Order Number 9432331

Sleep disruption in fatigued versus non-fatigued persons with multiple sclerosis

Caruso, Lauren S., Ph.D.

City University of New York, 1994

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

SLEEP DISRUPTION IN FATIGUED VERSUS NON-FATIGUED PERSONS WITH MULTIPLE SCLEROSIS

BY

LAUREN S. CARUSO

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.

1994.

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.

4/19/94
Date

Chair of Examining Committee

4/22/94
Date

Executive Officer

Dr. Arthur J. Spielman

Dr. Nicholas G. LaRocca

Dr. Frederick W. Foley

Supervisory Committee

The City University of New York

Abstract

Sleep Disruption in Fatigued and Non-Fatigued

Persons with Multiple Sclerosis

by

Lauren S. Caruso

Advisor: Professor Arthur J. Spielman

Disabling fatigue, sleepiness, sleep changes, and sleep complaints are commonly reported by persons with MS. However, few studies have examined sleep and fatigue in the MS population. The present study examines MS related fatigue's relationship to sleepiness and sleep in 16 subjects with clinically definite MS, eight reporting fatigue (F) and eight not reporting fatigue (NF). Subjective measures of fatigue, sleep, sleepiness, depression, and mood scales as well as objective measures of sleepiness (Multiple Sleep Latency Test; MSLT) and sleep (nocturnal polysomnographic [NPSG] recordings) were used to test three hypotheses: 1) Persons with MS who complain of excessive fatigue will have higher indices of sleepiness and experience more sleep-disruptive behaviors and brain wave abnormalities during sleep than those persons with MS who do not report excessive fatigue; 2) Persons with MS will have more sleep-disruptive behaviors and brain wave abnormalities during nocturnal sleep than would be expected for persons without neurologic or psychiatric disorders; and 3) Persons with MS will manifest more variation in percentage of specific sleep stages and changes in sleep architecture than

would be predicted by age and sex-appropriate norms for persons without neurological or psychiatric disorders.

Results indicated that in accordance with the first hypothesis, the F subjects reported significantly greater levels of sleepiness before and after nap (MSLT) opportunities. However, objective measures of sleepiness (MSLT), amounts of sleep disruptive behavior, and presence of brain wave abnormalities did not support a F versus NF group differentiation. In accordance with the second hypothesis, periodic limb movements (PLMs) and alpha EEG sleep were prevalent on NPSG recordings. However, PLMs and alpha EEG sleep were almost mutually exclusive, differentially affected stage two sleep, and were gender specific. In accordance with the third hypothesis, significant changes on NPSG recording were seen in percentage of REM sleep, sleep efficiency, and total sleep time. However, when Bonferroni corrections were applied to control for multiple tests of significance, only the presence of PLMs, alpha EEG sleep, and decreases in sleep efficiency remained significant.

Acknowledgements

Writing this dissertation highlighted for me the importance of good mentors, friends, and family. I am very fortunate to have all three, with several persons embodying two or more of those roles. I would like to start by thanking my mentors, Dr. Arthur J. Spielman and Dr. Nicholas G. LaRocca. Dr. Spielman is the reason I went into sleep research. His ingenuity, knowledge, and passion for research remain with me each time I take on yet another study. Dr. LaRocca made the dream of doing this study a reality. He selflessly spent time helping me get funding, reeling me in when need be, and then stayed at the Montefiore sleep lab throughout several nights. He graciously played the role of supervisor, friend, and, in those critical moments, therapist, without a second thought.

I would also like to express my sincere thanks to my third committee member, Dr. Frederick Foley from Albert Einstein College of Medicine who, besides always being a fund of encouraging words, enthusiastically helped me through those long Montefiore nights. Although playing a different role as outside readers, I thank Dr. Paul Glovinsky from The City College of the City University of New York and Dr. Michael J. Thorpy from Montefiore Sleep/Wake Disorders Center for their time and insight. More generally, I would like to thank the 16 subjects who enthusiastically gave of their time in hopes of helping perhaps themselves and others with MS.

In addition, I would like to thank all my friends who listened to me as I excitedly discovered new angles in my research as well as when I was the picture of doom. I thank Keith Savel for encouraging me to enter the doctoral program and then volunteering for any study I conducted. I express my thanks to my girlfriends, Rochelle

"Alpha EEG" Zozula for helping me sort out the multitude of conflicting findings, and Dr. Lauren Westbrook who "kindly" reminded me that I did not have to complete my dissertation if I did not really want to, inciting me to no end. Many thanks go to my cousin Patricia Hessing who was agreeable to any help I needed, at any time, and then swore that she truly enjoyed typing in references and proofreading my entire dissertation. I also want to thank my "brother" Joseph Alhadeff for always being ready to take me out for dinner whenever I needed a break. Last, but not least, I would like to express my gratitude to my friend Stephen Berkowitz who stood by me throughout this ordeal, trying to rationally respond to my unanswerable questions, and never questioning why I could only start writing after 11 P.M.

I also need to thank the lovely home owners who let me use their homes when I needed a change of atmosphere. Francis and Martin Berkowitz, thank-you for having such wonderful tulips. Catherine Alhadeff and Dr. Nissim Alhadeff, my spare set of parents, thanks for the beautiful sunsets over the water. My only question is now that I have finished, Nissim, what will you bother me about?

The biggest thanks, and largest embrace, go to my parents Silvana Caruso and Dr. Robert Caruso as well as my grandmother Candida Marchetti. Thank-you for your generosity, support, faith, and love. It is to you that I owe everything.

Lastly, I dedicate this dissertation to my grandparents who were not able to be here to share in my accomplishment: Anna and Anthony Caruso, and Alberto Marchetti. Each of them still lives on within me and their love gives me the courage to carry on.

Table of Contents

List of Tables

List of Figures

List of Appendices

Review of the Literature

Multiple Sclerosis: An Overview

Multiple Sclerosis (MS) is a chronic and often disabling disease of the central nervous system (CNS). The most common initial symptoms include numbness and tingling in the extremities, facial numbness, weakness in one or both legs, loss of vision (optic, or retrobulbar neuritis), vertigo, diplopia (double vision), dysarthria (slurred speech), dysphagia (swallowing problems), ataxia (poor coordination), and urinary frequency, urgency and incontinence. Another common MS phenomenon is L'hermitte's sign, a transient paresthesia resembling an electrical shock, that travels down the spine and anterior portion of the thighs, and which can be recurrently elicited upon forward flexion of the head (Sibley, 1990).

The course of MS is highly variable with some individuals having two to three exacerbations in a lifetime with minimal disability, while others may have frequent attacks leading to death within a few months (Sibley, 1990). By definition, an exacerbation of symptoms must last at least 24 hours in order to be considered MS related, and usually continues 4 to 12 weeks before remitting. MS course is often described by presenting symptomatology. A benign-sensory course is typified by the presence of sensory symptoms, such as numbness and tingling. A relapsing-remitting course is described by episodes of exacerbations in which at least 80 percent of the symptoms subsequently remit. In a relapsing-progressive course less than 80 percent of the symptoms are seen to remit. Conversely, in a chronic progressive course

the MS symptoms are seen to progressively worsen without the presence of exacerbations or remissions. However, MS symptoms and course are unpredictable. Although a long-standing benign course with minimal disability often predicts a favorable outcome, and cerebellar symptoms (i.e., ataxia) often predict a poor outcome, there are many exceptions. In addition, MS course can change. A person whose MS symptoms have consistently followed one course (i.e., benign-sensory) can suddenly start to follow another course (i.e., relapsing-remitting). Studies suggest that 20 to 30 percent of persons with MS do not become seriously disabled and may continue to work productively 20 to 25 years after the onset (Bauer & Firnhaber, 1965; MacKay & Hirano, 1967). In approximately 15 percent of the persons, remissions do not occur and the symptoms slowly progress from onset (Sibley, 1990).

Approximately 300,000 persons between the ages of 15 and 60 years in the United States have been diagnosed with MS (Anderson et al., 1992). MS has been shown to have a greater prevalence in the northern latitudes as well as a greater prevalence in Caucasian populations with whites being twice as likely to get MS as blacks. It is more likely to affect females than males in a ratio of 1.7:1 (Baum & Rothschild, 1981). With an average age of onset in the early 30's, the MS population is comprised largely of persons in the prime of their life, who are members of the work force, and of child bearing and rearing age. Thus, the disabling effects of the disease process have severe socioeconomic and psychological impact on individuals and on our society as a whole.

Affective disturbances are frequent in the MS population. A lifetime history of depressive symptoms and depressive episodes is reported in approximately 42 percent of the population (Joffe et al., 1987). Bipolar disease is also more common than would be expected in the general population. In a study of 100 persons with MS, Joffe et al. (1987) found that 13 percent had a lifetime diagnosis of bipolar affective disorder compared to 1 percent in the general population ($p<.001$). It is thus important to consider affective disorders when dealing with MS symptomatology, especially fatigue which can be a frequent concomitant to depression, dysthymia, and sensations of malaise. Depression and depressive episodes have also been shown to alter sleep patterns (Reynolds et al., 1985; Reynolds et al., 1986) and therefore, must be considered as a possible confounding variable in studies of MS and sleep.

Neuropsychological studies have demonstrated that intellectual changes occur in approximately 65 percent of persons with MS (Rao, 1986). In most cases the impairments are mild to moderate with long term memory deficits being the most widely noted. However, approximately 10 percent of persons with MS experience severe intellectual dysfunction or dementia. In the early stages this dementia shows a subcortical pattern but later may assume a cortical pattern. The subcortical and cortical stages of MS dementia may thus resemble Parkinson's disease and Alzheimer's disease, respectively.

Although the exact etiology of MS is unknown, studies suggest that there is a genetic predisposition operating in conjunction with exposure to some viral or other environmental factor around the age of puberty. Much controversy exists

concerning the genetic versus viral factors involved in the etiology of MS. Several twin studies have investigated the genetic contribution involved in the development of MS (MacKay & Myrianthopoulos, 1966, Bobowick et al., 1978, Williams et al., 1980, Kinnumen et al., 1987, Sadovnick et al.,1988). Ebers et al. (1986) conducted a genetic study designed to determine if there is an environmental influence on the concordance found in twin studies. Surveying 5463 persons with MS and identifying 27 monozygotic twin pairs and 43 dizygotic twin pairs, they discovered that 25.9 percent of the monozygotic group and 2.3 percent of the dizygotic group were concordant for MS. Additionally, among non-twin siblings the concordance rate was only 1.9 percent. Assuming that basic environmental factors remain a constant within sibling groups, a major genetic susceptibility for MS was supported.

In contrast, an epidemiological study of three epidemics in the Faroe Islands supports the environmental theory of MS onset (Kurtzke & Hyllested, 1987). The study hypothesized that the original epidemic was brought to the Faroes by British occupation troops during World War II. Clinical onset of MS started approximately 2 years later (1943-1961). The two subsequent epidemics (1946-1951 & 1958-1963, respectively) were significantly later in time and lower in incidence than the first epidemic. The nature of this "primary MS affection" was described as being widespread, specifically systemic, infectious, rarely affecting the CNS immediately, but manifesting itself in clinical neurologic MS symptoms years later. The authors concluded that a minimum of two years of exposure from approximately age 11 to 45 years was necessary for the

disease to be acquired. An average of six to twelve years of incubation was estimated to occur before the virus was introduced to the CNS, and then was only transmissible during part or all of the primary MS affection. Present etiological hypotheses of MS still stress the combination of genetic predisposition and a viral infection at or around the age of puberty as being the best explanation for the development of MS.

There also appears to be an autoimmune component to MS etiology and pathogenesis. In MS the body's immune system attacks and destroys its own myelin. Presently, the common hypothesis is that an intercurrent viral infection or some other unknown event precedes the release of lymphokines into the circulatory system. This may cause class II major histocompatibility complex molecules, HLA-DR (or Ia) to be expressed on endothelial cells. This Ia molecule, normally not expressed by CNS tissue, combines with some fragment of myelin to form an Ia/antigen complex which initiates the immune response against myelin. The residual effects are the formation of scar tissue, or plaques, throughout the brain with a particular propensity for large areas of white matter such as the periventricular areas, optic nerve, brainstem, and cerebellar regions of the brain. The plaques impair saltatory conduction, resulting in reduced CNS activity on affected nerves (Raine, 1990).

Although lesion location varies greatly between individuals with MS, certain regions of the brain appear to have a greater affinity for plaque formation. Brownell and Hughes (1962) were among the first to examine the distribution of MS plaques in the cerebrum. On post-mortem evaluation using

coronal cut 1 cm. slices of the cerebrums of 22 persons with MS, a total of 1594 plaques, an average of 72 per person, were counted. A large majority, 40 percent (637 plaques) were located in the periventricular, or lateral ventricular system. Twenty-two percent (348 plaques) were located in the frontal lobes. Fifteen percent of the total plaque distribution (233 plaques) were located in the parietal lobe. In the temporal lobes 12 percent of the total (193 plaques) were found with 4 percent (60 plaques) found in the corpus callosum. Approximately one percent of the total number of plaques were detected in the occipital lobe, insula, internal capsule, and amygdaloid nucleus and habenulopeduncular tract, respectively. The last 4 percent were distributed across other sections of the cerebrum. In sum, 94% of the lesions detected were divided among the periventricular, frontal lobe, parietal lobe, and temporal regions of the cerebrum.

A significant affinity for white matter over grey matter was evident in that a total of 74 percent (1184 plaques) were located in the white matter of the cerebrum. Another 17 percent (256 plaques) were located in the cortex and gray-white matter junction. The remaining 9 percent (145 plaques) were divided between the cortex and central grey matter in approximately a 3:4 ratio. Therefore, MS plaques were almost three times as likely to appear in the white matter compared to other areas of the brain. No significant distinction in lesion totals between the right and left hemispheres was found.

