in the sample of six records was at the 100% level. The scorer is currently employed as a PSG sleep scorer and technician for an accredited sleep center.

CHAPTER THREE

FINDINGS

Data will be presented in several manners in this section. Individual sleep statistics for all subjects are to be found in Tables 18-25. Graphic representations of selected individual subject PSGs are contained in the appendix.

Secondary sleep statistics are reported in three areas: differences between narcoleptics and normal controls for primary sleep data pertaining to adaptation nights, RD nights, and MSLTs, utilizing a standard two tailed T Test to measure differences between means for unequal groups; within group differences for data on adaptation versus RD night, and for pre versus post MSLT, utilizing a correlated T Test; and correlations between awakening data and primary sleep statistics for adaptation night and MSLTs, utilizing a Pearson Correlation Test. Comparisons of narcoleptic sleep statistics for this study with those reported in the literature will be discussed in Chapter Four.

Comparisons of Primary Sleep Statistics for Narcoleptics and Normal Controls

Adaptation Night Statistics

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As described in Chapter One, differences are described in the literature regarding polysomnographic aspects of normal and narcoleptic sleep. Most frequently differences are reported for sleep latency (SL), REM latency (RL), percentages of stages I and IV, REM cycle variability, and sleep phenomena associated with disturbed nocturnal sleep, such as number or awakenings and changes to stage I sleep.

Tables 1-3 reports summary sleep statistics for 11 normal and 13 narcoleptic subjects for adaptation nights. Reported are group means, standard deviations, and ranges, and differences between groups using a two-tailed T test. No differences between groups were found for total sleep time (mean narc.=395', normal=396') or total recording time (narc.=452', normal=450'). Interestingly, all subjects spent at least 7 hours in bed with the exception of the two subjects over 55 years, a narcoleptic and a normal. Both their TRgT was about 6 hours. As expected, narcoleptic sleep latencies were shorter than those of normal controls (narc.=6.4', normal=19.6', $p<.05$). Both groups produced shorter sleep latencies on the second (RD) night, and again showed differences in the same direction (narc.=3.4', normal=9.1', $p<.05$). All narcoleptic sleep latencies were under 14 minutes, whereas one normal had substantial delayed sleep initiation, with a latency of 55 minutes. This was 2 SDs in excess of the mean.

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Indicators of disturbed nocturnal sleep were examined. These include brief awakenings, awakenings lasting at least 5', wake after sleep onset, total wake time, changes to stage I, percent of stage I, and sleep efficiency. All these measures displayed trends supporting increased sleep disturbance in narcolepsy, with the exception of sleep efficiency, which was essentially the same between groups (narc.=88.5%, normal=87.8%). These findings can be considered as presumptive evidence of increased DNS in narcolepsy, although no differences were found for total wake time (narc.=57', normal =55'); for wake after sleep onset (narc.=50', normal=34'); the number of epochal awakenings (narc.=37, normal=28); and the number five minute awakenings (narc.=2, normal=1.2). Differences ($p<.005$) were found for the percent stage I (narc.=26%, normal=12%) and amount (narc.=101', normal=50'). Differences in the number of changes to stage I were also found (narc.=46, normal=31).

No differences were found for REM latency on adaptation night, whereas differences were found for REM latency for the RD night. Adaptation night mean RL was 45' for narcoleptics, and 87' for normals. Standard deviations were 44' and 65' respectively, with one outlier in each group close to 3 SD's greater than the mean. This may account for the lack of differences for RL for the adaptation night. On RD, narcoleptic RL was 23', and normal RL was 75' ($p<.01$).

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Findings for sleep stage amounts and percentages for the AD night are reported in Table Two. Most notable is the relative elevation in amount and percent of stage I in the narcoleptics versus normals. Narcoleptics spent on average 101' in stage I, as opposed to 50' for normals ($p < .005$). Relative percents of stage I sleep were 26% for narcoleptics, and 12% for normals ($p < .005$). A trend for narcoleptics to have less stage II than normals reached significance for percent of sleep (narc.=46, normal=55, $p < .05$), but not for minutes of stage II. No differences were found in amounts or percentages of stage III-IV between groups, although a trend existed towards less stage III-IV in the narcoleptics (narc.=40', normals=48'; narc.=10%, normal=12%).

Differences between groups for total REM time and percent for the AD night were not significant. REM% for normals was 21%, and for narcoleptics 18.5%. Total REM time for normals was 87.2', and for narcoleptics 71'. Neither group appears to have had substantially reduced REM % or REM time on the adaptation night, based on sleep log data. The range and SD in the normal group (3.2-34%; 8%) is larger than that of the narcoleptics (13-27%; 4.5%).

Of interest were possible differences between group for REM period data on adaptation night, inasmuch as differences are

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reported in the literature for this relevant REM statistic. Differences between groups for these measures are striking on RD night. One might ask whether this was due solely to the RD awakening intervention, or whether differences existed notwithstanding this procedure. Interestingly, no differences were found between groups for mean REMP data on AD night. All normals had either 4 or 5 REMPs on adaptation night, with the exception of J.C., the normal subject with lowered sleep efficiency and lowered REM percent for adaptation night. Eleven of thirteen narcoleptics had between 4-6 REMPs, with one having 7, and one 3. The mean number of REMPs for adaptation night was narc.=4.8, and normal=4.2, using the 10' REMP convention. Mean REMP length (narc.=21', normal=22') and REMP interval (cycle) -as calculated from REM onset to onset, was narc.=100, normal=101.

REMP statistics were considered to be of special interest inasmuch as they allowed for the within group comparison of certain sleep statistics for adaptation versus RD nights, particularly those statistics pertaining to changes in sleep architecture as a consequence of the REM deprivation challenge. Whereas experimental awakenings can be compared only for the RD night between groups, REMP analysis allows for comparisons between nights, and REMP architecture can be seen as a dependent variable in the manipulation. Findings pertaining to architectonic changes secondary to the experimental awakenings

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and REM deprivation are reported as T tests for differences between group means for REMPs on the RD night; and as correlated T tests comparing within groups changes from adaptation to RD night. Additionally, Pearson correlations were used to examine relationships between changes in architecture, experimental awakenings, and MSLT data.

The number of SOREMPs for both PSG nights is reported in Table Ten. Differences ($p < .005$) between groups are reported for the adaptation night. Narcoleptics had 8/13 possible SOREMPs, normals = 0/11. On the RD night, narcoleptics had 11/13, normals 0/11. For both nights combined the data were narc. = 19/26; normal = 0/22. Two normals, JS (s.# 10) and RM (s.# 6) had short REM latencies, with one 16' RL for JS on the second night.

REM Deprivation Night Statistics

Differences between means for groups for sleep statistics on the REM deprivation night are reported in Tables 4-7. Table Four reports differences in primary sleep statistics on RD; total recording time (TRgT), total sleep time (TST), sleep latency, and REM latency. Findings for sleep and REM latency are reported in the previous section. No differences were found for TRgT on RD between groups (narc. = 479', normal = 456'), although narcoleptics on RD had an average of 23' more TRgT than did normals. Increased TRgT of 25' for narcoleptics on RD versus adaptation was due to

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the inadvertent delay of lights out time on AD for several subjects.

Total Sleep Time was significantly greater for the narcoleptics versus normals on RD, a perhaps surprising finding given the greater number of times they were awakened from REM sleep. Mean narcoleptic TST on RD was 388.7' (62'), versus 344.7' (26') for normals ($p < .05$). As will be reported further on, narcoleptics returned to sleep following EAs more quickly than did normals. Both SL and RL were significantly shorter for narcoleptics on the RD night.

REM Deprivation statistics reflect the degree of REM deprivation on the RD night, and consist of statistics for total REM time (TREMT) and REM percent (REM%). These findings are reported in Table Five. No differences were found between groups for the RD night for TREMT or REM%. Normals had means of 6.5 percent REM sleep, and 22' TREMT; narcoleptics had a mean REM% of 7.1 with 23.2' of TREMT. Although some other authors have reported smaller amounts of REM sleep on deprivation nights, awakening criteria used in this study was conservative thus allowing for small amounts of REM sleep before EAs. This was done because the number of awakenings themselves were the investigated variable. This may have accounted for slightly elevated amounts and percents of REM sleep for both groups on the RD night.

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Two normals and two narcoleptics had higher percentages of REM sleep on the RD night than did other subjects, each with a REM % in excess of 10%. In one narcoleptic, EG, two awakenings were preceded by 5' of REM during which the criteria for eye movements was not met. Additionally, EG had a lowered amount of TST which in part accounted for increased REM%. A second narcoleptic, BA, had no periods of REM in excess of a few minutes; however, all EAs for BA were preceded by several epochs of REM sleep. This was due to individual differences in the latency to production of eye movements in subjects. Thus those subjects who did not produce eye movements rapidly tended to accumulate REM sleep. In general, some narcoleptics tended to have more REM on RD due to their persistence in remaining in REM after EAs.

A normal control, RM, presented with a similar record to BA--no long periods of REM, but generally longer periods of REM prior to EAs, due a delay in eye movements. Additionally, TST on RD for this subject was low, thus increasing REM percent. A second normal, OA, was allowed to accumulate 20' of REM sleep at the end of the night due to the failure of the technician to awaken her. Differences for this subject for REM sleep between adaptation and RD were substantial, notwithstanding this missed awakening (TREM AD=98', RD=47'; REM% AD=25%, RD=13%). All four subjects had substantially diminished REM sleep on RD when compared with adaptation night levels.

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Several interesting differences between narcoleptics and normals were noted for REMP data for the RD night, and are reported on Table Six and Seven. Table Six reports REMP data using the 10' REMP convention. Normals had more REMPs than narcoleptics on RD (normal=7.6, SD=1.2; narc.=5.4, SD=1.6; $p<.005$). No differences between groups were found on adaptation night. Narcoleptic REMPs were longer (narc.=34.9', normal=12.3', $p<.005$), as were the REMP to REMP intervals (narc.=92.8', normal= 53.4', $p<.005$). Differences for number of REMPs, length, and interval using the 15' REMP scoring convention are reported on Table Seven, and are essentially similar to those on Table Six. In general, whereas REMP data for normals and narcoleptics showed no differences for adaptation, on RD narcoleptics had fewer, longer REMPs with longer intervals between REMPs (longer REM/NREM period length). No differences were found for sleep efficiency between REMPs (normal=63%, narc.=66%). Differences were found for the longest REMP for the night for each subject (narc.=92', normal=46', $p<.02$). The REMP data reflects the fact that the increased number of EAs for the narcoleptic group was expressed in the clustering of numerous awakenings within fewer REMPs.

The Experimental Awakening data reflects the primary investigative interest of the study as it was conceived. Findings for EAs on RD are reported in several ways: Total number; as a ratio of TST; as a function of REMP statistics, that

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is, how they are clustered; in terms of the propensity to remain in REM sleep after an EA; and the latency to sleep onset after EAs, of interest due to a possible relationship between REM sleep and sleepiness.

Experimental awakening data is reported on Table Eight and Nine. Narcoleptics had significantly more EAs than did normals (the number of EAs is the number of times a subject was awoken from REM sleep in order to achieve REM deprivation). Narcoleptics required 27.7 EAs (SD=7.7), and normals required 14 (SD=5.7, $p<.005$). Differences were found for the number of EAs per hour sleep (narc.=5.2, normal=2.5, $p<.005$). Narcoleptics returned to sleep after EAs faster than did normals (narc.=1.3', normal=4.1', $p<.005$). No differences were found in the actual length of the enforced awakening, with both groups being kept awake on average of 3.3'.

Table Nine reports EA data as a function of REMPs. Differences were found for the number of EAs per REMP (narc.=5.8, normal=1.6, $p<.005$); for the number of EAs during the first REMP (narc.= 2.8, normal =1, $p<.005$); and for the number of EAs for the last REMP (narc.=14.6, normal =3.8, $p<.005$). No normal had more than one EA for the first REMP, whereas 9/13 narcoleptics had more than one. One narcoleptic subject has 32 EAs during the last REMP. About 2/3s of subjects from both groups had the largest number of

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EAs during the last REMP.