Of all the areas of the brain affected by MS, the brainstem may have the most significant implications for sleep. Topographical studies on MS plaque

location in the brainstem were completed by Baum et al. (1988) using brainstem auditory evoked potentials (BAEP). Of a total of 43 subjects, 39 diagnosed with clinically definite MS and with probable MS, 23 (53.5%) had clinically acute brainstem symptoms, 37 (86%) showed abnormal visual evoked potentials, and 38 (88.4%) showed oligoclonal bands in the cerebral spinal fluid. Abnormal BAEP findings were found in 19 (44.2%) of the 43 persons studied, or 73.7 percent of the subjects with acute clinical brainstem symptoms. Twenty-six subjects (60.5%) exhibited pathologically high signal intensities in the brainstem region. Specifically, 12 subjects (27.9%) evidenced lesions in the rostral pons, 6 subjects (14%) in the caudal pons, 4 subjects (9.3%) in the mesencephalon, and 4 subjects (9.3%) in the medulla oblongata. A high degree of location consistency was found between BAEP and magnetic resonance imaging (MRI) evaluations. Since the brainstem is a central mechanism for the regulation of the sleep-wake cycle and rapid eye movement sleep (REM), the implications of lesion formation in the brainstem leading to sleep disruption need to be considered.

Sleep Physiology

Sleep has been defined by Carskadon and Dement (1987), as a reversible behavioral state of perceptual disengagement from and responsiveness to the environment. Sleep is internally regulated by the nervous system and can be divided into two basic physiologic stages: REM sleep and non-rapid eye movement (NREM) sleep. Rechschaffen and Kales (1968) further divided NREM sleep, using standardized EEG criteria, into 4 stages. Stage 1 sleep is

considered a transitional stage between waking and the onset of sleep. It is often typified by hypnogogic hallucinations (a waking dream-like state) and feelings of "dropping off." Stage 2 sleep is typified by the slowing of wave activity (theta waves), which indicates that the firing of brain neurons becoming synchronized, and the appearance of spindles and K-complexes. Stages 3 and 4 sleep are essentially determined by increasing proportions of this delta wave activity. In contrast to NREM sleep, REM sleep is characterized by rapid asynchronous brain waves mostly resembling those seen on EEG monitoring of persons who are awake. However, unlike the waking or NREM states, REM sleep activity is characterized by loss of muscle tone (atonia).

Mechanisms of the Sleep-Wake Cycle.

Numerous studies conducted on the chronic decerebrate cat (Bazett & Penfield, 1922; Head, 1923; Hobson, 1965; Villablanca, 1966; & Jouvet, 1967) have demonstrated the brain stem's ability to autonomously maintain the sleep-wake cycle, provided that the pons and medulla remain intact. This ability implies that the neural mechanisms underlying the alternation of sleep and wake states exist in the brain stem without input from the cerebral cortex. Furthermore, these studies have provided evidence of two, coexisting, opposite systems within the brain stem that drive the sleep-wake cycle. Although both systems remain tonically active, phasic effects are seen at the moment of sleep onset as well as the moment of arousal (Moruzzi, 1974). These sleep-wake inducing systems also synthesize, store, and release 5-hydroxytryptamine and

noradrenaline which respectively act upon the receptor terminals of the ascending and descending pathways (Moruzzi, 1974). The brain stem driven alternation between sleep and wake states is best explained by the reciprocal influences between the two antagonistic systems, the reticular activating system and the deactivating structures of the lower brain stem (Moruzzi, 1974). However, whether the brain stem is the primary modulator of the sleep-wake cycle, rather than a secondary backup of an intact brain, remains uncertain.

Similarly, experiments conducted on the chronic cerveau isole cat (Genovesi, et al., 1956; Villablanca, 1962; Villablanca, 1965; & Jouvet, 1967), in which the mesencephalon is transected creating a cerebrum which is "detached" from brainstem structures, show that the neuronal discharges arising in the pons during desynchronized sleep and underlying the electroencephalographic (EEG) parameters seen during synchronized sleep and wakefulness are potentially present when the cerebral cortex has been detached from the brain stem by a precollicular section (rostral to the third nuclei; high mesencephalic animal). Consequently, in the intact brain, it would appear that the two antagonistic systems of the brain stem modulate the reciprocally organized, cerebral responses to create the sleep-wake cycle.

Mechanisms of Sleep Onset.

REM and slow wave sleep (SWS) are characterized by distinctly different patterns of EEG waveforms. EEG synchronization, as seen in SWS, and desynchronization, as seen in wake states and REM, have been shown to originate from distinctly different areas of the brain. Numerous studies in

brain-transected cats have shown SWS to appear in the isolated forebrain (Bremer, 1970; Villablanca, 1966; Villablanca, 1966; & Slosarka and Zernicki, 1969), while REM has appeared in the isolated brain stem (Jouvet, 1965; Jouvet, 1965; & Matsuzaki et al., 1964). Kleitman's studies (1963 & 1967) found that the underlying mechanism controlling the SWS-REM cycle periodicity throughout the night, or "basic rest-activity cycle," was also located in the brain stem and would also be retained in surgical or neurochemical isolation. In fact, studies on the pontine cat have shown SWS and REM recordings to have been obtained simultaneously from the separated forebrain and brain stem, respectively, with the periodic occurrence of REM in the isolated brain stem remaining fairly consistent to that seen in normal animals (Sterman & Clemente, 1974). These findings are consistent with Jouvet's (1969, 1969) conclusions that the underlying neural substrate of REM sleep resides in the pontine level of the brain stem, and that the REM mechanism is "independent of sleep and represents a neural integration functionally more basic and phylogenetically antecedent to the mammalian sleep-waking rhythm" (Sterman & Clemente, 1974; p.85). Sterman and Clemente further hypothesize that the capacity to maintain a waking state is dependent on the functional evolution of a nonspecific, mesodiencephalic reticular formation, and that sleep is the result of the parallel development of forebrain mechanisms antagonistic to this activating system. Therefore, it could be said that the mechanisms for sleep onset reside in the forebrain, while those for sleep termination or "wake-like" states reside in the brainstem.

The preoptic area of the hypothalamus and adjacent basal telencephalic structures are collectively referred to as the "basal forebrain region." When electrically stimulated, this area elicits EEG delta waves and behavioral sleep in cats (Sterman & Clemente, 1962; Doty, 1969). Further studies show that bilateral destruction of the basal forebrain region of the cat markedly reduces the presence of sleep while eliciting high degrees of wakefulness and hyperactivity (Sterman et al., 1964; McGinty & Sterman, 1968). Lucas and Sterman (1972) have shown that bilateral lesions in the basal forebrain region of the cat sparing the posterior thalamus and dorsal midbrain, have produced immediate and profound suppression of sleep with hyperactivity and a disruption of temporal organization of sleep-wake patterns but no significant changes in the SWS-REM rest-activity cycle. Others have shown that projections from the basal forebrain region directly communicate with the orbital cortex, hippocampus, amygdala, midline thalamus, and mesencephalic reticular formation (Clemente & Sterman, 1963; Clemente & Sterman, 1967; & Mizuno et al., 1969).

The basal forebrain's influences on SWS onset and maintenance is in part derived from its proximity to the hypothalamus and its regulatory mechanisms. Thermoregulatory mechanisms in mammals have been associated with the preoptic-anterior hypothalamic region (Sterman & Clemente, 1974). Thermal stimulation of an area overlapping the basal forebrain region produced SWS EEG patterns and behavioral manifestations of sleep. Roberts and Robinson (1969) concluded that the thermoreceptors in this area were an

intrinsic part of the regulatory mechanism of sleep onset. Thus, both direct electrical stimulation of the basal forebrain region and thermal stimulation of an overlapping area produced the same response: suppression of ongoing behavior. Moreover, stimulation of the basal forebrain region and its projections to the thalamus and midbrain reticular activating formation block motor reflex responses and afferent input (Clemente & Sterman, 1967). Similarly, stimulation of the basal forebrain region and related areas also blocks reticular formation evoked potentials to initiate EEG synchronization through the suppression of sensory and motor functions (Bremer, 1970). The basal forebrain region receives afferent impulses from the frontal cortex and thalamus, is involved in limbic feedback pathways, and responds to thermal and neurochemical influences, while the efferent projections relay impulses to the medial and midline thalamus, epithalamus, and mesencephalic tegmentum.

Harper and McGinty (1973) found that preoptic cells demonstrate a distinctive change in their pattern of firing at the moment of SWS onset. During wake states, the pattern of discharge was irregular and slow in rate, but then showed a marked increase in firing rate with an intense bursting pattern occurring concurrently with the initiation of sleep behavior and the onset of EEG slow wave activity. Once stage 2 sleep was achieved, the preoptic cells quieted and returned to their pre-sleep discharge pattern. Sterman & Clemente (1974) concluded that the preoptic cells' behavior may "give rise to a diffuse descending pathway whose projections into the midbrain

tegmentum act to terminate or inhibit ongoing behavior, elicit resting postures, and reduce corticipetal discharge, such that a changed central integration can be achieved which results in sleep behavior" (p.91).

It has been well established that high frequency stimulation of the thalamus or of brain stem components in the ascending reticular activating system (BSRS [brain stem reticular system]) induces EEG desynchronization. Purpura and Shofer's (1963) work in intracellular research has demonstrated that the thalamic neurons participating in the underlying mechanism of evoked EEG synchronization are also responsible for changes in the underlying mechanism of EEG desynchronization. The primary differences in the discharge of these neurons in the two contrasting modes of activation lie in the changes in pattern in their synaptic inputs. Specifically, changes in the temporal organization or prolongation of the inhibitory postsynaptic potentials (IPSP) are prominently displayed during both evoked EEG desynchronization and/or the operation of recurrent inhibitory pathways. During BSRS stimulation, the IPSPs are attenuated or inhibited. Consequently, the inhibition of thalamic inhibition contributes to the development of reticulocortical activation. In conjunction with other excitatory synaptic inputs, this accounts for the alterations in thalamic neural activity seen in the transition from EEG synchronization to desynchronization. It also follows that lesions, or any neuronal conduction disruption, could lead to the disruption of the continuity of the aforementioned alterations in overall EEG state.

REM or desynchronized sleep requires the simultaneous activation of

both an ascending and a descending system. According to Broughton (1972), the ascending system appears to begin in the nucleus reticularis pontis caudalis. It then sequentially follows the ocularmotor nuclei until it ascends further producing cortical activation. It appears that then a phasic input, perhaps from the medial and descending vestibular nuclei, is introduced into the system, leading to the REM bursts, and subsequently, connects to the lateral geniculate body and striate cortex, and ultimately, elicits the characteristics ponto-geniculo-occipital (PGO) spikes. At the same time, the descending system apparently begins in the locus coeruleus, and then connects to the inhibitory reticulospinal system which leads to loss of axial muscle tone.

In contrast, NREM or synchronized "slow wave" sleep appears to result from active inhibition by basal forebrain areas (i.e., preoptic area) and by a brainstem synchronizing area (i.e., pons) of the midbrain tegmental reticular formation. "This results in reduced ascending reticulocortical impulses (...descending from the cortex) passing at least in part through unspecific thalamic nuclei and giving rise to EEG slow waves. Concomitant reduced reticulospinal impulses lead to progressive hypotonia" (Broughton, 1972; p.365).

The Breakdown of Sleep

The breakdown of sleep architecture, as expressed by deviations in sleep EEG parameters, results in the fragmentation of sleep and the loss of many of its restorative benefits. Common complaints associated with sleep fragmentation are sensations of tiredness, sleepiness, fatigue, and/or malaise. Since these complaints are common in the MS population, it is important that

the continuity and ability of persons with MS to maintain consistent sleep cycles be investigated. Consequently, the following study will examine some of the more common causes of sleep fragmentation found in neurologic populations which best anticipate the problems that may be expected in MS. Specifically, alterations in sleep architecture, depression and intellectual changes, narcoleptic tetrad symptomatology, the interaction of lesion sites with underlying sleep mechanisms, periodic limb movements during sleep, the alpha-delta or alpha EEG NREM sleep anomaly, and sleep apnea will be discussed.

Sleep Architecture Fragmentation.

Given that approximately one third of a person's life is spent sleeping, the quality and quantity of that time is significant. Sleep architecture commonly refers to the pattern in which the different stages of sleep occur throughout the night. Any changes in the pattern or rhythm of an individual's sleep can adversely affect his/her level of daily functioning, elicit sensations of tiredness, sleepiness or fatigue, and/or disrupt sensations of well being. Since fatigue is a common concomitant of MS, investigation into the nightly sleep patterns, deviations in normal sleep architecture, and resultant sensations of sleepiness is important.

Typically, at sleep onset, NREM sleep occurs first with REM sleep appearing approximately 80 minutes after sleep onset. Subsequently, NREM and REM sleep alternate throughout the rest of the night in approximately a 90 minute cycle. As the night progresses, each REM period increases in length

from an initial 1 to 5 minute per episode to an average of 90 to 110 minutes per episode. As the REM period increases, the average length of each NREM episode declines. Therefore, NREM sleep predominates during the first third of the night and is linked to sleep initiation; whereas REM sleep predominates during the last third of the night. Total "normal" nightly sleep time is comprised of approximately 5% or less of wakefulness, 2 to 5% of stage 1 (S1; NREM) sleep, 45 to 55% stage 2 (S2; NREM) sleep, 3 to 8% stage 3 (S3; NREM) sleep, 10 to 15% stage 4 (S4; NREM) sleep, and 20 to 25% REM sleep occurring in 4 to 6 discrete episodes.

The disruption of this standard pattern of sleep results in sleep fragmentation and can be produced by psychological, behavioral or physiological factors. The most common disrupting factor is the aging process. Infants up to year 1 are said to have "active" sleep in which wakefulness is directly followed by REM sleep. The REM-NREM cycle is still present but has a 50 to 60 minute period rather than the 90 minutes seen in adults. Slow wave sleep (SWS; stages 3 & 4) is maximal in young children and markedly decreases with age. In contrast, REM sleep, as a percentage of total sleep time, is well maintained into healthy old age. In a 1977 article, Prinz reported that the absolute amount of REM is related to intellectual function and markedly declines in cases of organic brain dysfunction in the elderly. Awakenings during sleep dramatically increase with age and total time asleep is significantly fragmentated. As a result, sleep efficiency (total amount of time asleep over total time in bed) drops to between 70 and 80 percent.

Changes in Psychological State.

In severe depression, sleep continuity is disturbed by an increase in time needed to get to sleep, early morning awakenings, increased number of awakenings during the night, and increased amount of REM sleep relative to total sleep time. Slow wave sleep (SWS) is also seen to decrease. An abbreviated first NREM sleep period results in the increase of the appearance of REM sleep, especially during the first part the night. Each REM period has also been described as more "dense" with an increase in the number of eye movements (Foster et al., 1976).

Intellectual change is also seen in the MS population. Few studies have adequately documented sleep changes as related to intellectual change. However, studies conducted in the elderly have shown changes in intellect to be related to the absolute amount of REM sleep and warrant investigation in the MS population.

Narcolepsy.

Narcolepsy is a sleep related nervous system disorder typically characterized by an inability to adequately inhibit REM sleep. A class II antigen of the major histocompatibility complex (MHC) - the HLA-DR2 antigen - has been found to have practically a 100% concordance with narcolepsy in the caucasian population. Similarly, the HLA-DR2 marker has been found to have approximately a 50 percent concordance with the presence of MS. The prevalence rates in the United States for both of these conditions has been estimated to be between 250,000 to 300,000 persons. Interestingly, narcolepsy

is more common among families with a member who has MS than would be expected in the general population. Although persons with MS and narcoleptics often have similar descriptions of sleepiness and fatigue, there has thus far been no evidence of any similarity in sleep changes between the two populations (Ekbom, 1966; Poirer, et al., 1987; Rumbach, et al., 1989). However, the changes in the underlying sleep physiology that accompany narcolepsy may lend insight into which changes in sleep parameters could be expected in MS.

The major symptoms of narcolepsy are true disorders of sleep-wake mechanisms, and are referred to as the narcoleptic tetrad: excessive daytime sleepiness, cataplexy (sudden loss of postural tone and collapsing usually triggered by intense emotions such as laughter and fright), sleep paralysis (paralysis experienced upon awakening from REM sleep), and hypnagogic hallucinations (dreams associated with REM onset sleep periods which are more intense and dream-like than those normally experienced when falling into NREM sleep; Broughton, 1972). Sleep onset REM is the hallmark EEG phenomenon that differentiates narcolepsy from other disorders of excessive daytime sleepiness (DOES). Zorick et al. (1986) outline two hypotheses that attempt to explain the etiology of narcolepsy. The first considers that the symptoms of the narcoleptic tetrad are manifestations of REM sleep, and therefore, narcolepsy is primarily a dysfunction of REM sleep. The alternative hypothesis describes narcolepsy as "an abnormality involving the reciprocal inhibition between wake and both REM and NREM" (p.189). In fact, based on

polysomnographically determined daytime sleep latencies, Zorick et al.'s data suggest that "narcolepsy is not exclusively a REM related disorder, but involves an inability to sustain a specific neural state for periods comparable to those in normal subjects or other DOES patients".

Broughton (1972) describes the changes in REM sleep physiology underlying the symptoms of the narcoleptic tetrad. In a cataplectic attack, the sudden loss of postural tone is associated with the inappropriate and selective triggering of the descending motor component (locus coeruleus) of REM sleep during wakefulness. Similarly, in sleep paralysis the awakening from REM sleep is also believed to be associated with dissociated REM mechanisms. Specifically, the descending pontospinal component remains in the REM state and the ascending REM mechanisms are replaced by those of normal wakefulness. The hypnogogic hallucinations experienced by narcoleptics differ from those reported by normal sleepers in intensity and dream-like quality. It appears that in narcolepsy the dreams are more vivid primarily because they stem from the abnormal sleep onset REM periods experienced by narcoleptics rather than from the NREM sleep onset periods experienced in the normal population. In addition to having sleep onset REM periods, the nocturnal sleep of narcoleptics with auxiliary symptoms shows poorly regulated REM-NREM cycles, frequent sleep stage shifts, and numerous awakenings which can be associated with prolonged episodes of nighttime insomnia. The following study examines the presence of the aforementioned narcoleptic related sleep abnormalities in the sleep of persons with MS.

Periodic Limb Movements.

Periodic limb movements (PLM) or periodic movements during sleep (PMS) are stereotypical, repetitive movements that occur as frequently as 200 to 400 times during nocturnal sleep (Rosenthal, 1984), usually during non-rapid eye movement (NREM) sleep, and often causing arousals as well as sleep fragmentation. Originally called "nocturnal myoclonus" (Symonds, 1953), PLMs are best described as rhythmic extensions of the big toe, often similar in appearance to the Babinski reflex, dorsiflexions of the ankle, and sometimes flexions in the knee and hip. Movements typically last from 0.5 to 5.0 seconds and occur in 20 to 40 second intervals (Montplaisir & Godbout, 1989). Most often PLMs cluster into discrete episodes which can last from a few minutes to several hours. Although they can recur throughout the sleep period, because of their affinity for NREM sleep, the episodes tend to be more numerous during the late night or very early morning hours, or late morning or early afternoon hours. Most often, the greater movements cause arousals from sleep, and consequently, sleep complaints. However, individuals who experience mild movements may report being asymptomatic and remain unaware of the behavior. Although no specific etiology has been found, PLMs have been associated with various underlying medical conditions (Mosko & Nudleman, 1986).

Bixler et al. (1982) estimated the prevalence of PLMs in healthy, non-complaining adults to be between 5 and 6 percent, whereas, others report the prevalence in sleep disorder clinic samples to be closer to 18 percent (Coleman,

1983, Kales et al., 1982; Soldatos et al., 1976; & Guilleminault et al., 1975). However, numerous studies have shown that the prevalence and severity of PLMs increase with age (Ancoli-Isreal et al., 1989; & Coleman et al., 1981). In one study (Coleman, 1979) a review of 441 persons seen at a sleep disorders center revealed that patients with PLMs were significantly older than those without PLMs. In another review, Ancoli-Isreal (1989) found that from 25 to 37 percent of healthy elderly men and women manifested PLMs during nocturnal sleep. In a more recent study, Ancoli-Isreal (1991) found that on polysomnographic recording of 420 men and women over 65 years of age, the prevalence of PLMs was approximately 45 percent (men = 44 %; women = 46%). However, when the severity of PLMs was examined more closely (i.e. $\geq$5 movements per hour of sleep), men had significantly more movements than women. In summary, the literature in otherwise healthy adults, suggests that PLMs are more commonly seen in NREM sleep, in the first half of nightly sleep, in older persons (especially over 65 yrs.), and in men.

Little is known about sleep in persons with MS. However, when considering the neuropathology involved in plaque formation throughout cortical and subcortical regions of the brain, the possibilities for the disruption of the sleep - wake cycle are numerous. Only one study to date has looked at PLMs in persons with MS (Yokota, et al., 1991). In 3 persons with MS, PLMs were seen during NREM sleep with the amplitude and frequency of these movements being suppressed during REM sleep. In the following study, the phenomenon of PLMs and MS are examined, and differentiations are made

between PLMs and the nocturnal spasms often seen in MS.

The Alpha EEG NREM Sleep Anomaly.

Alpha-delta sleep (later referred to as alpha EEG NREM or alpha EEG sleep by Moldofsky et al., 1975) was first described by Hauri and Hawkins in 1973 who observed this phenomenon in sleep studies conducted in a psychiatric population. In their study, alpha EEG sleep was described as an EEG defined sleep stage containing "a mixture of 5-20% delta waves (>75μV, 0.5-2 c/sec) combined with relatively large amplitude, alpha-like rhythms (7-10 c/sec), [however,] these alpha rhythms are usually 1-2 c/sec slower than waking alpha." The presence of alpha EEG sleep was seen in all 9 of the nocturnal sleep records evaluated from their psychiatric population carrying diagnoses ranging from depressive to schizoaffective disorders. Alpha EEG sleep nights were characterized by an unsustained, "vacillating" presence of stage 3 and absence of stage 4 delta sleep; higher auditory awakening thresholds than is typical during stage 2 sleep (thereby suggesting a deeper sleep during stage 2), more "dream-like" sleep mentation reports than typical during NREM; unaffected REM sleep parameters (amount of REM sleep and eye movement intensity during REM sleep); lengthened intervals between REM periods throughout the night; and were often accompanied by complaints of chronic, somatic malaise and fatigue. Although Hauri and Hawkins (1973) were unable to discern the etiology of the alpha EEG sleep anomaly, they suggest that "one possible unifying factor among patients with alpha EEG sleep lies in the fact that a disturbed or immature brain metabolism is very strongly

suggested in some cases and cannot be ruled out in others,....[and, perhaps, they] suffer from some common, as yet undefined CNS dysfunction and that their final psychiatric diagnosis represents more the manner in which they try to cope with this disability rather than reflecting the disease state itself." Apart from depressed and schizophrenic persons, Hauri & Hawkins (1973) also found alpha EEG sleep to be present for a few nights in a patient with a leukotomy, in chronic insomniacs, in morphine addicts, in a patient with uremic syndrome, in temporal lobe epilepsy, and in normal pre-schoolers (more commonly in 2 than 4-year olds).

Alpha EEG sleep has also been investigated in various studies of fibrositis syndrome or rheumatic pain modulation disorder (RPMD). Fibrositis is a common disorder characterized by fatigue, morning stiffness, disturbed sleep, generalized musculoskeletal aching and multiple tender points (Wolfe et al., 1984). Moldofsky et al. (1975; & Saskin et al., 1986) described the presence of alpha EEG (7.5-11 Hz) NREM sleep to be consistent with the appearance of musculoskeletal pain, and mood symptoms such as fatigue and malaise. In later studies, Moldofsky et al. suggested that the alpha EEG sleep anomaly coupled with nonarticular pain and mood symptoms comprise an internally induced sleep-arousing mechanism. This mechanism has been described as possibly similar to the NREM stage 4 changes triggered by: 1) emotional distress and external noise stimuli in normal sleepers (Moldofsky et al., 1976); 2) sleep which is disturbed by sleep related periodic involuntary leg movements (nocturnal myoclonus; Moldofsky et al., 1984); and 3) the intrusion

of inflamed articular pain stimuli disturbing nocturnal sleep in rheumatoid arthritis (RA) patients (Moldofsky et al., 1983). Saskin et al. (1986) compared persons with RPMD to persons experiencing post-accident pain (PAP) who had no evidence of structural pathology, yet, were clinically and physiologically comparable to persons with RPMD. Both groups manifest a constellation of uniform complaints comprised of chronic fatigue and nonrestorative sleep, widespread musculoskeletal pain, specific regions of localized tenderness in the absence of physical disease, and significant levels of emotional distress (Moldofsky et al., 1975). Although more prominent in the RPMD group, the alpha EEG anomaly was observed to persist throughout stages 2 through 4 in all 11 RPMD subjects and 10 out of the 11 PAP subjects. Subsequently, although the reports of fatigue between both groups were similar, the fact that the PAP subjects showed less alpha EEG NREM sleep suggests that the quality of fatigue reported may not be directly comparable to the "actual observed sleep disturbance as characterized by the pattern of nocturnal arousal and alpha EEG intrusion into NREM sleep" (Saskin et al., 1986). The similarity of symptomatology and sleep physiology between the groups suggests that a diagnosis of PAP may be compatible with that of RPMD (Saskin et al., 1986). Also, in accordance with the hypotheses suggested by Moldofsky et al. (1983), a psychophysiologic arousal mechanism present during NREM sleep or emotional stress may trigger the manifestation of the alpha EEG NREM anomaly in both groups. Although not specific for fibrositis, the alpha EEG NREM sleep anomaly appears to be the biological correlate of the

nonrestorative sleep, fatigue, and pain symptoms seen in fibrositis (Moldofsky, 1989).

The etiology and exact consequences of the alpha EEG sleep anomaly still require further definition and explanation. Numerous studies by Moldofsky and his colleagues suggest that the presence of definitive amounts of alpha EEG clusters in NREM sleep are indicative of an arousal disorder during sleep and result in complaints of light and unrefreshing sleep and chronic fatigue in the RPMD, PAD, and RA populations. Since complaints of fatigue are prevalent in the MS population, as discussed earlier in the text, the following study reviews the nocturnal sleep records of 16 persons with MS, of which half were complaining of fatigue at the time of the study, in an effort to detect the presence of an alpha EEG anomaly in any stage of NREM sleep.

Sleep Apnea and MS.

Respiratory changes are well documented in the elderly (Carskadon & Dement, 1981; Ancoli-Israel et al., 1991) and preliminary reports indicate that a significant number of persons with MS show evidence of sleep apnea above the expected range for their age group (Kapen et al., 1989). These changes involve periods of sleep apnea in which the individual momentarily fails to respond to the body's physiological impetus to breath. Although rarely fatal in itself, this type of sleep disturbance can significantly increase sleep fragmentation and, consequently, drastically augment daytime sleepiness.

Sleep apnea is generally described as obstructive (eg. the air passage is blocked by bone structure or by extra fleshy material), central (neural failure

to initiate a "breathe" response) or mixed (components of both). As a result of this condition, sleep continuity is severely disrupted and persons with sleep apnea are often chronically sleepy and report feelings of fatigue. Since persons with MS also report fatigue, it is possible that even mild amounts of apnea may be compounding an already pre-existing sense of fatigue. Similarly, changes in sleep associated with intricate drug regimens and increased nocturnal movements associated with loss of sleep continuity, can be a source of maladaptive sleep changes for persons with MS.