No differences were found for EA density between groups, a statistic that measures the total number of EAs/total REMP time. This is reported on Table Nine. This statistic includes the time spent in stage VIII (lights on during an EA) and stage 0 after each EA when it is part of a REMP. Thus the additional time spent in stage VIII and 0 for the narcoleptic group due to their greater number of EAs influenced this statistic.

The post EA SOREMP probability is reported on Table Nine, and is a measure of the percentage of EAs that are followed by SOREMP (a second study is now investigating this phenomena following EAs from NREM sleep in the same subjects). An EA is said to be followed by a non-SOREMP (SONREMP) when it is followed by at least 15' of consecutive recording time that does not contain either REM sleep or another EA, not including time spent in stage VIII or enforced awake time, . Thus an EA followed by 15' of wakefulness would mean it was followed by a SONREMP. When either REM sleep or another EA occurs within 15' of an EA, then a post EA SOREMP is said to occur. Thus in a REMP with 10 EAs, 9 will be followed by SOREMPs.

Using this statistic, narcoleptic EAs were on average followed by SOREMPs 81% of the time, whereas non-narcoleptic EAs were followed by SOREMPs 44% of the time, a difference significant at

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the .005 level.

In evaluating data for EAs, and post EA SOREMP percent, this study had as an aim to investigate the usefulness of these criteria as diagnostic instruments in known cases of narcoleptics and normal subjects. Sensitivity, specificity, and diagnostic confidence for positive and negative findings are conventional measures of diagnostic utility and validity. The setting of criterion values for diagnosis in narcolepsy, as reported in the literature, such as 2 SOREMPs on MSLT, has no face validity and is based on its coherence with a definitive history of narcolepsy. In order to assess the usefulness of both the number of EAs and post EA SOREMP percent for diagnosis, 3 criterion levels were selected for sample tests. These were: A value which would be 100% sensitive, that is that would correctly identify all narcoleptic cases. This value was more than 17 EAs, or greater than 65% SOREMP %. A value that would be 100% specific, that is correctly exclude all normal controls (EAs<25, or SOREMP %<75%); and a criterion level that was in between.

Findings for sensitivity, specificity, and diagnostic confidence are reported on Table Seventeen A and B. When the two diagnostic measures, the number of EAs and the SOREMP % were compared, no differences were found in terms of their sensitivity, specificity, and diagnostic confidence when using the sensitive criterion value (SOREMPs>65%, EAs>17). For the most specific

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measure (EAs<25, SOREMPs<75%) the SOREMP % measure was clearly superior, with better sensitivity and negative diagnostic confidence. Differences between measures when a middle value (EAs>19, SOREMP %>69) was selected were small, and favored the EA measure. Both measures, SOREMP % and number of EAs, produced values for sensitivity, specificity, and negative and positive diagnostic confidence with a range of 82-92% when the middle criterion value was utilized.

Data from pre and post MSLTs for sleep latency and frequency of SOREMPs was compared for the normal and narcoleptic groups. Findings are reported on Table Eleven and Twelve. Differences between groups for sleep latency were found for both the pre and post MSLT procedures ($p<.005$). Mean sleep latency on five pre MSLT naps for normals was 11.8'(4.9'), and for narcoleptics was 2.43'(1.6'). One normal control, JS, had pre MSLT sleep latency within the pathological EDS range (under 5'). On the post MSLT, normal mean sleep latency was 12.4'(4.4'), and narcoleptic sleep latency was 2.3'(1.2', $p<.005$). Individuals who did not sleep on a nap were assigned a sleep latency of 20', as is customary.

Differences were found between groups for the pre MSLT for number of SOREMPs produced on naps ($p<.005$). On the pre MSLT, the narcoleptic mean for SOREMPs produced was 2.8(1.2) for 5 naps,

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whereas only one normal subject produced a SOREMP (mean=11,.3). On post MSLT, the normal mean was 1.0(1.7) for SOREMPs produced, and the narcoleptic mean was 4.27(.47). Only 3 normals produced SOREMPs on the post RD MSLT, with 2 (JH & JS) subjects having 4 each.

Correlated T tests were utilized to measure differences between means within groups. Comparisons were made for statistics for pre versus post MSLT, and for adaptation versus RD nights. Findings for correlated T tests are reported on Tables Thirteen and Fourteen.

No differences were found when sleep latency for pre versus post MSLTs were compared for normals (mean pre SL=11.8', post SL=12.4'). Neither were differences found for this comparison for the narcoleptic group (pre=2.4',post=2.3'). This was not especially surprising for the narcoleptic group, since it has been previously noted that the MSLT is not especially sensitive to variations in sleepiness for patients in the pathological range, perhaps due to a floor effect. However, this was notable for the normal group, inasmuch as a correlated T Test for differences in total sleep time between adaptation and RD nights for normals indicated significant sleep loss on RD, as reported in Table Fourteen. Carskadon has reported, however, that the MSLT may not be sensitive to the effects of a single nights sleep deprivation in normal adults. Sleep deprivation in this instance

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was more on the order of 50 minutes for the normals as compared with AD night TST. In any event, although normals as individuals displayed a relationship between both basal and REM deprived sleep tendency on MSLT and REM deprivation related findings (#EAs), as a group REM deprivation did not effect next day sleep tendency.

A comparison of the number of SOREMPs on narcoleptic MSLTs showed a significant increase for the post versus pre MSLT. Narcoleptics averaged 2.8 SOREMPs for five naps on pre MSLT, and 4.3 SOREMPs for the post MSLT ($p < .005$). Normals showed a trend towards increased SOREMPs following RD, but this was limited to three subjects, the other six subjects having no SOREMPs for either procedure. Means and standard deviations for this comparison were .11(.3) for pre versus 1.0(1.7) for post MSLT. It is of interest that both groups showed increases in SOREMP production for the post MSLT. This finding for the narcoleptic group implies that they did experience REM deprivation for the RD night and are displaying a rebound (RD dependent) phenomena. It remains unclear whether narcoleptics display RD effects, i.e. rebound phenomena, on a nocturnal PSG subsequent to RD. This finding implies they will show it on the day following the RD if they are allowed to sleep (and perhaps even during wakefulness). In either event, this tendency might result in decreased or absent rebound at night, and appears to be more robust in the

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narcoleptics than in the normals.

Correlated T Tests for changes in nocturnal sleep statistics for both groups for adaptation and RD night recordings are reported on Table Fourteen. Both groups showed trends towards increased total recording time for the RD night. Significant differences were not found for the normals (AD=450', RD=455', ns). Differences were found for the narcoleptics for total recording time (AD=452', RD=479', $p < .05$). Differences for total sleep time were found for both groups. Normal mean TST for adaptation was 396'(67), and for RD was 344'(26), ($p < .05$). For narcoleptics, AD TST was 395' and for RD was 389'(62), ($p < .005$).

Changes in REMP architecture were measured by comparing the number of REMPs and interREMP interval for the adaptation versus RD nights. Normal controls produced differences at the $p < .001$ level for both measures. These differences were in the direction of faster REM/NREM cycling and a greater number of shorter REMPs on RD in response to the EAs. Normals had an average of 4.2 REMPs for AD, lasting on average 22', with a REM cycle from onset to onset of 101'. On RD, the mean number of REMPs increased to 7.6 ($p < .001$), with a length of 12.3' and a cycle length of 53' ($p < .001$). Narcoleptics, on the other hand, did not show significant differences for REMP measures for this comparison. The mean narcoleptic number of REMPs for AD was 4.8, with a

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length of 21' and a cycle length of 100'. On RD, the number of REMPs increased slightly to 5.4 (ns), with a length of 34.9' and cycle length of 93' (ns). Both REMP length and cycle length are calculated to include the EA time itself, making this data less interpretable. Thus if a REMP contained five EAs, its length would include 15' of enforced awakening.

Measures of changes in total REM time and percent were considered to be important as indicators of successful REM deprivation. Both groups showed highly significant decrease in REM time and percent for the RD night. Normal REM time was 87' for AD versus 22' on RD ($p < .005$), and percent of sleep was 21% on AD versus 6.5% for RD ($p < .001$). For narcoleptics, AD REM time was 72' versus 23' on RD ($p < .001$), and percent for Ad was 18.55 versus 7.15 for RD ($p < .001$).

Pearson correlation statistics were utilized to determine relationships between REM deprivation findings, in particular data pertaining to experimental awakenings, and other sleep measures. Pilot data had indicated that narcoleptics responded to the RD challenge with increased numbers of awakenings. It was thought that this characteristic might be related to several factors, including disturbed nocturnal sleep in narcoleptics, EDS, and the REM manifestations of the illness. Thus correlations were performed between EA data and stage I sleep, total sleep time, stage III-IV sleep, REM latencies and SOREMPs,

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REM % and time, and sleep latencies. It was predicted that high numbers of EAs, high post EA SOREMP percent, and low numbers of RD REMPs, as indicators of strong narcoleptic loading, would correlate with high stage I percent, low stage III-IV percent, short REM latencies and high numbers of SOREMPs, and short REM latencies. Similarly, individual differences for EA data for normals might be expected to show a relationship with these narcoleptic factors. No predictions were made regarding the relationship of EA data to TST, REM percent and REM time for adaptation night, based on unclear findings in the literature.

Findings for Pearson correlations are reported on Table Fifteen and Sixteen. The number of EAs for narcoleptics was negatively correlated with SOREMP propensity for both pre and post MSLT. Narcoleptics who had more EAs had fewer MSLT SOREMPs, an unanticipated finding. Correlation values were $-.34$ for the pre and $-.32$ for the post MSLT. No correlations were found for number of EAs when compared with recording time for adaptation night ($r=.02$) or for RD night ($r=.13$). Small correlations in the expected direction were found for #EAs versus adaptation night stage I and stage III-IV for narcoleptics ($r=.23$ for st.I; $r=-.29$ for st.III-IV). No relationship was apparent between #EAs and either adaptation night REM% or time ($r=.13$ for TREMT; $r=-.002$ for REM%). Adaptation night TST was not related to #EAs ($r=.03$). Narcoleptic REM latency for RD night was negatively correlated

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with #EAs ($r=-.44$), an expected finding since the first REMP occurred earlier and perhaps allowed for more awakenings.

Correlations for normal subjects are found on Table Sixteen. No relationship was found between #EAs and percent stage I for adaptation night ($r=-.005$). Percent stage III-IV was negatively correlated with #EAs ($r=-.32$). Positive correlations were found for TST, TREMT, and REM% on adaptation night versus #EAs. Amount of adaptation sleep was correlated at $r=.43$; amount of adaptation REM time was correlated at $r=.51$; and adaptation REM% at $r=.54$. No correlation was found for TST on RD and #EAs ($r=.02$), or for recording time for RD versus #EAs ($r=.02$), indicating increased numbers of EAs were not a function of RD recording time. As with the narcoleptics, RD REM latency was negatively correlated with #EAs ($r=-.40$). It is known that depressives, who have short REM latencies, tend to require numerous RD awakenings in order to accomplish REM deprivation. This is consistent with the finding that shorter REM latencies go with increased numbers of EAs for both groups.

Of particular interest was findings of correlations for measures of sleep latency for normals with their EA data. Correlations were found for both pre and post mean sleep latency for five naps with number of EAs and percent of post EA SOREMPs. Nap latencies for the pre-MSLT were correlated with #EAs at $r=-.82$, and with

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the post EA SOREMP percent at $r=-.9$. Thus normals who were sleepier as measured by nap latencies had greater numbers of EAs on RD, and their EAs were more frequently followed by SOREMPs. A similar finding was noted for the post-MSLT nap latencies, where #EAs was correlated with sleep latency at $r=-.42$. Mean sleep latency for combined adaptation and RD nights for normals was correlated with #EAs at $r=-.37$. Thus all measures for sleep latency-both MSLTs, and both PSGs, were negatively correlated with #EAs in normals.

CHAPTER FOUR

DISCUSSION

Due to the design of the study, and the existence of an extensive literature relevant to findings from this study, results must be discussed within a variety contexts. These include findings for narcoleptics; findings for normals; and findings of differences between narcoleptics and normals. For each group, within group results for this study will be discussed, such as changes in sleep latency in normals for pre versus post MSLT. In conjunction with this, findings for this study will be compared with those in the literature, for example, MSLT sleep latency findings for study versus literature findings for normals. It is of concern to establish initially, in this regard, that findings for basic sleep patterns for nocturnal and nap PSGs conform to those reported in the literature. Findings of differences between the groups in this study will be discussed; for example, differences in sleep latency on pre MSLT. This chapter will then conclude with a general discussion and speculation regarding the major findings for the study- the relationship of number of experimental awakenings to sleep latency in normals, and the unique response of narcoleptics to experimental REM deprivation awakenings. How these issues pertain to the relationship of REM sleep, sleepiness, and theories of the pathophysiology of

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narcolepsy will be discussed.

Narcoleptic Sleep Parameters for Adaptation Night and Pre MSLT

Several studies report baseline sleep parameters for both narcoleptics and normal controls. It is of interest to compare findings from this study with those reports, although quite naturally certain limitations are imposed when making this sort of comparison. Thus total sleep time (TST) for the first night of this study (adaptation/baseline) may be compared with reports in the literature, but must be interpreted under the constraint of differing experimental conditions, such as time in bed and number of adaptation and baseline nights. Specifically, results from the present study pertain to one night in bed with no prior adaptation, and must be viewed within the constraints of the first night effect literature. Notwithstanding this limitation, findings for the present study for narcoleptic sleep compared favorably with those in the literature.

Several PSG studies report nocturnal and MSLT sleep parameters for narcoleptics, including Richardson et al (1978), Rechtschaffen et al (1963), Montplaisir (1976), Hishakawa et al (1976), Mitler et al (1979), Mosko et al (1983), and Spielman et al (1979). TST for this study for narcoleptics was 395', as compared with an average for two nights of 417' in Richardson, an average of 345' for three nights in Mosko, and an average of

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390' for ten baseline nights in Spielman. Total recording time (TRgT) for the Richardson study was greater by 90', indicating decreased sleep efficiency in his study. Sleep latency for narcoleptics compared well with reports in the literature. Narcoleptics fell asleep at night in 6', as compared with 5' (De Barros-Ferreiera et al 1976), and 7' for both Richardson and Mosko.

Indicators of disturbed nocturnal sleep are reported in several of the above mentioned studies. Higher numbers of spontaneous awakenings were found in this study than are reported in the literature, probably due to both first night effects and different criteria, inasmuch as study criteria for a spontaneous awakening was one epoch of stage 0. Narcoleptics in this study had a mean of 37 epochal awakenings versus 25 (De Barros), 15 (Hishakawa), 10 (Mosko) and 18 (Montplasilir). Data for wake after sleep onset (WASO) was very similar to literature reports. Study findings for narcoleptics for WASO was 50', as compared with 55' (De Barros), 60' (Montplasilir), 70' (Mosko), and 98' (Richardson). Sleep efficiency as reported in the study (88%) was the same as reported by Van Der Hoed (88%), whereas Mosko reported 82%.

Findings of increased stage I sleep in the literature were replicated in the study. Stage I sleep occupied 26% of the narcoleptic record, when compared with 23% for Hishakawa, 24% for

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the initial night for Mosko, and 22% for Montplasilir.

Studies in the literature report non-significant reductions in slow wave sleep (SWS) for narcoleptics, a finding that was found during the one adaptation night in the present study. This study found narcoleptic SWS to be 10% of TST, as compared to 10% (Montplasilir) and 14% for both Hishakawa and Mosko.

REM statistics for this study may be compared for REM latency (RL), REM percent (REM %), total REM time (TREMT), and REMP interval. Accross two nights, the average RL for narcoleptics was 39', as compared with 34' (Montplasilir), and 68' (Richardson). REM % for the adaptation night was 18.5%, as compared with 20% (Montplasilir), 19% (Hishakawa), 17% (Richardson), 14% (Mosko), and 19% (both Rechtschaffen and Spielman). TREMT was found to be 71', as compared with 71' (Richardson), 74' for ten nights (Spielman) and 90' (Montplasilir). REMP interval was found to be 100', as compared with 98' (Hishakawa) and 105' (Montplasilir). Findings for SOREMP probability for the two nights indicate 19/26 possible SOREMPs, or 74%. This compares with 37/52 (Hishawakwa), 7/9 (Rechtschaffen), and 6/9 (Montplasilir).

In general, it appears that findings for narcoleptics for one adaptation night are generally consistent with reports by other authors, espeically in those important areas of REM amounts and percents, REM latency, sleep latency, sleep efficiency, percents

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of stage I and III-IV, and indicators of poor sleep. Nocturnal narcoleptic sleep has been characterized as disturbed based on increased WASO, numbers of awakenings, body movements, stage I, and decreased SWS; as showing no REM facilitation in terms of amount of REM sleep, other than its phase advance; and in showing no NREM facilitation in either TST or sleep efficiency, other than in its rapid onset (short latency). Findings for this study confirmed these tendencies. Narcoleptics showed non-significant tendencies for increased WASO and spontaneous awakenings, significant increases in stage I, non-significant decreases in REM latency, stage II, SWS, and REM sleep, and significant decrease in sleep latency, when compared with the normals in this study. All T tests were two tailed; it might be assumed that several of these trends would achieve significance had one tailed tests been utilized.

Unfortunately neither consensus nor cogent explanation exists regarding the etiology and pathogenesis of this constellation. Whereas clinical findings and results from this study imply that narcoleptics appear as if they are REM deprived-they have high numbers of awakenings, dissociated REM phenomena, and short REM latencies-their baseline sleep does not exhibit increased REM fractionals, nor does it conform to the expected profile of a sleep deprived sleepy person, inasmuch as nocturnal sleep is disturbed, with average or below average sleep efficiency and no

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SWS facilitation. Explanations have relied on the breakdown of diurnal, monophasic sleep patterns and circadian rhythms as explanatory, yet the cause of this perturbation of rhythm remains unclear. This issue will be addressed at more length at the end of this chapter.

It should be noted that non-significant differences existed between group for AD night REM amounts and percent. How does one interpret this in light of subsequent #EA for each group for the RD night, i.e. is the EA data a reflection smaller amounts of baseline REM for the narcoleptics? Several arguments pertain. At least among normals, such a small loss of REM would not cause dramatic increases in numbers of RD EAs to be required, as is evident from Vogel's work with consecutive nights of RD. Furthermore, narcoleptic subjects one and thirteen had both the largest percent of REM on AD night and the most EAs (40) on RD. The lack of significant group differences or individual correlations between REM on AD and EAs on RD for narcoleptics ($r=.002$) lead on to assume that subsequent RD data may be assumed to relate to the differential responses of normals and narcoleptics to the RD challenge rather than to differences pertaining to a prior state (REM deprived). However, this assumption is based on the notion that narcoleptic REM fractionals would be higher on baseline were they in such a REM deprived state, and does not adequately consider the possibility

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of a REM deprived state that produced no increased REM sleep (rebound). Thus, as an added constraint, one can not assume that the absence of differences for REM sleep amounts on baseline implies similarity between groups with regards to REM state (non-deprived).

The comparison of total recording time (TRgT) and total sleep time (TST) on adaptation night was considered an important relationship as well. The control of these variables between groups was not part of the design of this study. TRgT was based on habitual lights off and on time for subjects, and TST was a variant of this. The absence of recovery nights in the protocol did not necessitate the control of TST. Finally, TRgT was controlled within subject for AD versus RD night, so as not to bias the awakening data. It was, non-the-less, of interest to compare adaptation night TST and TRgT between groups, inasmuch as these factors are known to effect REM sleep. Factors effecting REM sleep on AD night may be thought to influence the number of experimental awakening (EAs) on RD. It may be hypothesized that the length of TRgT might influence the number of EAs in a non-linear manner, due to the disproportionate amount of REM sleep at the end of the night (Verdone 1968). However, no differences were found for TST on AD, nor for TRgT for either night.

It is of interest to compare MSLT data for narcoleptics in this study with findings in the literature, inasmuch as MSLT data,

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particular SL and SOREMPs, are cornerstones of diagnosis. Sleep latency for the pre MSLT for narcoleptics was 2.4', and compared with 3.2' (Richardson), 3' (Mitler et al 1979), 2.4' (Hartse et al 1982) and 2.4' (Mitler et al 1982). SOREMP percent was 56% for the study, compared with 74% (Mitler 1979), 72% (Zorick et al 1982) and 70% (Mitler 1982). Since no adaptation is customary for this procedure, it may be assumed that these statistics are comparable. The difference in SOREMP percent for the study and literature reports can perhaps be accounted for by some individual differences within the patient group. However, if this were so, it would be in a direction unfavorable to the hypothesis of the study, namely increased number of EAs for narcoleptics compared with controls, since fewer SOREMPs on MSLT might imply milder narcolepsy within the narcoleptic sample.

Study findings for normals for pre MSLT indicated average sleep latency of 11.8', as compared with 10' (Richardson) and 12' (Hartse), and replicated the finding of significant differences between groups. Overlap between subject groups for sleep latency occurred in only one instance. In most nap studies of normals, few, if any, SOREMPs are reported, which conforms to data from this study. Again, overlap was confined to one subject, a different normal who had one SOREMP. Since occasional daytime SOREMPs on naps for normals is not unusual, this finding was not surprising. The finding of one normal within the

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"pathological sleepiness" range for pre MSLT (under 5') is again not surprising- some people can readily fall asleep if given daytime opportunity without experiencing significant subjective daytime sleepiness. The finding of two narcoleptics with only one SOREMP each on the pre MSLT illustrates again problems of sensitivity for this measure, inasmuch as both of these narcoleptics had clear history of cataplexy and other symptoms, and had multiple SOREMPs on prior MSLT opportunities. Although several authors have reported SOREMP percents for narcoleptics for MSLT to be between 60-70%, the likelihood that one in ten will produce but one SOREMP remains strong.

The tendency in narcoleptics to have SOREMPs, both at night and during daytime sleep, is not well understood when taken in conjunction with the tendency to have daytime sleepiness and NREM daytime and nocturnal sleep onsets. Once again, what is of interest is the apparent facilitation, at least in some areas, of both NREM and REM sleep, which have traditionally been viewed as inhibitory to each other. Findings in this study that related, in both normals and narcoleptics, sleepiness to aspects of REM sleep will hopefully help to bridge the conceptual space between theories of sleepiness and REM phenomena.

Sleep Statistics for the RD Night

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Inasmuch as this study investigates both the same night response to repeated REM deprivation awakenings, as well as next day effects on sleepiness and REM sleep, it is important to consider the amounts and quality of sleep for the RD night. Two initial concerns are the significant increase in TST and decrease in REM latency for narcoleptics versus controls for RD night. Although expected, one could argue that shortened RL for narcoleptics could result in a higher total number of EAs. However, this would be so only if shortened RL resulted in additional REMPs for the narcoleptic group. In fact, it was the narcoleptic's tendency to have few, long REMPs on RD, not more REMPs, that resulted in the greater number of EAs. Additionally, the tendency of narcoleptics to have multiple EAs during the first REMP was in clear contrast to that of normals, none of whom had more than one EA. Nine of the narcoleptics had more than 1 EA for the initial REMP. Thus it seems fair to say that the amount of REM opportunity for the RD night based on the start of the first REMP was not as significant as was the amount of EAs during the first REMP, an occurrence not obviously related to amount of REM time.

Narcoleptics did have more TST on RD, but no differences were found for recording time. This difference is accounted for by greater interREMP sleep efficiency, and shorter sleep latencies after experimental awakenings. Thus narcoleptics appeared

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sleepier during the RD night. This may be due to a differential response to the REM interruptions- one theory is that REM sleep is responsible for narcoleptic sleepiness; or it may be considered to be consistent with general increased sleepiness and short latencies for this patient group.