The Concept of Tiredness

Hartmann (1973) describes the phenomenon of tiredness as a parallel to fatigue. He explains tiredness to differ from fatigue after exercise in that one does not simply overcome it by lying down without sleeping. Rather, he explained that tiredness, such as one feels at the end of the day, was only reversible by sleep. He identifies two patterns of tiredness of which most persons experience some combination. The first he labels as "physical" or "simple" tiredness akin to that which one experiences at the end of the day after prolonged activity. Usually this sensation is accompanied by a sense of muscle relaxation, including that of the face and head, and rarely is associated with tightness or headache. Affectively it is described as pleasant or neutral, and is rarely associated with any cognitive changes. This sort of tiredness has been hypothesized as representing a need for SWS.

The second kind of tiredness Hartmann describes as "mental" in nature and is most frequently reported at the end of the day after prolonged

intellectual and/or emotional activity. This sensation is usually accompanied by tension or tightness, especially those of the face and head, and is often associated with headache. Affectively it is described as unpleasant or neutral, and often is accompanied by a sense of irritability, anger, difficulty in sustaining attention, difficulty excluding extraneous information, an inability to fall asleep, a lack of energy, an unwillingness to place effort into anything new, a tendency to be socially uncomfortable, a desire to be left alone, and a tendency to engage in wish-fulfilling daydreaming. This sort of tiredness has been hypothesized as representing a need for REM. Although Hartmann presents an important description of tiredness and possibilities for defining the fatigue experienced by persons with MS in a self-report or clinically impressionistic manner, tiredness, as an individual entity, lacks objective methods of measurement.

Sleepiness

Although sleepiness is a universal phenomenon experienced by nearly all adults during the midday, research investigating the physiological substrates and biological tendencies of sleepiness has only recently gained scientific importance because of quantification discrepancies. Surveys have demonstrated sleepiness to have a 4 to 5 percent prevalence in the general population (Lavie, 1981; & Bixler et al., 1979). Coleman (1983) has found that excessive sleepiness was the most common presenting complaint in patients evaluated in sleep disorder centers in the United States. Broughton et al. (1981) found nearly half of persons suffering from excessive sleepiness reported

significant real life consequences such as automobile accidents, occupational accidents, loss of jobs, and disruption of family life. Kripke et al. (1979) linked excessive sleep and mortality rates to reveal that persons that sleep 10 or more hours daily were approximately 8 times more likely to die prematurely than those sleeping between 7 to 8 hours daily. However, these findings primarily highlight the association between the malfunctioning of some underlying neurological substrate and the consequent need for more sleep.

Sleepiness is considered a basic physiological need state whose intensity is described by how readily sleep onset occurs, how easily it is disrupted, or how long it endures (Roth et al., 1989). When the sleep cycle is disrupted, both physiological and psychological sequelae such as loss of energy, fatigue, weariness, dysthymia, difficulties in concentration, and memory lapses are seen. Environmental factors, such as heavy meals, warm rooms, boring lectures, and long-distance drives, often unmask sleepiness, but rarely cause it (Roth et al., 1989).

However, despite the preponderance of behavioral evidence, the actual physiological substrates of sleepiness remain unknown. In general the assumption remains that sleepiness is a CNS phenomenon with identifiable neural mechanisms and neurochemical correlates. Electrophysiological events in sleep deprived animals show ventral hippocampal spike activity (typically associated with NREM sleep) during behaviorally awake states (Friedman et al., 1979). Similarly, in sleep deprived, yet behaviorally awake, humans, brief intrusions of sleep (or microsleeps) and increased amounts of alpha and theta

activity are seen on polysomnographic recordings (Webb, 1972; Akerstedt et al., 1982).

The neurochemical basis of the sleepiness-alertness continuum remains unclear. Controversy surrounds whether the neurochemistry is controlled by the same factors that control the sleep process. In fact, whether or not sleepiness and alertness represent an actual neurochemical continuum or are in reality two separate processes is also in question. In CNS pathologies, discovery of the underlying neuropathological and neurochemical substrates controlling sleepiness and alertness is crucial for understanding the possible neuro-breakdowns that could be exacerbating sensations of sleepiness, fatigue, and dysphoria. Further research to delineate these conflicts is necessary to direct future understanding of behavioral treatments and pharmacological intervention.

In neurophysiological studies of the neurotransmitters involved in the sleep process, serotonin, the catecholamines, and acetylcholine have been implicated in the control of the sleep-wake cycle, and are hypothesized to provide the same role in the sleepiness-alertness continuum (Monnier & Gaillard, 1980). Inoue et al. (1985) proposed that sleep-inducing peptides and endocrines may provide a similar regulatory effect for sleepiness-alertness, as they do for the sleep process. On the other hand, evidence from pharmacological studies shows that sedatives, such as the benzodiazepines, induce sleepiness while they facilitate gamma-aminobutyric acid's (GABA) inhibitory function at the receptor complex (Gallager, 1982). Similarly, in the

CNS, histamine is found to have alerting effects (Snyder & Taylor, 1972) which are reversed by antihistamines that penetrate the CNS to produce sleepiness (Pollard & Schwartz, 1987).

Other transmitters are implied in pharmacological studies using stimulants. Amphetamines produce alerting effects by blocking catecholamine uptake (Chiarello & Cole, 1987). Similarly, caffeine and theophylline act as an adenosine receptor antagonist, and thereby, produce alerting effects by altering transmitter modulation activity (Dunwiddie, 1985).

In the clinical setting, sleepiness is regarded as the behavioral manifestation of some underlying sleep pathology. In order to scientifically examine sleepiness as a separate phenomenon from sleep, the ability to distinctly describe, quantify, and qualify it is mandatory. Until recently, most of the sleepiness-driven protocols employed have relied on subjective measures. Presently, more objective, polysomnographically determined measures allow sleepiness to be implemented as a viable dependent measure.

Apart from self-report, sleepiness can be reliably measured from a number of vantage points including subjective sleepiness scales, such as the Stanford Sleepiness Scale (SSS; Hoddes et al. , 1972), and visual analog mood scale. Performance testing, which has been traditionally used to test levels of vigilance and sleepiness, can be influenced by motivation and environmental factors and are insensitive to sleep loss (Wilkinson, 1968). Long, monotonous tasks, however, are seen to be reliably sensitive to changes in quantity and quality of sleep (Roth et al., 1989). More objective behavioral paradigms, such

as the Multiple Sleep Latency Test (MSLT; Carskadon, et al., 1986) and the Maintenance of Wakefulness Test (MWT; Mitler et al., 1982) have, more recently, become the more standardized method for assessing sleepiness. However, each measures sleepiness differently. The MSLT measures sleep latency by creating optimal conditions for falling asleep. On the other hand, the MWT assesses ability to resist sleep, but does not provide any motivating factors to help sustain wakefulness.

The amount of nocturnal sleep needed, and the consequential manifestation of sleepiness, varies greatly between individuals. Once an individual's optimal sleep time is determined, sleepiness may be produced by a diverse set of factors, decreasing sleep continuity, such as sleep loss, fragmentation of sleep, selective sleep stage deprivation, and drug interactions. Carskadon and Dement (1982) have found that partial or total sleep deprivation elicits sleepiness and sensations of dysphoria during the subsequent day. Furthermore, Carskadon and Dement (1981) have also found that sleep restriction of only one hour per night accumulates over subsequent nights to progressively increase levels of daytime sleepiness. Conversely, increasing sleep time one hour per night (from 7 to 8 hours) in young adults has been shown to progressively produce increases in alertness and sensations of well-being (Carskadon & Dement, 1979). Similarly, in the elderly, pharmacologically-driven increases in nocturnal sleep of approximately one hour also produced increases in alertness, as seen on MSLT evaluations (Roehrs, et al., 1985; Carskadon et al., 1982).

The quality of sleep is equally as important as the quantity of sleep. Daytime sleepiness is most often related to the quality and continuity of an individual's nocturnal sleep. Sleep efficiency, or the proportion of time actually spent sleeping relative to the amount of time spent in bed trying to sleep, is often used as a description of sleep quality. The underlying neuropathology of many sleep disorders elicits periodic brief arousals, polysomnographically characterized by bursts of EEG speeding or alpha activity and often transient skeletomuscular increases, which disrupt sleep continuity but often go undetected by the individual. Since the individual does not reach consciousness, these episodes must often be reported by others, such as bed partners. The compilation of these brief arousals and resulting loss of sleep continuity does not result in shortened sleep, but rather fragmentation of sleep, producing daytime sleepiness. Carskadon et al. (1982) have shown strong correlational evidence supporting the relationship between sleep fragmentation and sleepiness. More specifically, Stepanski et al. (1984) found that fragmentation, as defined by the number of shifts from REM, stage 2, stage 3 or stage 4 to stage 1 or waking, and the overall percentage of stage 1 sleep throughout the night, is significantly correlated with excessive daytime sleepiness in persons with sleep complaints. Treatment studies in persons with sleep apnea have shown that after successful surgical procedures, significantly reduced amounts of apnea, significantly less arousals during the night, and significantly reduced levels of daytime sleepiness were observed. When apnea related surgery has been unsuccessful, no decreases were seen (Zorick, et al.,

1983).

In healthy populations, induced sleep fragmentation has been shown to produce similar effects on daytime sleepiness. Several studies using auditory stimulation to awaken individuals at various intervals throughout the night, have shown increased levels of daytime sleepiness, as well as performance decrements, on the subsequent day (Bonnet, 1985 & 1986). In addition, later studies that also used auditory stimulation at various intervals throughout the night, that did not awaken subjects (as defined by EEG criteria), have shown similar results in levels of subsequent daytime sleepiness and performance abilities (Stepanski, et al., 1984; Levine, et al., 1987). Concomitant with the aging process, sleep mechanisms are seen to deteriorate and the quality of sleep to diminish. In the elderly population, sleep fragmentation is an important determinant of subsequent daytime sleepiness. Several studies have shown that even in elderly individuals without subjective reports of sleep disturbances, an increased number of apneas and periodic limb movements were seen during nocturnal sleep (Ancoli-Isreal, 1981; Carskadon & Dement, 1981). In addition, it has been shown that elderly individuals with the greatest number of arousals during the night were also those demonstrating higher levels of daytime sleepiness on MSLT evaluation the following day (Carskadon et al., 1982).

A general tendency towards sleepiness, which is not determined by previous nocturnal sleep continuity, is experienced by all individuals twice daily. A clear circadian rhythm, occurring daily in a biphasic pattern, has been

well documented (Akerstedt & Gillberg, 1981; Strogatz, 1986). Richardson et al. (1982) described two troughs of alertness: the first during nocturnal hours at approximately 0200 to 0600 h and the second during daytime hours at approximately 1400 to 1800 h. In one time-isolation study, a biphasic circadian rhythmicity of self-rated fatigue, similar to that seen for sleepiness, was observed to be superimposed on the expected increase in self-rated fatigue resulting from the sleep deprivation (Froberg et al., 1972;). In a similarly designed study, Carskadon (1985) noted that a biphasic pattern of unintentional sleep progressively emerged as the study continued. When individuals in time-free environments have been permitted to freely nap, this biphasic circadian pattern becomes evident in a mid-cycle proclivity for chosen nap-time (Zulley & Campbell, 1985).

Shift-workers and transcontinental jet-travelers are two populations that exemplify the tenacity of the circadian bimodal pattern. Sleepiness in both of these groups is a result of shifting sleep and wakefulness out of phase with the underlying circadian rhythm, shortening and fragmenting nocturnal sleep, and enforcing wakefulness in troughs of alertness (Nicholson et al., 1986). Most interestingly, although daytime sleepiness can be diminished by pharmacological intervention, the circadian rhythm of sleepiness has been shown to remain intact with the outward manifestations of sleepiness being masked (Seidel et al., 1984; Nicholson et al., 1986).

CNS pathologies are another determinant of physiological daytime sleepiness. As previously discussed, narcolepsy is a CNS disorder, with

unidentified underlying CNS regulatory malfunctions, in which excessive sleepiness is prevalent (Kilduff, et al., 1986). Similarly, idiopathic CNS hypersomnolence is also a CNS disorder in which the neuropathological substrates involved remain unknown (Association of Sleep Disorders Centers, 1979). The prevalence of these conditions and their associated levels of excessive sleepiness implicate CNS involvement in the manifestations of sleepiness and suggest possible CNS involvement in other disorders in which sleepiness, tiredness, or fatigue is present and in which neuropathological mechanisms may be altered.

Increased levels of SWS have been shown to be associated with complaints of fatigue or an analog such as: deep sleepers who are difficult to awaken at night and in the morning, HIV positive individuals without an AIDS diagnosis complaining of fatigue (Norman et al, 1990), and high metabolic output exercise in normal individuals (Berger et al, 1988). The demonstration of polysomnographically supported sleep increases in SWS in men with MS (Kapen et al, 1989), along with the large proportion of persons with MS reporting fatigue, suggest that MS related fatigue may be a mixture of sleepiness and fatigue. Sleepiness has been a neglected variable in MS research despite the fact that it can be measured more objectively and reliably. Therefore, it is one of the major aims of the following study to investigate the levels of sleepiness, sleep related causes of sleepiness, and contributions of sleepiness to fatigue in persons with MS. Since the person with MS's experience of fatigue and sleepiness may have significant overlap, it is an

additional aim of the following study to define and differentiate between fatigue and sleepiness so that further research may focus on appropriate interventions for each. Specifically, we assess individual sleep change parameters, sleep fragmentation, total sleep time, and indices of daytime sleepiness at different time intervals and investigate their association with fatigue.

Sleep Studies in Fatigue

Sleep related fatigue has been described in several neurological populations. Namely, various changes in sleep parameters resulting in fragmentation and complaints of fatigue have been observed in acquired immunodeficiency syndrome (AIDS), the fibrositis syndrome, rheumatoid arthritis (RA), and chronic fatigue syndrome (CFS). The sleep related changes observed in each are described as possible etiological analogies for contributing factors in MS related fatigue.

Acquired Immunodeficiency Syndrome.