Of special importance is the amount of REM sleep on the RD night, inasmuch as this pertains directly to the RD intervention and its success. In this regard, it is noted that a) both groups showed significant decreases in REM sleep time and percent when compared with adaptation night; and b) no differences in REM time and percent between groups existed for the deprivation night. It can thus be said that both groups incurred commensurate decreases in REM sleep on the deprivation night, at least under the constraints of conventional sleep scoring. However, as Ellman has suggested (oral communication), it is reasonable to assume that narcoleptics attained additional REM sleep during RD that was not scorable as such. This is based on evidence of their propensity to dissociate aspects of REM sleep into NREM and waking states. However, this eventuality would not be favorable to the prediction of increased number of experimental awakenings within the narcoleptic group. It might be argued that this possible REM leakage or dissociation during the RD night might prejudice findings for the post MSLT procedure. The basis of this assumption is an underlying tenant in the notion of absent

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REM rebound in narcolepsy and narcoleptic sleepiness as secondary to disinhibited REM sleep. However, significant changes in SOREMP percent were noted in the expected direction for narcoleptics for the post MSLT, indicating some deprivation did occur.

Since no "rebound" and recovery were part of this study, the importance of this apparent equal REM deprivation must be explored. It is assumed that RD would have some effect on subsequent day MSLT parameters, and in fact in some instances this was true- significant changes in SOREMP production for both groups occurred, although surprisingly no changes in sleep latency for either group were noted. However, the effects of REM deprivation on same night sleep architecture have never been systematically investigated in humans. It is thus not possible to say, for instance, with any certainty, whether larger numbers of RD awakenings required during the last REMP are a function of prior RD, a function of greater REM persistence secondary to circadian (timing) factors, or a combination of both.

We can now turn to a discussion of the two primary findings for the study, which are most intimately connected with the initial hypotheses. These are the differential response to a REM deprivation challenge in narcoleptics versus normals controls; and the effects of REM deprivation on daytime sleepiness. It should be remembered that narcoleptics provide the only example

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in humans, both naturalistic and experimental, of the simultaneous presence of chronic EDS and dissociated REM phenomena, and in this sense, the pathophysiology of narcolepsy should be most instructive in understanding the relationship between REM sleep and sleepiness. With regards to this relationship, we can examine the findings pertaining to the effects of RD on following day sleep latencies for groups and individuals, SOREMP propensity, and the relationship of basal daytime sleep tendency to same night response to the RD challenge.

Of note in this regard is the very terminology that I have used-REM deprivation challenge. In a certain sense, findings pertaining to this part of the study must be viewed within the framework of standard REM deprivation literature. However, the challenge to the REM system and sleep architecture during the nichthemeron can be viewed as well as REM sleep interruption-that is, it may not be the deprivation of REM sleep per se that has produced some of these findings, but rather the differential response to the repeated interruption of REM sleep.

Fiss and Ellman (1973) have demonstrated that normals respond to non-deprivation REM interruptions by a shortening of the REM-NREM cycle length on recovery nights; that is, on recovery nights, they are conditioned to prematurely terminate their REM periods,

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and to begin them again with shorter than usual latency. Fiss and Ellman do not report REMP findings for the deprivation night itself. This issue is of interest for two reasons. Normals in fact did show this same pattern during the deprivation night; shorter, more frequent REMPs.

Secondly, if narcoleptics have a predisposition to enter REM sleep rather than NREM sleep from wakefulness due to hypopotent NREM mechanisms, or; if they demonstrate difficulty in disengaging REM sleep despite wakeful interruption due to hyperpotent REM or hypopotent waking mechanisms, then certain aspects of these findings would pertain notwithstanding actual REM deprivation effects. Narcoleptics would have a tendency to re-enter REM right away, before any deprivation had accrued; normals, on the other hand, would only develop this tendency gradually, with accruing deprivation (and increased circadian pressures for REM expression). Unfortunately, most prior work in this area has focused on the accumulation of REM pressure secondary to loss of REM sleep and the subsequent rebound effects- increased awakenings in order to effectuate deprivation of REM; shortened REM latency; and increased REM fractionals on recovery nights. Even Fiss and Ellman do not report the effects of REM interruptions on same night sleep architecture.

Let us briefly reiterate some of the theoretical issues involved in a discussion of the major findings. Firstly, there appears to

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be an intimate connection, at least in narcolepsy, between sleepiness and REM phenomena. However, if this is believed to be true by some authors regarding narcolepsy, this has not been the case regarding normals. It has widely been thought that sleep deprivation and SWS deprivation in particular accounted for sleepiness in normals.

This notion has received support from findings of the preferential recovery and protection of SWS after acute and chronic sleep loss, at the expense of REM sleep, under a variety of conditions, even for certain persons following selective REM deprivation. Indeed, when some subjects are REM deprived, they recover small amounts of lost SWS first (Dement and Rechtschaffen, 1968; Dement Greenberg and Klein, 1966; Cartwright et al 1967). Recovery of REM sleep frequently does not occur until the second night, and sometimes not until the third. Furthermore, many subjects tend to recover their deprived REM sleep late in the night, rather than preempt SWS with early or onset REMs. Recovery of SWS seems to be a ubiquitous phenomena; recovery of REM sleep is apparently subject to some individual differences.

This appears true for both groups and individuals. Group differences have been reported for narcoleptics by Dement and Rechtschaffen and by Spielman, who asserted that narcoleptics may

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show no REM recovery. Several authors have described absent recovery in schizophrenics, and phase advanced recovery in depressives.

This recent emphasis on the ascendancy of SWS in humans is somewhat remarkable given the earlier focus on the biological role of REM sleep and its priority (Dement 1968). In fact, in a recent edition of the journal Sleep (1982) devoted to Current Perspectives of Daytime Sleepiness, REM sleep is largely ignored. In their article on determinants of daytime sleepiness describing sleep extension, acute and chronic sleep restriction, and sleep deprivation, Carskadon and Dement (1982) do not discuss REM sleep at all!

The protection of SWS is especially salient when sleep is restricted in humans; SWS, especially stage IV, assumes disproportionate amounts of total sleep time, generally at the expense of REM and stage II sleep. This finding has been reported for both acute and chronic sleep restriction by Webb and Agnew (1965, 1974, and 1975), and by Webb and Freil (1971). These studies indicated that when sleep was subsequently extended or recovery allowed, stages REM and II comprised almost all of the "oversleep" or recovery. These findings are further confirmed by Johnson and McLoed (1977) and Mulleney et al (1977) during gradual sleep reduction.

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Findings for animals are different than those for humans, inasmuch as total sleep deprivation can lead to SOREMPs and immediate REM rebound with preference over SWS. One can regard the production of SOREMPs at nocturnal sleep onset as the ascendancy of REM sleep over SWS mechanisms, which are thought to be inhibitory towards REM expression. In this context, nocturnal SOREMP production in normal humans is unlikely. Yet even in animals selective REM deprivation does not lead to preemptive sleepiness, even in instances of 70 consecutive days of RD (Dement and Rechtschaffen, 1968). When humans are completely deprived of sleep, they do not tend to have SOREMPs; this is true as well when sleep is chronically restricted. Even when humans are selectively REM deprived, the occurrence of SOREMPs is unusual, and frequently limited to a few select persons who exhibit tendencies for frequent SOREMPs. Only when normal sleep is fragmented, as in polyphasic sleep schedules such as those of Carskadon, Moses, and Weitzman, or when onset corresponds to high REM propensity, such as in radical 180 degree phase shifting, does REM sleep precede the occurrence of SWS.

The production of SOREMPs is important because narcoleptics are both sleepy and have sleep onset REMPs, and in other respects appear to be REM deprived. They alone seem to display some clear relationship between REM sleep and sleepiness. Normals have shown great variability concerning SOREMP production, but no

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systematic comparison of this tendency with sleepiness and the ability to store REM exists. Certain normals will tend to have repeated SOREMPs under deprivation conditions- as reported by Dement and Rechtschaffen (95/78 subjects), Mulleney (2/6), and Carskadon.

Carskadon and Dement have reported some relationship between REM sleep and sleepiness in normals. The 1977 study reported a significant positive relationship between pre-nap subjective sleepiness and the occurrence of nap REM sleep. Furthermore, REM sleep predicted decreased subjective sleepiness after the naps. Conversely, SWS during naps without REM predicted increased post-nap sleepiness. The authors stated that this suggested "that subjective reports of sleepiness may reflect a prodromal state for REM sleep in much the same manner that SWS or NREM sleep normally precedes REM sleep in nocturnal sleep periods" (pg. 132, 1977). Finally, the 1981 study by these authors clearly shows that sleep restriction with no decrease in SWS results in daytime sleepiness. It is unclear if this is caused by lost sleep (any kind) or lost REM sleep in particular.

Explanations for the differential preservation and recovery of SWS versus REM sleep have taken two approaches. One, supported by Webb and Hartmann, indicates that since REM occurs during the latter part of recovery or oversleep, and that its need or pressure accounts for increases TST or sleep period-that is,

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oversleep. An extension of this idea is that REM sleep, or its need, serves to extend sleep and recover lost sleep, inasmuch as it occurs predominately at the end of the night. It can as well be thought of as having a unifying effect on sleep architecture, tying together stretches of NREM. Thus the presence of SOREMPs and early REM would interfere with the maintenance of late night sleep, as in the case of certain depressive patients.

Generally, when sleep is lost, late night REM propensity seems to extend it on the subsequent night, when allowed. A similar idea is suggested by Gillen et al in their schizophrenia study. In this regard, disturbed nocturnal sleep may be related to disturbed REM mechanisms-the inability of REM to smoothly tie together sleep architecture and to maintain sleep in the early morning hours.

This could be explained on a circadian basis-early morning awakenings result in REM deprivation that lead to SOREMPs.

It would follow that sleepiness would result from this sort of scenario, especially if disturbed REM mechanisms included some inability to store and recover REM sleep, for this would directly constrain the individual's ability to extend sleep during the preponderately REM hours. In this regard, it should be recalled that REM sleep is the most vulnerable part of the sleep system, in that sleep restriction, especially arising early, will reduce REM amounts. REM is thus most susceptible to sleep loss, and the

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ability to store and recoup it may be essential to maintaining alertness and recovering lost sleep. It may thus function to protect daytime alertness by storing its need until the next sleep opportunity, its expression being commonly inhibited by wakefulness. Nap or MSLT opportunity will unmask this need during daytime, and narcolepsy can be seen as impairment of its inhibition by wakefulness.

A second explanation is that increased REM fractionals are a function of circadian REM sleep propensity and oversleep, and not that oversleep is caused by REM pressure. This is in line with findings for sleep extension reported by Verdone. In both of these instances increased REM sleep is associated with increased total sleep, although when sleep time is held constant, REM rebound will still occur.

There is then the issue of the relationship of REM sleep to mood. This is of interest to us inasmuch as precocious REM sleep, that is, SOREMPs, appears to be related to mood states. Both narcoleptics and certain depressives are prone to have SOREMPs. Furthermore, these depressives are also prone to have SOREMPs after mid-nichthemeron experiemental awakenings (Schulz and Tetzlaff, 1982), a finding similar to the one in this study for narcoleptics, to findings in a companion study of NREM awakenings in narcoleptics (Spielman et al, 1982) and the findings of N'Nano et al (1971) for narcoleptics. This tendency to produce SOREMPs

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after awakenings occurs in these depressives even during clear cut remission, and is thus in some respects mood independent. It is thus clear that the tendency to have SOREMPs during the night following awakenings is not unique to narcoleptics. Although the Schulz study did not awaken subjects from REM sleep, the Spielman study illustrates that narcoleptics are susceptible to having SOREMPs when awakened from mid-nichthemeron NREM sleep as well, whereas normals are not.

Thirdly, the findings of this study bear on the etiology and pathophysiology of narcolepsy, in particular the relationship of sleepiness to the REM phenomena of narcolepsy. It should be emphasized that this is a very poorly understood relationship, and has been refractory to clarification through experimental manipulation. In fact, the Dement and Rechtschaffen article of 1968 is perhaps the only cogent article that attempts to explain this relationship. Yet even this excellent article concludes by positing an interactional, non-specific model of waking, NREM, circumstantial, and constitutional factors in the development of this illness. A review of critical findings for narcolepsy should thus precede a disucsussion of the study findings.

Dement and Rechtschaffen have asked, how can REM win out over NREM in narcolepsy? Although narcoleptics are pathologically sleepy, and this symptom generally appears prior to any REM

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aspects, the illness can not be viewed as a mere potentiation of NREM, or of sleep in general. Narcoleptics do not sleep significantly more than normals during 24-hours, or at night. Sleep efficiency is often poorer for this group than normals. Nocturnal dyssomnias such as those in narcolepsy are often associated with daytime sleepiness, but not with NREM facilitation or hypoarousal per se, as in hypnichthemeron phenomena. NREM is not prepotent, for REM onsets common. The need for sleep is not excessive, as in the sleep deprived, for daytime naps are generally brief, often with low voltage mixed EEG, yet are still refreshing. Important phenomena connected with the illness-cataplexy and hypnagogic hallucinations, are clearly REM related and occur during waking, not sleep.

On the other hand, the illness is clearly not merely a case of prepotent REM systems. EDS routinely precedes, by several years, the development of observable REM phenomenon in this illness-sleepiness and daytime sleep behavior, including so-called sleep attacks may precede, by as much as ten to twenty years, the occurrence of SOREMPs and cataplexy, the cardinal REM features of the illness. Although SOREMPs are common, NREM daytime onset are equally common, as are short naps and microsleeps without REM sleep. No general increase in the amounts and percentages of REM sleep is seen. Narcolepsy is not merely a case of excessive REM pressure as per the model of REM deprivation; for although RD may

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produce SOREMPs, it has never, in humans or animals, produced cataplexy. Drugs that ameliorate REM symptoms, such as tricyclics, do not ameliorate narcoleptic sleepiness, and drugs that ameliorate sleepiness are not as successful in managing REM symptoms.

Inasmuch as DNS is often seen as an initial symptom in conjunction with EDS, the two phenomena have been felt to be linked. Additionally, alterations and disruptions of normal sleep schedules have been implicated as a possibly precipitating feature in this illness. Yet clearly insomnia and disturbed nocturnal sleep does not routinely cause narcolepsy; many people either participate in shift work with radical phase shifts, or suffer with dys and parasomnias without developing narcolepsy. Patients with obstructive sleep apnea may demonstrate the sleepiness and SOREMPs of the narcoleptic, but this is generally reversible, and these patients generally do not develop cataplexy, although it is of interest that a certain percentage have both illnesses. Finally, narcolepsy is not merely a condition involving hypoarousal; narcoleptics do not appear as individuals in chronic hypoalert states, nor is total wake time for 24-hours substantially less than in normals.

We can now examine the major findings in light of the above findings and theoretical propositions. Findings for the RD night for groups-normals versus narcoleptics demonstrate differences in

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numbers of experimental awakenings required to deprive REM sleep, differences in the number of REMPs, differences in the distribution of awakenings, and in the post EA SOREMP percent. In general, normals responded to the REM awakenings and deprivation by returning to NREM sleep in most instances, especially during the first and second REMP periods; they thus tended not to have a second awakening until the beginning of the subsequent REMP. Normals then tended to have increasing numbers of EAs/REMP as the night progressed (this was true regardless of the REMP scoring convention utilized). The average number of experimental awakenings was 14. This is relatively consistent with reports in the literature (the average for Dement, 1960, for the first night was 11) although due to differences in awakening criteria results are not comparable. Furthermore, normals tended to return to REM sleep within 15' (the SOREMP criteria)-far less frequently than did narcoleptics, 43% versus 81%. Two additional trends were noted. Normals significantly increased the number of REMPs for RD over baseline, going from 4 to 7 REMPs; and these REMPs were significantly shorter, with significantly reduced REMP to REMP cycle length. Secondly, no normals incurred more than one EA during the first REMP; all returned to NREM sleep after this awakening.

Narcoleptics, on the contrary, had essentially the same number of REMPs on RD as on adaptaion. These were significantly longer in

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length, and included enforced awake time. No differences for overall REMP cycle duration between AD and RD nights were noted.

In general then, normals responded to awakenings by delaying REM sleep, whereas narcoleptics tended to re-enter REM sleep almost immediately after an awakenings (80% of the time). This resulted in many short REMPs for normals, and fewer, very long ones for narcoleptics.

Some conclusions and suppositions may be made from the above striking trends. Normals do not tend to return to REM sleep when awakened from it unless a) they are REM deprived or b) they are awakened from REM at a circadian point when REM sleep propensity is very high, such as the end of the night. It is not possible to determine if the pattern of increased awakenings for normals throughout the night in this study is due to RD effects, circadian effects, or both. Narcoleptics, however, clearly have a tendency to re-enter REM sleep after an interruption notwithstanding REM deprivation. This is evident in the trend towards multiple EAs for the first REMP- 9/12 subjects had more than 1 EA in REMP number one. It is presumed that REM deprivation was not responsible for these awakenings, although two additional possibilities exist: Narcoleptics are chronically REM deprived but do not exhibit this on baseline; or they are exquisitively sensitive to small amounts of REM deprivation.

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However, since narcoleptics tend to enter REM sleep more frequently than do normals from NREM awakenings, the latter explanation seems unlikely.

Several explanations are possible for the above awakening and REMP phenomena. At sleep onset, narcoleptics may be more apt to enter REM sleep regardless of the prior state, i.e. wakefulness, REM, or NREM. This would imply that the increased #EAs was an artifact of the awakening procedure. A companion study (Spielman et al, 1982) that employed NREM awakenings in the same subjects indicated that this is to some extent true-narcoleptics entered REM from NREM twice as frequently as did controls, and were able to produce SOREMPs after awakenings that followed REMP termination by 15' and 30', whereas normals only produced SOREMPs when at least 45' had elapsed. This would then explain the tendency for narcoleptics to have repeated EAs during the first REMP, as well as at initial nocturnal sleep onset and during daytime naps. A second possibility is that SOREMPs in narcoleptics are a function of the preceding neural state. For example, if the REM process prior to an RD awakening is not disengaged by arousal mechanisms nor is inhibited by the NREM neural network, a SOREMP would appear at the resumption of sleep. Narcoleptics would then be viewed as impaired in their ability to disengage REM sleep when interrupted. In order for this argument to be cogent, it would have to account for REM onsets at night.

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Yet this study is not able to pinpoint this impairment in disengagement, should it exist. For it is possible that narcoleptic REM mechanisms when in the on position are too powerful to be inhibited; or that other mechanisms responsible for inhibition are too weak.

Findings for the NREM awakening study in conjunction with successful inhibition of REM mechanisms with medication and normal TREMT for nocturnal sleep imply that prepotent REM is not responsible for SOREMPs and narcolepsy. Rather clinical evidence seems to suggest that both hypopotent NREM and waking systems are responsible. At sleep onset, waking systems are lowered and NREM has not yet reached full engagement, and thus REM disinhibition is common—in SOREMPs, hallucinations, and sleep paralysis. Inasmuch as waking is lowered for all persons under these conditions, for narcoleptics disinhibition of NREM systems seems likely. When NREM is strongest, such as 15–30 minutes after the first REMP, narcoleptic SOREMP propensity is lowest (less than 30%, although normal propensity is virtually zero). When NREM systems are weakest, such as during early daytime, and REM is strong, SOREMP propensity is very high (about 85% for early morning MSLT naps, and close to 100% for end of night awakenings). NREM daytime onsets may be due to impaired arousal mechanisms in conjunction with low points on REM ultradian cycles, or secondary to either hypothesized 90' REM refractory periods or NREM (sleep)

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dependent mechanisms (Johnson et al 1980). At any rate, REM sleep propensity and SOREMP propensity are not equipotent at all times over 24 hours, but are rather modulated by both the NREM-REM cycle and time of day.

A basic relevant question would then be what occurs when normals disengage REM sleep when aroused, and respond by containing or putting off the expression of REM to the next appropriate time, that is either later in the night or on recovery. If normals, after RD, inhibit rebound until the end of the night on recovery, then it is not merely the arousal system that helps contain REM. Yet clearly, in narcolepsy, the occurrence of dissociated REM phenomena into waking states, especially the occurrence of cataplexy, imply arousal deficits as well. This leaves one with the less parsimonious conclusion that narcolepsy involves possible deficits in several semi-autonomous neural mechanisms-waking, NREM sleep, and REM sleep. This latter deficit rests on the notion of chronic REM deprivation in narcolepsy, due to an inability to store and delay expression of REM sleep after its loss. A study of rebound effects after deprivation would be necessary to test this concept.

One more likely scenario is related to the sleep fragmentation studies of Carskadon, which produced frequent SOREMPs in all subjects, unlike standard REM deprivation studies. Changes in sleep schedules, sleep restriction, radical phase shifts, or

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disturbed sleep secondary to stress or environment could lead to daytime napping, which is clearly associated with exacerbations in disturbed nocturnal sleep and daytime REM onsets. When nocturnal sleep is disturbed, the system protects SWS first, resulting in chronic nocturnal REM deprivation and recovery during daytime napping. This further deteriorates basic monophasic sleep/wake rhythms. REM loss and daytime sleepiness and napping would thus be connected. However some trait that prevents narcoleptics during the incipience of their illness from returning to normal regulation is postulated, a trait which involves the inability to contain and store REM expression adequately.

A possible phase advance in the REM sleep cycle of narcoleptics has been cited as the cause of SOREMPs and the apparent state of REM deprivation, a point Vogel makes about depressives with short REM latencies. However, what can account for the chronic REM deprivation, if not a trait which interferes with the ability to store and recover missed REM sleep in a temporally appropriate manner at the end of the night. Such a trait has been hypothesized for certain depressives, schizophrenics, and certain normals, although no clear findings are available. It is this sort of trait that might account for auxiliary symptomatology. However, since many normals have undergone periods of schedule change and REM deprivation without consequence, it appears that a

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deficit in the ability to shift sleep and wakefulness rhythms in an adaptive, flexible fashion is a basic ingredient. Thus, hypothetically, if arousal levels during REM resulted in sleep disruption, normals might then be able to shift to NREM sleep and return to REM sleep at a later point.

Sleepiness Findings

Of particular relevance to the above the findings for differential response to the RD challenge between groups was the finding of noteworthy individual differences between the normals. Narcoleptic like response to the RD challenge in certain normals (high numbers of EAs) was very highly correlated with daytime sleepiness as measured by sleep latency on the pre MSLT. Findings of a similar nature with greater apparent face validity have been reported by Roth et al (1980); normals with more frequent changes to stage I during nocturnal sleep have shorter MSLT sleep latencies. This corresponds with notions regarding disturbed nocturnal sleep and sleepiness. However, it is more surprising that the number of EAs required to deprive REM sleep should be related to sleep latency, inasmuch as the former is viewed as a direct reflection of REM deprivation, at least in normals. Although Roth et al found significant decreases in REM sleep percents in the apneic (very sleepy) versus control groups, he reports no data for individual differences in the control

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group for REM sleep versus daytime sleep latency.

The finding that post EA SOREMP percent was correlated with pre MSLT sleep latency for the normals at .90 may indicate that sleepiness in general is related to REM phenomena per se, and not just "sleep" in general, as has been believed. It is not possible based on data for this study to determine whether this sleepiness is due to chronic or acute REM sleep loss due to schedule, or whether this reflects a trait that is similar to one in narcolepsy. It is, in fact, problematic whether one might expect higher or lower REM fractionals for baseline to correspond with high numbers of EAs. High REM fractionals might imply rebound from prior RD perhaps due to sleep restriction, whereas low REM fractionals would imply current RD. It should be remembered that narcoleptics had normal REM percents on adaptation night, and that no correlation was found between #EAs and REM amounts for the narcoleptic group.