Fatigue and myalgia are common complaints in persons with AIDS (Miller et al., 1991). Norman et al. (1990) attempted to describe the possible sleep related changes that may contribute to sensations of fatigue and myalgia in HIV-infected homosexual males. Ten clinically asymptomatic, HIV-infected and 5 healthy HIV-seronegative males were interviewed, completed sleep questionnaires, and underwent nocturnal polysomnographic evaluations. Interviews and sleep questionnaires revealed prominent sleep complaints in 9 of the 10 HIV-positive group. Various changes in overall sleep architecture and

sleep continuity were also observed. Specifically, an increase in total percentage of SWS, as well as percentage of SWS in later sleep periods, was seen. The number of shifts in S1 sleep, number of REM periods throughout the night, and number of arousals were also significantly higher. In contrast, a significant decrease in sleep onset latency, total percentage of S2 sleep, and the average duration of REM sleep were observed. These sleep architecture anomalies could not be explained by existing primary sleep disorders, medications, first-night-effects, and anxiety and/or depression. The investigators concluded that these sleep related changes indicated that sleep disturbances occur early in the course of HIV-infection and that these disturbances may be the result of CNS involvement and/or immunological defensive mechanisms present in the early phases of HIV-infection.

Fibrositis Syndrome.

Nonrestorative sleep and waking feeling unrested are the primary features associated with the fibrositis syndrome, and are commonly reported in up to 100 percent of persons with fibrositis (Moldofsky, 1989; Wolfe, et al., 1985; Yunus, et al., 1985; & Campbell, et al., 1983). Similarly, sleep disturbances have been estimated to occur in 60 to 90 percent of these persons (Moldofsky, 1989). In efforts to characterize the sleep physiology of fibrositis, Moldofsky et al. (1975) detected the alpha EEG NREM sleep anomaly which is considered to be the biological basis for the nonrestorative sleep, sensations of fatigue, pain, and malaise commonly reported in fibrositis. Several studies suggest that the emergence of the fibrositis syndrome may be attributed to the

onset of stressful, psychological periods (Moldofsky, et al., 1975; Saskin, et al., 1986; & Saskin, et al., 1987). Although less prominent than that found in fibrositis, the alpha EEG NREM sleep anomaly, as well as sensations of diffuse pain and fatigue were also observed in persons having endured automobile or industrial accidents (Saskin, et al., 1986). Persons with fibrosis also complain of an increased sensitivity to noxious environmental situations such as noise, weather, and allergens, which may also contribute to the disruption of sleep continuity.

Rheumatoid Arthritis.

Fatigue is commonly reported in nearly 80 percent of persons with RA, and is often used to evaluate disease activity and treatment response (Lansbury, 1968). In fact, the absence of fatigue is one of the 5 criteria establishing "remission" in RA (Pinals, et al., 1981). In an effort to discern the contributions of sleep difficulties to these sensations of fatigue, Mahowald et al. (1989) conducted nocturnal polysomnographic recordings and multiple sleep latency tests (MSLT) on 16 persons with chronic, active RA with early onset fatigue. On analysis, significant amounts of sleep fragmentation, without significant sleep deprivation, occurred in all subjects throughout the night and daytime recordings. Extremity movements were also observed in all subjects, with extremity movement-associated sleep fragmentation being physiologically the same as reports of PLMs in other populations. The movement arousal indices reported in these subjects were significantly greater than those reported in elderly populations (Carskadon, et al., 1982) but unlike elderly populations,

episodes of sleep apnea were observed in only 2 subjects. Similar to persons with fibrositis, the alpha EEG NREM sleep anomaly was seen in 13 of the 16 subjects studied. Seven subjects were seen to be hypersomnolent on MSLT evaluation, further supporting the presence of sleep fragmentation. Interestingly, discrepancies between subjective impressions on morning questionnaires and objective polysomnographic recordings indicated that none of the subjects accurately recognized the degree of sleep disruption they were experiencing throughout the night.

Chronic Fatigue Syndrome.

Although the etiology remains unknown, both psychological and immunological factors appear to contribute to the sensations of fatigue associated with CFS (Krupp, et al., 1991). Because of the close associations between CFS and fibrositis, Krupp & Mendelson (1990) investigated sleep related complaints that might be contributing to the reported sensations of fatigue. Nocturnal polysomnographic recordings, MSLT, and psychiatric evaluations were conducted on 10 persons who met criteria for CFS. Psychological factors were attributed to sensations of fatigue in 2 subjects who were diagnosed with major depression. However, 7 of the 8 non-depressed subjects showed polysomnographic findings commonly related to sleep disruption. Sleep apnea, with indices of 29 and 61, was observed in 2 subjects. PLMs associated with arousals were seen in 3 subjects with PLM arousal indices of 90, 146, and 463, respectively. Finally, numerous episodes of sleep onset REM periods, typically considered a hallmark of narcolepsy, were seen

on MSLTs for 2 subjects (2 episodes, x = 5.5 min. & 3 episodes, x = 8.5 min., respectively) complaining of hypersomnolence. The investigators interpreted these results as implying that sleep disorders may be contributing to the complaints of fatigue associated with CFS, and that in some persons with CFS, psychiatric conditions and unrelated underlying sleep disorders may combine to produce complaints of fatigue that resemble those of CFS.

MS Related Fatigue

More than 80% of persons with MS complain of fatigue as one of their primary symptoms (Freal & Kraft, 1984; LaRocca et al, 1984). Murray (1985) reported that abnormal amounts of fatigue are experienced by 96% of the MS population. A significant majority of those with MS fatigue report that it is qualitatively different from normal fatigue in that it interferes with daily activity (Murray, 1985; MacAlpine et al, 1972; Herndon et al, 1981; Sandy, 1983). Most importantly, fatigue often appears as one of the earliest and most disabling symptoms of MS (Sandy, 1983; Krupp et al, 1988). Krupp et al. (1988) reported six characteristics that significantly discriminated MS related fatigue from that experiences by normal healthy adults. Specifically, fatigue in MS was found to: 1) prevent sustained physical activity; 2) worsen in hotter temperatures; 3) interfere with responsibilities; 4) come on easily; 5) interfere with physical functioning; and 6) cause frequent problems. Despite its importance, no reliable measures of fatigue have been found that are acceptable for clinical use. MS fatigue remains poorly understood with assessments generally being made in a subjective manner with a heavy reliance

on impressionistic, clinical methods.

Despite the large percentage of persons with MS who complain of MS related fatigue, little is known concerning the underlying pathophysiology. The lack of a specific definition of fatigue and the large variance found in the descriptive reports among persons with MS, have made the detection of related physiological variables difficult. Biological systems require the maintenance of a stable homeostatic environment in order to maintain an optimum level of continuous performance. When the homogeneity of the organism is compromised in any manner, one or a sum of its components can fail, and thereby, disrupt the flow of the system in either a temporary or progressive fashion. Fatigue may work to engage either inhibitory or disinhibitory response systems at the cellular, axon potential level signaling the body that it is time to rest and cease activity or that the engagement of activity at the given moment cannot be successfully completed. It is known that MS related fatigue has a diurnal variation (Freal et al, 1984) with sensations of fatigue worsening in the late afternoon (Krupp et al, 1988). Although physical activity has been reported to aggravate fatigue, many persons with MS report that the diurnal variation continues to operate even when activity levels are lessened. The perpetuation of this periodicity, independent of environmental contingencies, indicates the existence of an underlying endogenous mechanism or "biological clock."

Most people experience a bimodal fluctuation between "alertness" and "tiredness" within a 25 hour period or approximately a day. This pattern elicits

a sense of alertness and well being in morning and evening hours making sleep onset difficult, and a sense of tiredness in the afternoon and night creating a drive for sleep. In "normal" sleepers, those without any complaints of sleep disturbances and report sensations of well-being during the day, this bimodal pattern of alertness is closely linked to the individual's core body temperature or circadian rhythm. When the core body temperature is rising, usually in morning and evening, an individual will experience a sense of alertness and well being, whereas when the temperature begins to drop, the individual will experience a sense of tiredness and desire to sleep. It is possible that in MS the individual lesion, or collective pattern of lesions, emphasizes part or all of this bimodal cycle and consequently creates a greater sensation of MS related "fatigue" or contrast in feelings of well-being throughout the day. Studies show that a rise in temperature causes impulse conduction to slow down and eventually block in peripheral (Rasminsky, 1973) or central (McDonald and Sears, 1970) nervous system mechanisms. Using a computer model, Schauf and Davis (1974) demonstrated that the effect of temperature elevation can be related to the degree of myelin loss. Many persons with MS show substantial neurological signs of CNS malfunction or change in relation to changes in body temperature. This heightened sensitivity to temperature change in the MS population versus healthy normals has been shown in visual system dysfunction (Michael and Davis, 1973). By using flickering light stimulation, Regan et al (1977) demonstrated a change in evoked potential (EP) latencies related to changes in environmental

temperatures. Further, Matthews et al (1977) and Bajada et al (1980) discovered that in persons with MS, the amplitude wave of the major positive EP potential, the P100 PSVEP, was significantly reduced by temperature elevation. However, despite the wealth of possible research suggestions, MS related fatigue is poorly defined and assessed primarily by self-report (Krupp et al, 1988), subjective clinical methods, or exercise paradigms that do not take temperature and diurnal variation into account (Olgiati et al, 1986). The need for an accurate definition and objective measures of fatigue remains a research imperative.

Sleep Studies in MS

Although sleep changes and sleep complaints are often reported by persons with MS, little is known about the nature of sleep in the MS population. Changes in sleep are of extreme importance for persons with MS. Physiological changes in sleep provide insights into how MS affects the individual both behaviorally and physically. Sleep changes may contribute to sensations of fatigue. Any chronic disruption of sleep continuity is detrimental to a person's sense of well-being and needs to be evaluated. Similarly, changes in an individual's sleep patterns related to physiological factors may lend insight into the nature of the disease. It is possible that even minor alterations in the sleep schedule (eg. bedtime, arise time, and napping) may help alleviate fatigue.

To date only a handful of abstracts or papers have been published that attempt to address any issues related to sleep and MS. In one study, the

coincidence of narcolepsy, narcoleptic symptoms, and MS was described in a case series approach in four extended families (Ekbom, 1966). Although the incidence rates in the United States for both narcolepsy or MS were relatively low when considering the population as a whole, the tendency for a given family to have occurrences of MS and narcolepsy within their genetic tree was much greater than chance could explain.

Another, more recent study compared similarities between the symptoms of the narcoleptic tetrad (sleep attacks, cataplexy, hypnogogic hallucinations and sleep paralysis) and those symptoms reported by persons with MS (Poirer, et al., 1987). In this study the results of the questionnaire evaluating the incidence of reported narcoleptic tetrad symptomatology revealed that persons with MS frequently reported the occurrence of daytime sleep attacks (78%) and cataplectic attacks (56%). However, despite these symptomatic similarities, persons with MS did not demonstrate narcoleptic-sleep features, such as sleep-onset rapid eye movement sleep periods (SOREMPs) on MSLT evaluations. No nocturnal polysomnographic recordings were conducted.

More recently Kapen et al. (1989) presented some preliminary data addressing the sleep architecture of men with MS. Interestingly, there were changes in the distribution of the different sleep stages. When compared to men of similar age without neurological, psychiatric, or sleep complaints, men with MS were seen to have increases in the percent time spent in SWS. Also a significant increase in number of episodes of sleep apnea were seen.

Although provocative, this study remains limited in that only men were evaluated and MS is a disease that is more common in women. Also, the men who participated in the study were residents of a veterans hospital, other possible aliments and drug regimes were not accounted for, and the average age range studied was older than that desirable for the study of a disease whose onset is usually during young adulthood. The following study takes these factors into account and use a sexually balanced population, largely medication free, who are primarily young adults and who have had a fairly recent MS diagnosis. The following study also further investigates the incidence of narcoleptic type symptoms during nocturnal and daytime napping polysomnographic recordings.

Rumbach et al. (1989) conducted a study investigating MS, sleep latencies, and HLA antigens. Specifically, the study examined the possible correlations between MS HLA typing and shortened sleep onset latencies and the presence of short sleep latencies and the HLA-DR2 or Dqw1 antigen seen in narcolepsy. The mean onset sleep latencies were reduced in 21 of the 37 persons with MS without complaints of sleep disturbances. Only 7 of the 15 DR2- and 12 of the 21 Dqw1-positive subjects showed significantly reduced sleep latencies. However, sleep latencies were reduced in 13 of the 16 B8- or B14-positive subjects. In contrast, subjects that did not demonstrate any significant shortening of sleep onset latency, also did not demonstrate any over-representations of HLA antigens. Rumbach et al. (1989) stated that these results suggest that the genes that code for the DR2 or Dqw1 antigens,

although present in nearly 100 percent of caucasian narcoleptics, cannot solely explain the appearance of the shortened sleep onset latencies seen in MS.

A recent study examined nocturnal sleep activity in persons with MS (Caruso et al., 1991). The amount of activity during sleep in relation to the reported complaints of fatigue was measured in 19 persons with clinically definite MS. Both subjective self-report and objective electronic monitoring were implemented. Fourteen-day sleep logs were completed by all subjects. Based on a score of 3 or 4 on the fatigue item of the Incapacity Status Scale (Haber & LaRocca, 1985), 11 patients were rated as "fatigued" (F) and 8 as "non-fatigued" (NF). Wrist actigraphy (Ambulatory Monitoring, Inc.), measuring physical activity for each 2 minute epoch over 14 days, was obtained in 10 subjects (F = 5 & NF =5). On the basis of the patient sleep logs, the F group reported taking twice as many naps ($p<.05$; F x = 0.5 vs. NF x = 0.23). When total nightly sleep time was added to the total time napping to yield a 24 hr. sleep-time measure, there was a trend for the F group to report more sleep than the NF group ($p<0.1$; F x = 7.82 vs. NF x = 7.16). Objective monitoring produced similar results. Analysis of movement time during nocturnal sleep revealed that the F group had significantly more activity ($p<.05$; F x = 3.73 vs. 5.91). Equal amounts of nocturnal sleep were analyzed for the 2 groups (F = 6.77hrs., NF = 6.70hrs.). The number of 2 minute epochs with activity throughout the night was compared to the number of epochs without activity. There was a trend for the F group to have a higher percentage of epochs disrupted by activity than the NF group (26% vs.16%;

$p<0.1$). These data suggested that the F group had more disrupted sleep, body movements, and sleep fragmentation all of which may produce daytime sleepiness and fatigue. Although the study was limited by a lack of polygraphic recordings to explicate these findings, it proposed that, alternatively, MS may have direct effects on sleep which remain unexplored, with self-reported fatigue perhaps highlighting underlying differences in the nature of sleep. The following study attempts to further explore these underlying differences.