There is some indication that normals with higher numbers of EAs also slept more on adaptation and had more REM sleep, although no differences for TRgT were noted ($r=.44$ for TST, $r=.51$ for TREMT). This might then favor an interpretation that these normals were in some sort of RD state that resulted in increased REM fractionals and TST on baseline, shortened REM latency on the RD night, repeated efforts to remain in REM sleep when it was interrupted and deprived, and increased sleepiness as indicated

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on three measures: pre MSLT SL (-.90), post MSLT SL (-.42), and combined adaptation and RD SL (-.37). This would imply that high REM need (perhaps related to prior RD, perhaps not) was assessed several ways-TST, TREMT, and #EAs. It at least appears that RD EAs are not a function of AD night RD or REM amounts, when limited to this two night paradigm (it is known that prior RD increases the number of EAs required for subsequent RD).

Another possibility is that increased TST on AD provided for subjects who were not sleep deprived and thus more available to the RD process, in the sense of lowered interference from ST.III-IV sleep need.. On the other hand, the longer sleeping on AD may reflect the greater REM need.

It is certainly noteworthy that all three measures of SL are negatively correlated to the #EAs for RD. It is of further interest that those two normals whose SL was shortest on post MSLT, JH and JS (#7 and #10), both had 4 SOREMPs on this test. In this sense they appear narcoleptic- shortened SLs with REM onsets on daytime naps, and it would appear that the short latencies are connected with the appearance of REM. However, as pointed out by Spielman (oral communication), the probability of an MSLT SOREMP produces a negative correlation with the EA frequency for both pre and post MSLT in the narcoleptics, surprising since one would think that short sleep latencies,

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SOREMPs on MSLT, and numerous RD EAs would form a constellation. This might be explained for the narcoleptic group in terms of other forms of dissociated REM.

Of interest was the finding that mean SL for both groups did not change (decrease) following RD, when compared with the pre MSLT. This was not especially surprising for the narcoleptic group, since it has been previously noted that the MSLT is not especially sensitive to variations in sleepiness for patients in the pathological range, perhaps due to a floor effect. However, this was remarkable for the normal group, inasmuch as a correlated T Test for differences in TST between AD and RD indicated significant sleep loss on RD (c.f. Table IX). The average loss of sleep on RD for the normals was 50', and might be expected to produce shorter sleep latencies on the MSLT. However, with respect to individual differences, those normals who were sleepy on pre MSLT remained so, although the strength of the relationship between #EAs and SL decreased to $-.41$, due in all likelihood to some leveling effects of the RD procedure.

The fact that SL did not decrease for post MSLT implies that it is not the loss of REM sleep per se that results in short SLs. The most direct explanation is that REM sleep mechanisms are directly related to sleepiness, although not necessarily to nocturnal REM sleep amounts and percents. In the case of hypersomnia sleep apnea patients, reduced REM sleep amounts are

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prominent as is daytime sleepiness and general nocturnal fragmentation of sleep. The fragmentation of sleep, and REM in particular, may be equally soporific when compared with actual REM sleep loss in time and percent. The findings of Schulz suggest that a trait for REM onsets during sleep after awakenings exists independent of narcolepsy. Data from this study is suggestive of such a trait in certain normals which may involve the inadequate gating of REM expression, although not to the extent of producing clinical auxillary phenomena, such as cataplexy and sleep paralysis. It is more likely that the sort of individual differences noted by Dement and Rechtschaffen regarding rebound and SOREMP production are involved as well in the number of EAs, and that this in turn is related to daytime sleepiness, when unmasked by nap opportunites.

Diagnostic Findings

Table XVII presents data for sensitivity, specificity, and diagnostic confidence for the RD measures. This table lists levels of sensitivity for 2 different criterion points, using both #EAs and post EA SOREMP percent. To reiterate, sensitivity and specificity refer to given cases, whereas confidence levels refer to given diagnoses. Findings for EA measures can be compared with those in the literature for MSLT, the current

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diagnostic test.

Based on the currently relied upon diagnostic criterion of 2 SOREMPs on MSLT, 11/13 narcoleptics produced 2 or more SOREMPs (sensitivity=.84). Specificity for this group was 100% (0/9 normals had 2 or more SOREMPs). Confidence for + diagnosis was also 100% (9/9 + diagnosed cases were all narcoleptics). Confidence for - diagnosis was .81 (9/11 negative findings were for normals). One criterion measure for the EAs, post EA SOREMP percent >74%, produced values equal to or greater than those above for the 2 SOREMP criterion. However, these differences were minor, and the population for this study does not represent the typically hard to diagnose population of sleep disorders centers. Thus although the RD procedure is able to distinguish with reasonable success normals from REM narcoleptics, its utility as a diagnostic procedure is in doubt. Of remaining concern is the development of a test to better identify those narcoleptic patients during the prodromal phase of the illness, when auxillary symptoms and SOREMPs are often not manifest.

TABLE ONE

COMPARISONS FOR NARCOLEPTICS AND NORMAL CONTROLS FOR ADAPTATION NIGHT SLEEPSUMMARY SLEEP STATISTICS

	<u>Normal controls</u> N=11 X (range; SD)	<u>Narcoleptics</u> N=13 X (range; SD)	Significance
Total Recording Time(Min)	450 (355-552; 51)	452 (315-585; 70)	ns
Total Sleep Time(Min)	396 (252-484; 67)	395 (267-468; 59)	ns
Sleep Latency(Min)	19.6 (2-55; 15.6)	6.4 (1-14; 4.4)	p<.05
Total Wake Time(Min)	55 (16-183; 44.8)	56.9 (14-117; 31.5)	ns
WASO(Min)	33.6 (9-125; 32)	49.9 (13-116; 31.7)	ns
# Awakenings(epochal)	28.3 (14-42; 10.9)	36.5 (18-76; 14.9)	ns
# 5 Min. Awakenings	1.2 (1-5; 1.5)	2 (1-8; 2.1)	ns
REM Latency(Min)	87.4 (38-204; 44)	45.4 (.3-181; 65.4)	ns
Sleep Efficiency(%)	87.8 (58-91; 10.3)	86.5 (77-97; 5.5)	ns

Description for Table One: Table One contains means, ranges, and standard deviations for one adaptation night (4D) for normal and narcoleptic subjects. Differences between group means are reported using a two-tailed T test. Included are amount of time awake after sleep onset (WASO), the number of spontaneous nocturnal awakenings (at least one 20" epoch of stage 0), the number of awakenings lasting at least 5', and sleep efficiency, which is the fraction total sleep time/total recording time x 100, as well as other standard sleep statistics.

TABLE TWO

COMPARISON FOR NARCOLEPTICS AND NORMAL CONTROLS FOR ADAPTATION NIGHT (AD) SLEEP STATISTICSSLEEP STAGE STATISTICS

	Normal Controls (N=11) X (range; SD)	Narcoleptics (N=13) X (range; SD)	Significance
Stage I(Min)	49.9 (16-89; 28.2)	101.1 (40-196; 41.7)	p<.005
Stage I(%)	12.4 (3.4-25; 8.6)	25.6 (9.9-43; 9.8)	p<.005
Stage II(Min)	207.7 (160-256; 34.7)	181.6 (109-241; 51)	ns
Stage II(%)	54.5 (45-70.5; 7.6)	46.2 (29-61.5; 8.6)	p<.05
Stage III-IV(Min)	47.8 (8-124; 37)	40.4 (1-119; 39)	ns
Stage III-IV(%)	12 (1.2-25; 8.6)	9.9 (0-29.4; 9.5)	ns
Total REM Time(Min)	87.2 (8-154; 41.1)	71.9 (46-99; 16)	ns
REM(%)	21 (3.2-34.3; 8.3)	18.5 (13-27.1; 4.5)	ns

Description for Table Two: Table Two contains means, ranges, and standard deviations for sleep stages for one adaptation night (AD) for the normal and narcoleptic groups. Differences between group means are reported using two-tailed T test. Included are statistics for sleep stages in minutes and as a percent of total sleep time.

TABLE THREE

COMPARISON FOR NARCOLEPTICS AND NORMAL CONTROLS FOR ADAPTATION NIGHT SLEEP STATISTICS

	<u>REM PERIOD (REMP) STATISTICS</u>		Significance
	Normal Controls N=11 X (range; SD)	Narcoleptics N=13 X (range; SD)	
# REMPs 10 Min. Rule	4.2 (2-5; .9)	4.8 (3-7; 1)	ns
Mean REM Length(Min)	22 (4-33; 8.9)	20.9 (13-30; 5)	ns
Mean REM Interval(Min)	100.9 (76-172; 26)	100.1 (73-170; 25.6)	ns

Description for Table Three: Table three contains means, ranges, and standard deviations for one adaptation night (AD) for normal and narcoleptic subjects. Differences between group means are reported using a two-tailed test. Included are statistics for REM periods (REMPs) based on the 10' REM rule, which states that a REM is ended when the last page of REM sleep is followed by 10' of NREM sleep. Means are presented for the number of REMPs on the AD, average REM length across AD night, and average REM interval across AD night, which was calculated as the interval from REM onset to REM onset.

TABLE FOUR
COMPARISON FOR NARCOLEPTICS AND NORMAL CONTROLS FOR REM DEPRIVATION (RD) NIGHT SLEEP STATISTICS

	Normal Controls N=11 X (range; SD)	Narcoleptics N=13 X (range; SD)	Significance
Total Recording Time(Min)	455.5 (380-551; 50.2)	479 (372-609; 61.1)	ns
Total Sleep Time(Min)	344.7 (297-381; 26.4)	388.7 (267-468; 62)	p<.05
Sleep Latency(Min)	9.1 (1-30; 8.2)	3.4 (1-13; 2.4)	p<.05
REM Latency(Min)	75.4 (16-132; 31)	22.8 (.3-169; 50.2)	p<.01

Description of Table Four: Table Four contains means, ranges, and standard deviations for sleep statistics for one REM deprivation (RD) night for normal and narcoleptic subjects. Differences between group means are reported using a two-tailed T test.

TABLE FIVE
COMPARISON FOR NARCOLEPTICS AND NORMAL CONTROLS FOR REM DEPRIVATION (RD) NIGHT SLEEP STATISTICS

<u>REM DEPRIVATION STATISTICS</u>			
	Normal Controls N=11 X (range; SD)	Narcoleptics N=13 X (range; SD)	Significance
Total REM Time(Min)	X=22.4 (2-48; SD=14.5)	X=23.2 (5-47; SD=12.4)	ns(p<.8)
REM(%)	X=6.5 (.6-13.5; SD=4.3)	X=7.1 (1.7-14.1; SD=3.9)	ns(p<.7)

Description for Table Five: Table Five contains means, ranges, and standard deviations for REM deprivation sleep statistics for one RD night for normals and controls. Differences between groups were calculated using a two-tailed T test, and represent effectiveness of REM deprivation for each group.

TABLE SIX

COMPARISON FOR NARCOLEPTICS AND NORMAL CONTROLS FOR REM DEPRIVATION (RD) NIGHT SLEEP STATISTICSREM PERIOD (REMP) STATISTICS

	Normal Controls N=11 X (range; SD)	Narcoleptics N=13 X (range; SD)	Significance
<u>Ten Minute REM Period Convention</u>			
Number of REMPs	7.6 (6-10; 1.2)	5.4 (3-8; 1.6)	p<.005
Average REM Length (Min)	12.3 (1-26; 7.3)	34.9 (14-79; 18.6)	p<.005
Average REM Interval (Min)	53.4 (44-71; 8.6)	92.8 (49-151; 25.6)	p<.005
Average InterREMP Sleep Efficiency (Min)	62.7 (50-71; 6.3)	65.5 (54-73; 6.4)	ns
Longest REM (Min)	46.5 (3.3-123; 36)	92.1 (27-176; 45.4)	p<.02

Description for Table Six: Table Six contains means, ranges, and standard deviations for narcoleptics and normals on one REM deprivation (RD) night for REM period sleep statistics utilizing the ten minute REM convention. Differences between group means are reported utilizing a two-tailed T test. Using this convention, a REM is concluded when the last page of REM is followed by 10' of NREM sleep. Group statistics are reported for the number of REMPs, the longest REM, and for the individual subject average REM length, interval, and interREMP sleep efficiency. The longest REM is based on the longest REM for each subject. Average interREMP sleep efficiency for each subject is calculated as follows: total sleep time/total recording time x 100 from REM offset to subsequent REM onset, and averaged across the night. REM interval is calculated from REM onset to subsequent REM onset, averaged across the night for each subject.