Most recently, two studies surveying sleep complaints in the MS population have shown that sleep complaints and depression are common in persons with MS (Leo, et al., 1991; & Saunders et al., 1991). Clark et al. (1992) studied sleep disturbance, depression and lesion site in MS. On nocturnal polysomnographic recordings, persons with clinically definite MS were found to have a prevalence of sleep difficulties that was three times greater than that found in a normal control group (25.2% vs. 8.2%), and these sleep complaints were associated with higher levels of depression. Three lesion sites subserving the supplementary motor areas were significantly correlated to the presence of sleep complaints: the right and left frontal white matter in the supraventricular section, and the deep white matter of the right insula. When the subjects with these lesion sites were removed from the sample, the incidence of sleep complaints in persons with MS was nearly equivalent to that of the control group. Clark et al. (1992) concluded that the presence of sleep disturbances and depression in MS may be "a function of the lesion site resulting in

nocturnal spasms". These studies suggest that lesion sites in MS can be attributed to levels of depression, fatigue, nocturnal spasms, and sleep disturbances.

There are other aspects of MS that may affect sleep. PLMs, polysomnographically different from muscle spasms, and nocturia, the need to urinate often throughout the night, are common causes of periodic arousals from sleep, and consequently, disruption of sleep cycle continuity. As mentioned earlier, depression and depressive episodes, which are known to fragment sleep, occur in approximately 50 percent of persons with MS. It is also important to consider how the more primary symptoms of MS such as bladder difficulties, spasticity, and periodic limb movements may also contribute to these sensations of depression, fatigue and malaise. Depression, in turn, has been correlated to sleep fragmentation and changes in sleep parameters such as increases in time spent in REM relative to total sleep time (termed REM percent). In addition, persons with MS often have complex drug regimes which may produce changes in sleep continuity, or artificially enhance or reduce the occurrence of selective sleep stages by direct changes in neurochemical reactions at the synaptic level, by interactions amongst the drugs themselves, and/or by drug schedules. How these arousals affect the continuity of "normal" sleep patterns as well as what compensatory measures can be undertaken need to be considered.

Predictions and Hypotheses

Despite complaints of sleep difficulties and MS related fatigue, few sleep studies have been conducted in the MS population. Numerous questions concerning the sleep of persons with MS remain unanswered. MS lesions have been shown to be prevalent in brain areas (i.e., forebrain, brainstem, pons) that house basic sleep mechanisms (i.e., sleep-wake cycle, NREM-REM cycle, REM sleep). MS lesions are also common in brain areas that control functions that, although not part of the sleep system, may adversely affect sleep (i.e., frontal lobe lesions leading to inhibition of motor control). Therefore, it must be considered that changes in sleep architecture and sleep maintenance may be derived in part from the formation of MS plaques.

In addition, persons with MS often have similar complaints of fatigue, hypersomnolence, and sleep disruptions, similar to those seen in other neurological populations (i.e., AIDS, RA, CFS, FS, narcolepsy). Therefore, MS related fatigue may be due in part to disruption and loss of sleep, and may be correlated with measures of sleepiness.

The following study tests three hypotheses which are based on a review of the literature on MS symptomatology, MS related fatigue, and MS plaque formation as well as the literature on sleep physiology, sleepiness, and sleep disruptions found in other neurologic populations.

1. Persons with MS who complain of excessive fatigue will have higher indices of daytime sleepiness (on subjective & objective measures) and experience more sleep-disruptive behaviors (i.e., PLMs, respiratory

difficulties) and brain wave abnormalities (i.e., alpha EEG sleep) during nocturnal sleep than those persons with MS who do not report excessive fatigue.

2. Persons with MS will have more sleep-disruptive behaviors (i.e., PLMs, respiratory difficulties) and brain wave abnormalities (i.e., alpha EEG sleep) during nocturnal sleep than would be expected for persons without neurologic or psychiatric disorders.

3. Persons with MS will manifest more variation in percentage of specific sleep stages (i.e., changes in percentage of stage 1, stage 2, stage 3, stage 4, REM sleep) and changes in sleep architecture (i.e., sleep efficiency, total sleep time) than would be predicted by age and sex-appropriate norms for persons without neurological or psychiatric disorders.

Method

Subjects

Sixteen subjects (8 men & 8 women) with clinically definite MS by the Poser et al. criteria (1983) were recruited from the patient population at the Research and Training Center (RTC) for MS at the Albert Einstein College of Medicine. The subjects were between the ages of 21 and 50 (mean: 38.25$\pm$10.14 years) and had an EDSS score (mean: 2.87$\pm$1.64) between 1 (no disability, minimal signs in one functional system) and 6.5 (constant bilateral assistance required to walk about 20 meters without resting) (Kurtzke, 1983). Five subjects were classified as benign-sensory, seven as relapsing-remitting, three as relapsing-progressive, and one as progressive from onset. Subjects that had any significant psychiatric condition, serious medical condition other than MS, or cognitive impairments were not considered for the study. Since complex medication regimes are common in MS and many medications may alter nightly sleep or sensations of fatigue or sleepiness, the selection of subjects who could be medication-free for the duration of the study were of primary interest. Subjects who, at the time of the study, were currently taking possible sleep-altering medications underwent a two-week wash-out period under the supervision of their neurologist and a clinic psychologist. Table 1 lists the inclusion and exclusion criteria.

The subjects were divided into two groups. The first group was comprised of 4 men and 4 women with current clinical complaints of MS related fatigue and with scores of 3 or 4 on the fatigue item of the Incapacity

Status Scale (ISS; Haber & LaRocca, 1985) which is regularly evaluated during neurological visits to the clinic. This group is referred to as the "fatigued" group. The second group was comprised of 4 men and 4 women without clinical complaints of fatigue and with scores of 1 or 2 on the ISS. This group is referred to as the "non-fatigued" group. Both the fatigued and non-fatigued groups underwent the same screening and study procedures.

Each prospective subject was given a copy of the study's consent form, and asked to read and sign it before continuing with the screening procedures. Screening procedures included medical, psychological, and neuropsychological screenings to rule out other neurological diseases, affective disorders, dementia, or intercurrent infections, all of which could have confounding sleep sequelae. The medical screenings required the review of all subject's medical chart, an outline of each individual's MS course along with changes in EDSS scores, and a full neurologic MRD examination administered by one of the clinic's attending neurologists. All episodes of infections and other medical conditions were noted.

Concurrently, any history of affective disorders were also noted during the subject's medical chart review, and a structured clinical interview (SCID) was administered by one of the clinic's licensed clinical psychologists to screen for psychiatric disorders. A brief (approximately 1.5 hrs.) neuropsychological battery designed to detect the presence of any dementing processes was administered by the clinic's neuropsychologist. The battery included a widely used dementia screening test (Blessed & Tomlinson, 1968), tests of verbal

fluency (Controlled Oral Word Fluency [FAS] & Retrieval from Semantic Categories), a test of short term storage, long term storage, and retrieval from verbal memory (Selective Reminding Test, Buschke and Fuld, 1974), immediate verbal memory span (Digit Span; Wechsler, 1945), and cancellation tasks. Upon satisfying the screening criteria, the subject entered the study protocol.

Measures of Nocturnal Sleep, Daytime Sleepiness, Depression, Fatigue, and Neurological Status

The Functional Systems (FS) and Expanded Disability Status Scale (EDSS).

Kurtzke's (1983) Functional Systems (FS) and Expanded Disability Status Scale (EDSS) are the most widely used assessment instruments in MS and form a portion of the MRD (Haber & LaRocca, 1985). The eight functional systems are rated based upon the neurological examination. These FS's are then used in conjunction with gait to derive a global score, or the EDSS, which ranges from 0 (normal function) to 10 (death due to MS) in .5 increments. The FS and EDSS are used in virtually all clinical research in MS and are also widely used by health care providers to track patient progression. In the following study the EDSS was used as an overall quantification of each individual's neurological status.

Incapacity Status Scale (ISS).

The Incapacity Status Scale (ISS) is a 16 item inventory of functional disability based in a large part on the PULSES Profile (Moskowitz & McCann, 1957) and the Barthel Index (Mahoney & Barthel, 1965). Each of the 16 items

is rated on a scale of 0 (no difficulty) to 4 (significant difficulty). In a large study, interrater agreement was excellent with an intraclass correlation coefficient of .94 (LaRocca et al., 1984). The total scale has a high coefficient of internal consistency, Chronbach's alpha = .93, however, use of individual subscales is also possible. In the following study, the fatigue item from the ISS differentiated the fatigued from the non-fatigued group.

Sleep Logs.

Upon satisfying all screening criteria, the subject were given a two-week sleep log that has been customized for the MS population. Each morning, upon awakening, the subject were asked to answer seventeen questions concerning his/her sleep the night before and the previous day's activities. Included are standard sleep questions such as nightly bedtimes and arise times, estimated amounts of time it took to fall asleep, numbers of awakenings during the night, reasons for those awakenings, and estimated total amount of sleep time. The questions concerning the previous day's activities include amount of naps taken during the day, amount and time of day of exercise, amount of caffeinated beverages consumed, amount of liquor consumed, a seven-point scale quantifying difficulty of getting up in the morning, a seven-point scale quantifying overall alertness, a seven-point scale quantifying overall fatigue, and a list of medications taken during the 24-hour period. This information provided a two-week pattern of the subject's sleep prior to the study as well as the subject's average bedtime and arise time which was used in the study's sleep recording protocol.

The Fatigue Severity Scale (FSS).

The Fatigue Severity Scale (FSS) (Krupp et al., 1989) has been shown to effectively discriminate between the fatigue described by normal healthy adults and that described by persons with MS. Specifically, nine of the 28-items were able to reliably identify the common features of fatigue in MS and systemic lupus erythematosus (SLE) (Table 2; Krupp et al., 1989). Furthermore, comparisons between five other items on the FSS were able to accurately differentiate MS related fatigue from the fatigue commonly associated with SLE (Table 3; Krupp et al., 1989). This questionnaire was administered on the study's adaptation night, and individual item response comparisons were made between the fatigued and non-fatigued groups, the CES-D scores, and indices of daytime sleepiness.

Center for Epidemiologic Studies - Depression (CES-D).

The CES-D is a self-report, twenty-item screening questionnaire originally developed by the Center for Epidemiologic Studies to detect depressive symptomatology (Radloff,1977). The questionnaire requires that the subject determine how many times in the past week the questionnaire statements seemed to be true (i.e., "I have been depressed, my appetite has been poor, people have been unfriendly"). According to the subject's responses, the numbers (0 to 3) are assigned with 0 denoting "rarely or none of the time [less than 1 day]" and 3 denoting "most or all the time [5-7 days]." After the numbers have been determined, they are tallied with total scores ranging from 0 to 60. A total score of 16 or greater on the CES-D has been

shown to indicate clinical depression (Radloff, 1977). In the following study CES-D scores were compared between groups, and correlated with scores on the FSS and indices of daytime sleepiness.

Nocturnal Polysomnographic Recording (NPSG).

The staff technicians at the Sleep-Wake Center at Montefiore Hospital calibrated the polysomnographic machines prior to the subject's arrival on the study recording night. The subject reported to the laboratory approximately three hours prior to his/her average bedtime as calculated from the subject's two-week sleep logs. A standard clinical sleep recording montage was used. Seventeen AC leads were placed on the subject: three referential electroencephalographic (EEG) (right-center central - C4, left-center central - C3 and right occipital - O2), two referential mastoid (A1 and A2), one central forehead ground, two horizontal referential eye movement (right and left outer canthus electro-oculogram [EOG]), two mental and one submental electromyogram (EMG), two electrocardiogram (EKG), two right anterior tibialis (RAT) and two left anterior tibialis (LAT). On the DC channels, two nasal and one oral thermistor were placed to monitor airflow, and one bellows around the rib cage was placed to monitor respiratory effort. An oximetry finger piece was placed on the subject's non-dominant index finger to monitor oxygen saturation levels throughout the night. An indwelling catheter (angiocath) was placed intravenously in the forearm of the subject's non-dominant arm.

The duration of each subject's NPSG recording was determined by the

average nightly bed time and habitual morning wake-up time reported on the subject's sleep logs. The polysomnographic recording was scored for sleep stages according to Rechtschaffen and Kales criteria (1968). Fifteen minutes prior to bedtime and upon awakening in the morning, bedtime and morning questionnaires were administered. These measures were used to rate the subject's anticipation and experience of sleep, and determine the accuracy of the subject's perception of his/her nightly sleep. In the following study NPSG results were compared between groups, re-grouped according to occurrence of specific sleep anomalies, and correlated with indices of daytime sleepiness, depression, and fatigue.

Multiple Sleep Latency Test (MSLT).

On the morning after the NPSG recording, each subject underwent Multiple Sleep Latency Testing (MSLT) (Carskadon & Dement, 1977). While previous methods of categorizing sleepiness have relied on subjective self-reports, the MSLT was the first standardized test to objectively measure daytime sleepiness according to Rechtschaffen & Kales (1968) sleep staging criteria. The following lead placements from the NPSG were monitored: EEG, EOG, EMG, mastoid, ground, and EKG. Starting two hours after the subject's habitual morning wake-up time, the standard MSLT protocol was performed (Carskadon, et al., 1986). The MSLT requires 5, 20-minute nap opportunities throughout the day given at two hour intervals from the scheduled arise time. For each nap opportunity, the time between "lights out" and when the subject has meet criteria for sleep onset, the first epoch of any stage sleep, is defined

as the subject's sleep latency. The amount of sleep allowed to accrue at each nap opportunity is generally limited to 15 minutes so that sleep accumulation is limited across naps. Between naps the subject is not allowed to sleep or stay in bed, but is asked to engage in some sort of activity (i.e., reading, watching TV). The rationale behind the MSLT protocol is that the more sleepy the subject is, the faster he/she should fall asleep, and consequently, the shorter his/her sleep latency should be. Therefore, the MSLT's dependent variable, sleep latency, is hypothesized to objectively measure the sleepiness-alertness continuum in units of time (i.e., minutes).

The MSLT has been used widely in clinical and research-based sleep studies to quantify sleepiness. Apart from being a sensitive indicator of either induced or naturally occurring changes in nocturnal sleep quantities and architecture (i.e., sleep deprivation, sleep extension, selective sleep stage deprivation), the MSLT has also been shown to have diagnostic qualities. Carskadon and Dement (1982) found that the MSLT was effective in creating diagnostic characterizations for specific sleep disorders (i.e., narcolepsy, sleep apnea, insomnia).

In the following study, the MSLT was used as an objective clinical determinant of sleepiness in persons with MS and was compared to the diagnostic patterns of sleepiness seen in other populations with sleep complaints. Sleep latencies for the fatigued versus non-fatigued groups were compared to determine commonalities between levels of sleepiness and clinical complaints of fatigue. The objective MSLT outcome measures were correlated

with the subjective self-report scores on the fatigue, depression, and sleepiness questionnaires: the Stanford Sleepiness and the Visual Analog Mood Scale.

Stanford Sleepiness Scale (SSS).

The Stanford Sleepiness Scale (SSS) (Hoddes et al., 1972) was administered to each subject immediately prior to and immediately after each of the MSLT nap opportunities for a total of 10 administrations. The scale consists of a list of seven single sentences that range from alert (i.e., 1-"Alert, Wide Awake") to extremely sleepy (i.e., 7-"Almost Asleep"). At each administration the subject is required to circle the number (1 through 7) that best describes how he/she is feeling at the moment. Although a subjective scale, the SSS has been found to significantly correlate with MSLT sleepiness indices (Carskadon & Dement, 1977). In the following study the results of the SSS were compared across the 10 administrations for each subject (within subject), between the fatigued and non-fatigued groups, and correlated with scores on the FSS, CES-D, MSLT, and Visual Analog Mood Scale.

Visual Analog Mood Scale (VAS).

The Visual Analog Mood Scale (VAS) was first used by Folstein and Luria (1973) and later revised by Monk et al. (1987). The VAS was administered to each subject immediately prior to and immediately after each of the MSLT nap opportunities for a total of 10 administrations. The scale consists of 9 questions ranging from "how alert do you feel" to "how sleepy do you feel." Above each question is a corresponding 100 mm horizontal visual analog scale. The subject is instructed to draw a vertical line through the

horizontal scale in accordance with how he/she feels on that particular measure from "very little" on the far left to "very much" on the far right. The VAS score is the measure, between 0 and 100 millimeters (mm), from the far left end of the scale (0) to the point at which the vertical line is drawn. An advantage of the VAS, as opposed to the SSS, is that the subject's response is not "anchored" to a numerical value since the line allows for a continuum of responses (Folstein & Luria, 1973). Monk et al. (1987) have shown that the VAS is a sensitive measure of non-pathological levels of subjective sleepiness especially in "within" subject designs. In the following study the scores on the VAS were compared within subject and between groups, and correlated with scores on the MSLT, SSS, FSS, and CES-D. Table 4 summaries these measures and their goals.

Study Procedures

The study procedures are summarized in figures 1 and 2. The study protocol consists of a screening day at the MS Care Center, 14 days of sleep logs, and 2 nights and 1 day at the Sleep-Wake Center. Demographic and basic MS data sheets were kept on all prospective subjects. After passing the neurological, psychological, and neuropsychological screenings on Day 1 (Screening Day) described earlier, the subject was scheduled for a consecutive Sunday night (Night 1: adaptation night), Monday night (Night 2: polysomnographic recording night) and Tuesday day (Day 2: MSLT recording day) stay at the Sleep-Wake Center. The subject was also given the two-week sleep log with directions to start on the Sunday two weeks prior to the sleep

center appointments. Two weeks prior to the appointments, the study coordinator called the subject to review the sleep log directions, confirm the dates, and answer any questions.

Night 1: Adaptation Night.

Two days before Night 1, the examiner called the subject to review the sleep logs, determine the approximate time of bed, and set the time of arrival at the sleep center for Night 1. On Night 1 the subject's completed sleep logs were reviewed, and the bedtime and arise times calculated. The subject was then given the FSS and CES-D, received a SCID update if necessary, and acclimated to the sleep laboratory environs and equipment. After having prepared for bed, electrodes, respiratory equipment, a mock angiocath, and a finger oximeter were placed on the subject. The subject was then allowed to roam about the lab and "get comfortable" before going to bed. No sleep recording measures were run. In the morning the subject was awakened at his/her scheduled arise time, given breakfast, and allowed to leave for the day. Night 1 served primarily as an adaptation night.

Night 2: Polysomnographic Recording Night.

Night 2 served as the polysomnographic recording night. The subject returned to the sleep center 3 hours prior to his/her scheduled bedtime and was asked to prepare for bed. Once the subject was ready and all lotions and make-up had been removed, the polysomnographic electrodes, respiratory monitoring equipment, an angiocath, and a finger oximeter were placed in accordance to the NPSG montage described earlier. The subject was free to

roam around the lab until 15 minutes before his/her scheduled bedtime. At that time the subject was asked to get into bed and given the bedtime questionnaire. The electrode box was plugged in to the polygraph lead, the subject was told to call the technician if he/she needed to arise, and the microphone and video camera were turned on. The technician performed subject-machine calibration (i.e., "look to the right, look to the left, breathe in, breathe out") and a 14 cc. baseline blood sample was attempted in subjects with successful angiocath placement. The technician then turned off the lights, asked the subject to go to sleep, started the machines, and marked the "lights out" time on the recording.

Subjects with successful angiocath placements were then monitored for sleep onset. Sleep onset was defined as three consecutive epochs of stage one sleep or any single epoch of any other stage of sleep. Upon establishing sleep onset, another 14cc. blood sample was attempted. Further attempts to obtain 14cc. blood samples were then made every 20 minutes for a total of 16 times during the night. Sleep stages were recorded and EEG was monitored during all blood drawings to secure samples from all sleep stages and limit any related arousals. Blood samples were spun down to serum samples and frozen for interleukin 1, interleukin 2, interferon gamma-alpha, and tumor necrosis factor assays to be performed. Those results will not be presented at this time but will be reported at a later date. Day 2 followed.

Day 2: MSLT Recording Day.

In the morning of Day 2 the subject was awakened at his/her scheduled

arise time and given the morning questionnaire. The respiratory monitors, finger oximeter, angiocath, and leg electrodes (RAT/LAT) were removed. The subject was then allowed to brush his/her teeth and wash up (trying not to disturb the electrodes), and was given breakfast. Nap 1 of the MSLT was scheduled to start exactly 2 hours after each subject's habitual morning wake-up time. Fifteen minutes prior to Nap 1, the subject's electrodes were checked and he/she was given the SSS and VAS to complete. Once completed, the subject's electrode box was re-plugged into the polygraph lead, the lights were turned off, and the subject was asked to "try and sleep." The machine was then started and lights out was designated on the recording. Once sleep onset was established, the subject was awakened after 15 minutes of sleep. If sleep onset was not established, the nap was ended 20 minutes after lights out. At the end of Nap 1, the subject was asked to complete identical forms of the SSS and VAS. Nap 2 started 2 hours after lights out of Nap 1 (4 hours after the subject's scheduled arise time). Similarly, Nap 3 started 6 hours after each subject's arise time, Nap 4 - 8 hours after the arise time, and Nap 5 - 10 hours after the arise time. All nap opportunities followed the same procedure outlined for Nap 1 (i.e., SSS & VAS, electrode checks). Between Naps 2 and 3 lunch was served. After Nap 5 the electrodes were removed and the subject was allowed to leave.

Table 1

Study Inclusion and Exclusion Criteria

INCLUSION CRITERIA	*EXCLUSION CRITERIA*
• Clinically Definite MS by Poser et al. (1983) Criteria	• Dementia or Any Significant Psychiatric Disturbance as validated by Neuropsychologicall Testing and SCID Interview
• Between the Ages of 21 and 50	• Other Major Medical Problems as Determined by History and Neurological Interview (e.g., Diabetes)
• EDSS Score between 1 and 6.5 by Kurtzke (1983) Criteria	• Currently Receiving Medical Treatment for Fatigue
• Free of Any Sleep - Altering Agents during the Course of the Study	• Any Other Condiition Present That May Induce Fatigue

Table 2

Fatigue Severity Scale Statements That Reliably Identify Systemic Lupus Erythematosus and Multiple Sclerosis

1. My motivation is lower when I am fatigued.
2. Exercise brings on my fatigue.
3. I am easily fatigued.
4. Fatigue interferes with my physical functioning.
5. Fatigues causes frequent problems for me.
6. My fatigue prevents sustained physical functioning.
7. Fatigue interferes with my carrying out certain duties and responsibilities.
8. Fatigue is among my three most disabling symptoms.
9. Fatigue interferes with my work, family, or social life.

* From Krupp et al. 1989, p. 1122

Table 3

Fatigue Severity Scale Statements That Accurately Differentiate Systemic Lupus Erythematosus from Multiple Sclerosis

1. Heat brings on my fatigue.
2. Cool temperatures improve my fatigue.
3. Fatigue predated other symptoms of MS.
4. Fatigue is my most disabling disease symptom.
5. Fatigue makes other MS symptoms worse.

* From Krupp et al. 1989, p. 1123

Table 4

List of Measures and Primary Objectives in Order of Administration

Test	*Type of Measure*	Objective
*Functional Systems (FS)	*Neurological*	Overall quantification of subject's neurological status
*Expanded Disability Status Scale (EDSS)	*Neurological*	Overall quantification of subject's neurological status
*Incapacity Status Scale (ISS)	*Neurological / Fatigue*	Fatigue item used to differentiate the fatigue (F) and non-fatigue (NF) groups
Structured Clinical Interview (SCID)	*Psychological*	Screen for the presence of any psychiatric disorders
Neuropsychological Screening Battery	*Neuropsychological*	Screen for the presence of any dementing disorders

* Subscale items of the Minimal Record of Disability (MRD) standard neurological examination

Table 4 (continued)

Sleep Logs	*Subjective Sleep Measure*	Two week logs of nightly bed times and morning wake up times
Fatigue Severity Scale (FSS)	*Subjective Measure of Fatigue*	Rate individual responses concerning experiences of fatigue
Center for Epidemiologic Studies-Depression (CES-D)	*Psychological*	Rate individual responses concerning experience of psychological distress during the prior week
Nocturnal Polysomnographic Recording (NPSG)	*Objective Sleep Measure*	Assess individual sleep parameters, and presence of abnormalities and sleep disruptions

Table 4 (continued)

Multiple Sleep Latency Test (MSLT)	*Objective Measure of Sleepiness*	Assess individual levels of sleepiness as indicated by sleep latencies on nap opportunities
Stanford Sleepiness Scale (SSS)	*Subjective Measure of Sleepiness*	Rate individual responses concerning levels of sleepiness before and after nap opportunities
Visual Analog Mood Scale (VAS)	*Subjective Measure of Mood*	Rate individual responses concerning mood before and after nap opportunities