TABLE SEVEN

COMPARISON FOR NARCOLEPTICS AND NORMAL CONTROLS FOR REM DEPRIVATION (RD) NIGHT SLEEP STATISTICSREM PERIOD (REMP) STATISTICS

	Normal Controls N=11 X (range; SD)	Narcoleptics N=13 X (range; SD)	Significance
<u>Fifteen Minute REM Period Convention</u>			
Number of REMPs	7.1 (6-10; 1.1)	5.4 (3-7; 1.2)	p<.005
Average REM Length (Min)	13.9 (1-26; 7.8)	33 (15-79; 16.3)	p<.005
Average REM Interval (Min)	53.2 (42-71; 7)	90.6 (52-151; 26.)	p<.005

Description for Table Seven: Table Seven contains means, ranges, and standard deviations for narcoleptics and normals on one REM deprivation (RD) night for REM period sleep statistics utilizing the fifteen minute REM convention. Differences between group means are reported utilizing a two-tailed T test. Using this convention, a REM is concluded when the last page of REM is followed by 15' of either NREM sleep or awake. Group statistics are reported for the number of REMPs, and for the individual subject average REM length and interval. REM interval is calculated from REM onset to subsequent REM onset, averaged across the night for each subject.

TABLE EIGHT

COMPARISON FOR NARCOLEPTICS AND NORMAL CONTROLS FOR REM DEPRIVATION (RD) NIGHT SLEEP STATISTICS

EXPERIMENTAL AWAKENING (EA) STATISTICS

	Normal Controls N=11 X (range; SD)	Narcoleptics N=13 X (range; SD)	Significance
Number of Exp. Awakenings (EAs)	14 (6-24; 5.7)	27.7 (18-43; 7.7)	p<.005
Number of EAs/Hour Sleep	2.5 (1.1-4.4; 1)	5.2 (2.4-8.4; 1.6)	p<.005
Average Individual Sleep Latency after an EA	4.1 (.4-14.9; 9.4)	1.3 (.5-2.9; .7)	p<.05
Average Individual Length of EAs (Min)	3.3 (3.1-3.3; .1)	3.3 (3.1-3.1; .2)	ns

Description of Table Eight: Table Eight contains means, ranges, and standard deviations for on REM deprivation (RD) night for normals and narcoleptics subjects. Differences between group means are reported using a two-tailed T test. Included are group means for the number of times subjects were experimentally awakened from REM sleep as part of the REM deprivation procedure, and group means for average number of awakenings per hour of sleep time for each subject. Average individual sleep latency after an experimental awakening was calculated as the average latency to three consecutive epochs of sleep from any stage following an experimental awakening. The average length of experimental awakenings was calculated as the average elapsed time from lights on to lights off during an experimental awakening.

TABLE NINE

COMPARISON FOR NARCOLEPTICS AND NORMAL CONTROLS FOR REM DEPRIVATION (RD) NIGHT SLEEP STATISTICSEXPERIMENTAL AWAKENING (EA) STATISTICS FOR REM PERIODS

	Normal Controls N=11 X (range; SD)	Narcoleptics N=13 X (range; SD)	Significance
Number of Exp. Awak./ REMP	1.6 (.3-3.4; .8)	5.8 (2.9-14.3; 3.2)	p<.005
Number of Exp. Awak. in 1st REM	1 (1-1; 0)	2.8 (1-6; 1.6) 9/13	p<.005
Number of Exp. Awak. in Last REM	3.8 (1-14; 3.6)	14.6 (5-32; 6.7)	p<.005
Most Exp. Awak. for any REM	4.9 (1-14; 3.6)	14.6 (5-32; 7)	p<.005
Exp. Awak. Density	.22 (.09-.75; .18)	.17 (.13-.22; .02)	ns
SOREMP Probability (%) After Exp. Awakenings	43.6 (0-74; 24)	80.7 (68-95; 9)	p<.005

Description of Table Nine: Table Nine contains means, ranges, and standard deviations for REM deprivation (RD) night for normals and narcoleptics subjects. Differences between group means are reported using a two-tailed T test. Included are group means for the average number of times per REM subjects were experimentally awakened from REM sleep as part of the REM deprivation procedure; group means for the number of experimental awakenings occurring during the first and last REM; and group means for the greatest number of experimental awakenings in any one REM. Also included is the awakening density as a function of total REM time (number of awakenings/TREMT for each subject); and the group mean for individual subject SOREMP probability, calculated as (number of instances experimental awakenings were followed by REM sleep within 15' of lights off/ total number of experimental awakenings) x 100. A 10' REM convention was used for this data (a REM is concluded when the last page of REM is followed by 10' of NREM sleep).

TABLE TEN

COMPARISON OF SLEEP ONSET REM PERIOD FREQUENCY FOR NARCOLEPTICS AND NORMAL CONTROLS

	<u>Number of SOREMPs on Adaptation and RD Nights</u>		
	Normal Controls (N=11) (# SOREMPS/# sleep onsets)	Narcoleptics (N=13) (# SOREMPS/# sleep onsets)	Significance
Adaptation Night	0/11	8/13	.005
REM Deprivation Night	0/11 (1 RL of 16')	11/13	.005
Combined Nights	0/22	19/26	.005

Description of Table Ten: Table Ten contains the number of sleep onset REM periods for normals and narcoleptics for both Adaptation and RD nights. Differences between groups are reported using a two-tailed T test.

TABLE ELEVEN

COMPARISON OF MSLT SLEEP STATISTICS FOR NORMALS AND NARCOLEPTICS

PRE MSLT COMPARISONS

	Normal Controls (N=09) X (range; SD)	Narcoleptics (N=11) X (range; SD)	Significance
Average Sleep Latency on Five Naps	11.8 (3.6-19.3; 4.9)	2.43 (.9-5.0; 1.6)	p<.005
Total Number of SOREMPs for Five Naps	.11 (0-1; .3)	2.8 (1-5; 1.2)	p<.005

Description of Table Eleven: Table Eleven contains means, ranges, and standard deviations for the pre multiple sleep latency test (MSLT) for normal and narcoleptic subjects. Pre MSLTs were administered either at least 7 days prior or subsequent to the start or conclusion of the nocturnal recordings, whichever was closer. Differences between group means are reported using a two-tailed T test. Included are group means for the average individual sleep latency on the five daytime naps, for the number of sleep onset REM periods for the five naps, and for the average pre and post nap scores on the Stanford Sleepiness Scale (SSS).

TABLE TWELVE

COMPARISON OF MSLT SLEEP STATISTICS FOR NORMALS AND NARCOLEPTICS

POST MSLT COMPARISONS

	Normal Controls (N=09) X (range; SD)	Narcoleptics (N=11) X (range; SD)	Significance
Average Sleep Latency on five Naps	12.4 (4.7-19.1; 4.4)	2.3 (.67-5.0; 1.2)	p<.005
Total Number of SOREMPs on Five Naps	1.0 (0-4; 1.7)	4.27 (4-5; .47)	p<.005

Description of Table Twelve: Table Twelve contains means, ranges, and standard deviations for the post multiple sleep latency test (MSLT) for normal and narcoleptic subjects. Post MSLTs were administered on the day following the night of the RD procedure. Differences between group means are reported using a two-tailed T test. Included are group means for the average individual sleep latency on the five daytime naps, for the number of sleep onset REM periods for the five naps, for the average pre and post nap scores on the Stanford Sleepiness Scale (SSS), and for the scaled scores for digit span and perceptual/motor speed performance tasks administered in conjunction with the SSS before and after all naps.

TABLE THIRTEEN

Correlated T Tests for Within Group Changes in MSLT Statistics:

Pre Versus Post MSLT

Normal Controls (n=9)

Statistic	Pre-MSLT Mean	Post-MSLT Mean	Significance
Average Sleep Latency	11.8'(4.9)	12.4'(4.4)	ns
Number SOREMPs-5 Nap Average	.11(.3)	1.0(1.7)	ns (p<.2)

Narcoleptics (n=11)

Statistic	Pre-MSLT Mean	Post-MSLT Mean	Significance
Average Sleep Latency	2.43'(1.6)	2.3'(1.2)	ns
Number SOREMPs-5 Nap Average	2.8(1.2)	4.27(.47)	p<.005

Table Thirteen: Table Thirteen reports differences on pre-MSLT and post-MSLT measures of sleep latency and number of SOREMPs for each group, using a correlated T test. Number of SOREMPs is the group mean of the average number per nap for each subject; sleep latency is the group mean of the average latency for each subject for the five naps. Naps with no sleep were scored as having a 20' latency.

TABLE FOURTEEN

Correlated T Tests for Within Group Changes in PSG Statistics:

Adaptation Night Versus REM Deprivation Night

Normal Controls (n=11)

Statistic	Adaptation Mean	RD Mean	Significance
Total Recording Time	450'(51')	455'(50')	ns
Number REMPs 10' Rule	4.2(.9)	7.6(1.2)	p<.001
REMP Interval	101'(26')	53.4'(8.6')	p<.001
Total REM Time	87.2'(41.1')	22.4'(14.5')	p<.005
REM Percent	21%(8.3)	6.5%(4.3)	p<.001
Total Sleep Time	396'(67')	344'(26')	p<.05

Narcoleptics (n=13)

Statistic	Adaptation Mean	RD Mean	Significance
Total Recording Time	452'(70')	479'(61')	ns(p<.1)
Number REMPs 10' Rule	4.8(1.)	5.4(1.6)	ns
REMP Interval	100'(26')	92.8'(25.')	ns
Total REM Time	71.9'(16.0')	23.2'(12.4')	p<.001
REM Percent	19%(4.5)	7.1%(3.9)	p<.001
Total Sleep Time	395'(59')	388'(62')	p<.005

Table Fourteen: Table Fourteen reports differences between Adaptation and REM Deprivation nights for measures of total recording time, average number of REMPs, average REMP interval or cycle length, total REM time and percent, and total sleep time for each group, using a correlated T test. Number of REMPs is the group mean of the average number per night for each subject; REMP interval is also a group mean of individual averages, and is scored from REMP onset to onset.

TABLE FIFTEEN

Pearson Correlations for Experimental Awakening Data With MSLT Data for Narcoleptics

	#EAs	# SOREMPs pre-MSLT	# SOREMPs post-MSLT
# Exp. Awakenings	1.0	-.3402	-.3147

With Adaptation Night PSG Data for Narcoleptics

	#EAs	%ST.I	%III-IV	%REM	TREMT	TST	TRgT
#EAs	1.0	.23	-.29	-.002	.13	.03	.13

With REM Deprivation Night PSG Data for Narcoleptics

REM latency

#EAs	-.44
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Table Fifteen: Table Fifteen reports correlations of PSG and MSLT sleep data with data from experimental awakenings (EAs) on REM deprivation nights for narcoleptics. Reported are correlations for the #EAs with SOREMP frequency for both MSLTs; and #EAs with data for sleep stages, total sleep time (TST), and total recording time (TRgT) for adaptation nights.

TABLE SIXTEEN

Pearson Correlations for Experimental Awakening Data

With MSLT Data for Normals

	#EAs	sleep latency pre-MSLT	sleep latency post-MSLT
# Exp. Awakenings	1.0	-.8180	-.4189
post-EA SOREMP %		-.9007	

With Adaptation Night PSG Data for Normals

	#EAs	%ST.I	%III-IV	%REM	TREMT	TST	TRgT
#EAs	1.0	-.01	-.32	^x .55	.51	.44	.02

With Sleep and REM Latencies for Adaptation and REM

Deprivation Night PSG Data for Normals

	REM latency	TST RD	sleep latency for RD	sleep latency for AD ± RD
#EAs	-.44	.02	-.06	-.37

Table Sixteen: Table Sixteen reports correlations of PSG and MSLT sleep data with data from experimental awakenings (EAs) on REM deprivation nights for normals. Reported are correlations for the #EAs with nap sleep latency for both MSLTs; and #EAs with data for sleep stages, total sleep time (TST), and total recording time (TRgT) for adaptation nights. Also reported are correlations for sleep latency and REM latency for PSG nights with EA data. Finally, the post EA SOREMP percent (the percentage of EAs that are followed by REM onsets) is correlated with pre-MSLT sleep latency.

TABLE SEVENTEEN

Criterion Tests for Diagnostic Sensitivity, Specificity
and Confidence for Normals and Narcoleptics for MSLT and RD Data

Post EA SOREMP Percent versus MSLT SOREMPs

	MSLT=2 SOREMPs	Post EA SOREMP %	>69%	>74%
Sensitivity	84%		85%	85%
Specificity	100%		82%	100%
+ Confidence	100%		85%	100%
- Confidence	81%		82%	85%

Number of EAs versus MSLT SOREMPs

	MSLT=2 SOREMPs	#EAs	>19	>24
Sensitivity	84%		92%	62%
Specificity	100%		82%	100%
+ Confidence	100%		86%	100%
- Confidence	81%		90%	69%

Description of Table Seventeen: Table Seventeen describes the comparative values for diagnostic sensitivity, specificity, and positive and negative confidence using the two SOREMP MSLT convention versus findings for this study for post EA SOREMP percent and the number of experimental awakenings. These latter measures are compared using two pre-selected criterion values for each measure, i.e. a positive diagnosis of narcolepsy is made if the #EAs is greater than 19 (sensitivity is then 92%).

TABLE EIGHTEEN

Individual Sleep Statistics for Narcoleptic Subjects on
Adaptation and REM Deprivation Nights

#	Name	TRgT		TST		SE		TREMT		REM % REM L.			
		AD	RD	AD	RD	AD	AD	RD	AD	RD	AD	RD	RD
1.	DM	486	486	422	302	87	63	24	25	9	.3	.6	
2.	HY	456	439	406	322	89	63	5	15.4	1.	2	71	
3.	RG	535	435	266	264	85	67	24	25	9.	.3	3	
4.	LL	407	408	393	272	96	64	24	16.4	9.	3	1	
5.	IL	495	440	462	332	94	86	18	18.6	5.3	69	3	
6.	VB	495	528	440	364	89	65	28	14.7	7.7	151	1	
7.	JH	458	525	366	337	80	48	10	13	2.9	5	15	
8.	MR	474	508	447	377	94	87	7	19.4	1.9	3	1	
9.	AM	463	497	406	404	88	89	29	22	7.7	125	1	
10.	CG	340	371	306	251	90	51	19	16.7	7.4	4	1	
11.	AF	585	609	468	450	80	64	20	13.7	4.5	180	169	
12.	BA	422	505	383	356	90	86	47	22.6	13.1	1	1	
13.	EG	476	476	366	307	77	99	43	27	14.1	43	1	

$\bar{X}$ (N=13)

Individual Sleep Statistics for Normal Subjects on Adaptaion
and REM Deprivation Nights

#	Name	TRgT		TST		SE		TREMT		REM % REM L.			
		AD	RD	AD	RD	AD	AD	RD	AD	RD	AD	RD	RD
1.	KR	552	551	483	369	88	108	22	22	6	71	69	
2.	AK	424	442	384	338	91	70	32	18	9	85	81	
3.	OA	436	438	390	360	89	98	48	25	13	105	61	
4.	RW	472	513	441	381	93	98	2	22	.6	94	109	
5.	RU	355	398	320	333	90	44	21	14	6	50	53	
6.	RM	464	408	444	320	96	154	44	34	13	38	52	
7.	JH	461	380	428	297	93	123	26	29	8.7	66	73	
8.	JC	435	472	252	329	58	8	8	3.4	2.4	203	88	
9.	AD	504	486	455	373	90	121	14	26	4	103	132	
10.	JS	425	456	366	326	86	73	19	20	6	58	16	
11.	MA	421	455	384	315	91	61	9	16	2.6	81	93	
12.													

$\bar{X}$ (N=11)

TABLE NINETEEN

Individual Sleep Statistics for Narcoleptic Subjects on
Adaptation and REM Deprivation Nights

#	% I	% II	% III-IV	TWT	WASO	#Awak.	#5' Awak.	SL(AD)	SL(RD)
1.	27	55	3	64	57	46	2	5	2
2.	43	29	7	50	41	40	1	7	1
3.	34	43	2	49	44	37	2	1	4
4.	41	42	0	14	13	25	0	1	4
5.	15	43	23	32	22	27	0	9	4
6.	21	55	10	54	47	34	2	7	3
7.	25	40	21	92	83	30	3	10	3
8.	29	48	3	28	26	18	2	1	2
9.	10	39	30	58	44	40	1	14	2
10.	28	54	2	34	28	30	0	6	5
11.	18	62	6	117	116	76	4	2	10
12.	23	43	12	39	26	21	2	12	5
13.	18	42	13	109	101	46	8	8	2

Normal Subjects

1.	3	49	26	67	27	31	1	35	30
2.	7	64	11	40	17	14	1	23	12
3.	6	45	23	46	36	23	1	10	5
4.	20	50	8	32	26	19	2	6	8
5.	13	50	23	36	31	35	1	2	3
6.	7	57	2	16	9	17	0	7	4
7.	5	60	7	34	22	40	0	12	1
8.	25	70	1	183	125	33	5	55	12
9.	5	56	12	50	26	42	0	23	12
10.	24	50	7	59	42	37	2	13	7
11.	22	50	12	38	9	15	0	29	9
12.									

Description: Table eighteen and nineteen describe individual subject statistics for normals and narcoleptics. Included are, in minutes, total recording time (TRgT), total sleep time (TST), total REM time (TREMT), REM latency (RL), total wake time (TWT), wake after sleep onset (WASO), sleep latency (SL); percent of stage I, II, III-IV, REM, and percent sleep efficiency (SE); and number of awakenings of one epoch or more (# awak.) and number greater than five minutes (# 5' awak.). Statistics are for adaptation (AD) and REM deprivation (RD) nights for all subjects.

TABLE TWENTY

Awakening Data for Individual Subjects on REM Deprivation Night

Narcoleptics

#	# Awak.	#/hr.slp.	#/REMP	Awak.Dens.	Changes to St.I(AD)
1.	43	8.4	14.3	.18	72
2.	23	4.3	3.8	.16	62
3.	27	6.1	5.4	.15	55
4.	33	7.2	8.2	.18	47
5.	22	4	4.4	.16	32
6.	35	5.7	5.8	.17	51
7.	26	4.6	4.3	.13	38
8.	27	4.3	3.8	.16	31
9.	20	2.9	2.8	.17	31
10.	20	4.8	5	.19	49
11.	18	2.4	3	.2	53
12.	39	6.5	7.8	.25	36
13.	27	5.3	4.5	.15	40

Description of Table Twenty: Table twenty lists for individual narcoleptic subjects the number of experimental awakenings on the RD night, the number per hour of sleep, the average number per REMP, the REMP awakening density (# of exp. awakenings/total REM period time), and the number of changes to stage I on adaptation night.

TABLE TWENTY-ONE

Awakening Data for Individual Subjects on REM
Deprivation Night

Normals

<u>#</u>	<u># Awak.</u>	<u>#/hr.slp.</u>	<u>#/REMP</u>	<u>Awak.Dens.</u>	<u>Changes to St.I(AD)</u>
1.	13	2.1	1.33	.15	41
2.	17	3.3	2.8	.15	17
3.	11	1.8	1.6	.10	21
4.	18	2.8	2.6	.12	45
5.	9	1.6	1.1	.20	32
6.	23	4.3	.38	.16	21
7.	11	2.2	1.8	.12	27
8.	6	1.0	1	.74	39
9.	13	2.0	1.9	.15	30
10.	24	4.4	3.4	.14	48
11.	10	1.7	1.4	.26	23
12.					

Description of Table Twenty-one: Table twenty lists for individual normal subjects the number of experimental awakenings on the RD night, the number per hour of sleep, the average number per REMP, the REMP awakening density (# of exp. awakenings/total REM period time), and the number of changes to stage I on adaptation night.

TABLE TWENTY-TWO

Individual Subject Data for Pre and Post
Multiple Sleep Latency Tests

Narcoleptics

#	# Soremps		REM Latency		Sleep Latency	
	Pre	Post	Pre	Post	Pre	Post
2.	3	4	4.7	3.7	2.0	1.4
3.	4	4	3	4	1.7	2.3
5.	4	5	10.7	6	4.3	3.3
6.	2	4	6	5	4.9	1.5
7.	1	5	6.7	11	2.9	2.9
8.	1	4	5	7	1.9	2.2
9.	5	5	1.3	4.7	.9	1.7
10.	3	4	8.3	3	1.3	5
11.	3	4	2	.7	.6	.7
12.	3	4	3.7	13.7	5	2.9
13.	2	4	5.3	8	1.1	1.5

Description of Table Twenty-Two: Table twenty-two lists for individual narcoleptic subjects data for pre and post multiple sleep latency tests. Included are the number of sleep onset REM periods for five naps, and, in minutes, the average REM latency and sleep latency (three consecutive epochs of any stage of sleep).

TABLE TWENTY-THREE

Individual Subject Data for Pre and Post
Multiple Sleep Latency Tests.

Normals

#	# Soremps		REM Latency		Sleep Latency	
	<u>Pre</u>	<u>Post</u>	<u>Pre</u>	<u>Post</u>	<u>Pre</u>	<u>Post</u>
1.	0	0	-	-	19.3	19.1
2.	0	0	-	-	10.2	13
3.	0	0	-	-	12.7	15.9
4.	0	0	-	-	9	9.4
5.	0	1	-	12.2	17.2	15.9
6.	0	0	-	-	7.9	14.5
7.	1	4	5	7	11	8.4
9.	0	0	-	-	15.2	11.5
10.	0	4	-	9.0	3.6	4.7
12.						

Description of Table Twenty-Three: Table twenty-three lists for individual normal subjects data for pre and post multiple sleep latency tests. Included are the number of sleep onset REM periods for five naps, and, in minutes, the average REM latency and sleep latency (three consecutive epochs of any stage of sleep).

TABLE TWENTY-FOUR

Individual SOREMP Probability (%) After Experimental Awakenings
for REM Deprivation Night

Narcoleptics

#	# Awak. followed by SOREMP	by SONREMP	SOREMP %
1.	43	40	2 95
2.	23	17	5 77
3.	27	22	5 81
4.	33	29	3 91
5.	22	17	5 77
6.	35	29	5 85
7.	26	22	4 81
8.	27	20	6 77
9.	20	13	6 68
10.	20	16	3 89
11.	18	12	6 66
12.	39	34	4 89
13.	27	21	6 78

Description of Table Twenty-Four: Table twenty-four lists for individual narcoleptic subjects the number of experimental awakenings on the RD night, the number of EAs that were followed by SOREMPs (10' rule), the number that were followed by SONREMPs, and the probability that an EA would be followed by a SOREMP.

TABLE TWENTY-FIVE

Individual SOREMP Probability (%) After Experimental Awakenings
for REM Deprivation Night

Normals

#	# Awak.	followed by SOREMP	by SONREMP	SOREMP %
1.	13	4	9	31
2.	17	11	5	69
3.	11	4	7	36
4.	18	11	6	65
5.	9	2	6	25
6.	23	16	6	73
7.	11	6	4	60
8.	6	0	6	0
9.	13	6	7	46
10.	24	17	6	74
11.	10	3	7	30
12.				

Description of Table Twenty-Five: Table twenty-five lists for individual normal subjects the number of experimental awakenings on the RD night, the number of EAs that were followed by SOREMPs (10' rule), the number that were followed by SONREMPs, and the probability that an EA would be followed by a SOREMP.

TABLE TWENTY-SIX

Experimental Awakening(EA) Reliability Statistics

Number of PSG Record Segments

	<u>EAs</u>	<u>St.0</u>	<u>St.I</u>	<u>St.II</u>	<u>St.III</u>	<u>REM</u>
normals	32	8	8	8	4	4
narcs.	76	20	22	18	8	8

Hits, Misses, and False Alarms

	<u>Hits</u>	<u>Misses</u>	<u>False Alarms</u>
normals	32/32	0	0
narcs.	76/76	0	0

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