Figure 1

Gantt Chart of Study Protocol

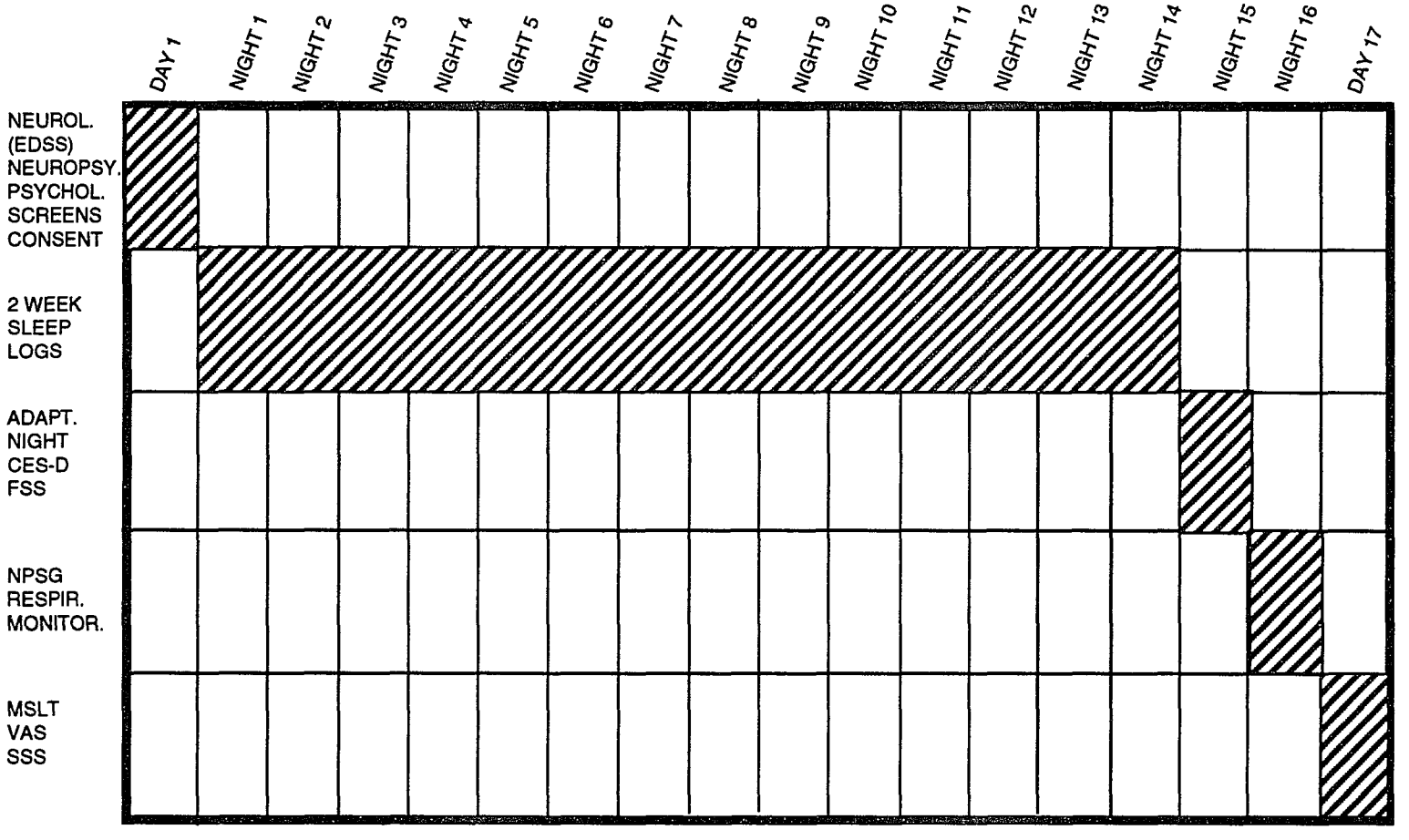


Figure 2

Data Collection Protocol

DAY 1	NIGHT 1	NIGHT 2	DAY2
SCREENING:	ADAPTATION NIGHT	NPSG RECORDING NIGHT	MULTIPLE SLEEP LATENCY TESTING
POTENTIAL SUBJECT UNDERGOES FULL MEDICAL, NEUROLOGIC, PSYCHOLOGICAL INTERVIEW (SCID) AND NEUROPSYCHOLOGICAL EXAMS TO RULE OUT OTHER MEDICAL PROBLEMS THAT COULD EFFECT SLEEP, ANY MAJOR AFFECTIVE DISORDER, OR ANY SIGNIFICANT AMOUNT OF COGNITIVE CHANGE 2 WEEK SLEEP LOG GIVEN	14 DAYS AFTER SCREENING 2 WEEK SLEEP LOG COLLECTED FSS AND CES-D QUESTIONNAIRES ADMINISTERED ADAPTATION TO SLEEP LAB & ELECTRODE PLACEMENT ELECTRODES , MOCK ANGIOCATH, AND RESPIRATORY MONITORING APPARATUS PLACED BEDTIME (BT) AS DETERMINED FROM SLEEP LOGS SUBJECT IS AWAKENED AT HABITUAL MORNING WAKE-UP TIME (HMW) ELECTODES ARE REMOVED	ELECTRODES, ANGIOCATH, AND RESPIRATORY APPARATUS PLACED SUBJECT RETURNS TO BED AT SCHEDULED BT (= TO NIGHT 1) BASELINE BLOOD SAMPLE IS ATTEMPTED SLEEP ONSET BLOOD SAMPLE IS ATTEMPTED ATTEMPTS TO TAKE 14 CC BLOOD SAMPLES ARE MADE EVERY 20 MIN. (TOTAL = 16) SUBJECT IS AWAKENED AT SCHEDULED HMW (= DAY2)	2 HRS. AFTER HMW, SSS & VAS ARE ADMINISTERED AND SUBJECT RETURNS TO BED NAP OPPORTUNITY 1 (MAX. = 20 MIN.) UP TO 15 MIN OF SLEEP ACCUMULATION IS ALLOWED IMMEDIATELY FOLLOWING NAP 1 TERMINATION, SSS & VAS ARE RE-ADMINISTERED 2 HRS. AFTER HMW, SSS & VAS ARE ADMINISTERED AND SUBJECT RETURNS TO BED NAP OPPORTUNITY 2 (MAX. = 20 MIN.) UP TO 15 MIN OF SLEEP ACCUMULATION IS ALLOWED IMMEDIATELY FOLLOWING NAP 1 TERMINATION, SSS & VAS ARE RE-ADMINISTERED 2 HRS. AFTER HMW, SSS & VAS ARE ADMINISTERED AND SUBJECT RETURNS TO BED NAP OPPORTUNITY 3 (MAX. = 20 MIN.) UP TO 15 MIN OF SLEEP ACCUMULATION IS ALLOWED IMMEDIATELY FOLLOWING NAP 1 TERMINATION, SSS & VAS ARE RE-ADMINISTERED 2 HRS. AFTER HMW, SSS & VAS ARE ADMINISTERED AND SUBJECT RETURNS TO BED. NAP OPPORTUNITY 4 (MAX. = 20 MIN.) UP TO 15 MIN OF SLEEP ACCUMULATION IS ALLOWED IMMEDIATELY FOLLOWING NAP 1 TERMINATION, SSS & VAS ARE RE-ADMINISTERED 2 HRS. AFTER HMW, SSS & VAS ARE ADMINISTERED AND SUBJECT RETURNS TO BED. NAP OPPORTUNITY 5 (MAX. = 20 MIN.) UP TO 15 MIN OF SLEEP ACCUMULATION IS ALLOWED. IMMEDIATELY FOLLOWING NAP 1 TERMINATION, SSS & VAS ARE RE-ADMINISTERED

Results

Figure 3 summarizes the data analysis. Two-tailed t-tests showed no significant differences between the mean age of the subjects in the F (40.38 $\pm$ 8.0 years) and NF (36.13 $\pm$ 12.22 years) groups. In addition, the average total nightly sleep time reported on the two-week sleep log did not differ significantly between the F (445.38 $\pm$ 39.3 minutes) and the NF groups (475.38 $\pm$ 73.6 minutes).

Ordinal scale subjective measures of neurologic disability, fatigue, psychological distress, mood, and sleepiness were compared between groups using the Mann-Whitney U - Wilcoxon Rank Sum W Test. Table 5 summarizes these results. No significant differences were seen in EDSS scores between the F and NF groups, indicating that the physical neurological impairments were similar. In contrast, when FSS responses were compared between the F and NF groups, a significant difference was seen, indicating that the F group was reporting more instances of fatigue and supporting the ISS group differentiation.

Comparisons Between Groups and Correlations

Subjective Mood Scales (CES-D and VAS)

As shown in table 5, CES-D scores differed significantly between the F and the NF groups, indicating that the F group was reliably reporting higher levels of psychological distress than the NF group.

VAS responses also showed significant differences between the F and NF groups on various parameters. Each of the nine questions on mood was

analyzed as an average response before nap opportunities (BE), average response after nap opportunities (AF), and average overall response (AV). On the Mann-Whitney U Test (see table 5) significant differences between the F and NF group responses were seen. F group responses indicated that they were significantly less alert (BE) and had less of a sense of overall well being (AF). The F group also reported higher levels of effort (AV), weariness (AF and AV), and sleepiness (AF). There was a trend for the F subjects to report lower levels of alertness (AV), overall sensations of happiness (BE, AF and AV), and overall sense of well being (BE) as well as higher levels of sleepiness (BE and AV). No noteworthy differences were seen on questions concerning levels of sadness (BE, AF, and AV), tension (BE, AF, and AV), effort (BE and AV), weariness (BE), calmness (BE, AF, and AV), and sense of well being (AV).

In addition, there was a significant association between FSS score and level of psychological distress (CES-D), alertness (BE and AV), effort (BE, AF, and AV), happiness (BE and AV), overall sense of well being (BE and AV), sleepiness (BE and AV), and weariness (AV). Table 6 summarizes these results.

CES-D scores were significantly correlated with levels of fatigue (FSS), effort (BE and AF), happiness (BE), sleepiness (BE, AF, and AV), tension (BE, AF, and AV), and weariness (BE, AF, and AV)(see Table 6).

Subjective Sleepiness Scale (SSS)

Responses on the SSS questionnaire were analyzed by the Mann-Whitney U - Wilcoxon Rank Sum W Test. F subjects reported significantly

higher level of sleepiness on all SSS parameters (BE, AF, and AV). Table 5 illustrates these findings.

Table 6 shows the correlational associations between SSS, FSS, CES-D, and VAS mood scale responses. Significant associations were seen between level of fatigue (FSS) and SSS levels of sleepiness (BE and AV). SSS (BE) responses were significantly associated with levels of alertness (BE, AF, and AV), effort (BE, AF and AV), happiness (AF), overall sense of well being (AF and AV), sleepiness (BE, AF, and AV), and weariness (BE, AF and AV). SSS(AF) responses were significantly associated with levels of alertness (BE, AF, and AV), effort (AF and AV), overall sense of well being (AF), sleepiness (AF and AV), and weariness (BE, AF, and AV). Significant correlations were seen between SSS (AV) responses and levels of alertness (BE, AF, and AV), effort (BE, AF, and AV), happiness (AF), overall sense of well being (AF and AV), sleepiness (BE, AF, and AV), and weariness (BE, AF, and AV). No significant associations were seen between CES-D scores and any SSS response parameters (BE, AF, and AV).

VAS (BE) and SSS (BE) responses were compared to respective (AF) responses on all five nap opportunities for the F and NF groups. Mann-Whitney U Test results found no significant differences between or across groups, suggesting that there was no restorative quality of the nap opportunities on mood and/or sleepiness for each group, respectively, or the MS group as a whole.

A multiple regression was used to determine the predictive ability of

overall sleepiness and depression (SSS AV and CES-D) for measures of fatigue (FSS). Results demonstrated that the SSS and CES-D together accounted for 38 percent of variance ($F(2,11) = 5.00$, $p<.05$). However, the betas for SSS (AV) and CES-D were not significant.

MSLT Findings

MSLT results revealed little differences in objective measures of sleep latencies between the F and NF groups. Two-tailed t-tests showed no significant differences between groups for all five nap opportunities. However, there was a trend for the F group to have shorter sleep latencies on nap two (7.75 ± 3.15 vs. 12.44 ± 6.59, t (14), $p<.1$). Table 7 lists the MSLT mean sleep latencies.

REM sleep was observed in three nap opportunities: one F group subject and two NF group subjects (19 percent of the MS sample). Statistical analysis was not possible because of the limited number of observed cases. However, in all three cases REM sleep was seen in the fourth nap opportunity with REM latencies ranging from 11 to 13 minutes.

Comparisons of Subjective and Objective Measures

Spearman correlations were performed between subjective responses, concerning sleepiness, mood, and psychological distress, and objective measures of sleepiness. Correlational analysis between SSS, select VAS mood scale, CES-D responses, and nap opportunity sleep latency measures, revealed a significant correlation between SSS reported level of sleepiness prior to nap two and MSLT sleep latency on nap two ($p<.05$). Figure 4 plots this

correlation. A trend ($p<.1$) was seen in the level of reported effort prior to nap one and MSLT sleep latency on nap one, the level of tension prior to nap 5 and MSLT sleep latency on nap five, and the general level of psychological distress and MSLT sleep latency on nap three. Table 8 outlines SSS, select VAS mood scale, and CES-D responses by sleep latencies on nap opportunities.

NPSG Findings.

Nocturnal Sleep Recording Parameters

Table 9 summarizes the NPSG sleep recording findings. Two-tailed t-tests were used to compare objective NPSG nocturnal sleep variables between the F and NF subject groups. Since total time allowed for nocturnal sleep was determined by average bed time and morning arise time on the two week sleep logs, a variable of awake time after nocturnal sleep (WANS: scheduled morning arise time minus spontaneous awake time) was created. Frequency analysis revealed that only one F group subject, as opposed to five NF subjects, experienced wakefulness after the nocturnal sleep period had ended. Fisher's Exact Test showed a trend for the NF group to be awake and spend more time waiting for their morning arise time than the F group ($p = .059$). There were no significant differences between groups were seen on other NPSG sleep architecture variables: total wake time during sleep (TWT), total sleep time (TST), wake after sleep onset (WASO), sleep efficiency (SLPEFF), latency to sleep onset (SLAT), latency to REM sleep (REMLAT), total number of awakenings (TOTAWK), arousals less than or equal to 30 seconds (ARO30), percentage of stage 1 sleep (S1PER), percentage of stage 2 sleep (S2PER),

percentage of stage 3 sleep (S3PER), percentage of stage 4 sleep (S4PER), percentage of SWS (SWSPER), percentage of NREM sleep (NREMPER), percentage of REM sleep (REMPER), latency to the first epoch of stage 1 sleep (S1EPLAT), latency to the first epoch of stage 2 sleep (S2EPLAT), latency to the first epoch of stage 3 sleep (S3EPLAT), latency to the first epoch of stage 4 sleep (S4EPLAT), and latency to the first epoch of REM sleep (REMEPLAT).

Alpha EEG Sleep

Fifty percent of the MS sample showed the alpha EEG sleep anomaly during NPSG sleep recording. Of the eight subjects, five were in the F group and three were in the NF group. Two-tailed analysis using Fisher's Exact Test revealed no significant differences between groups.

The alpha EEG sleep anomaly subsample was comprised of six women (75 percent) and two men (25 percent). There was a trend for the alpha EEG subsample to be younger (33.62 $\pm$ 9.74 years) than those subjects in which the alpha EEG sleep anomaly did not occur (42.88 $\pm$ 8.94 years; $t(13.9)= 1.98$, $p<.1$). No significant differences between the alpha EEG sleep subsample and the other MS subjects was seen in the percentage stage one sleep, stage three sleep, stage four sleep, SWS, REM sleep, or sleep efficiency on NPSG recording. However, stage two sleep for the alpha EEG subsample was significantly reduced when compared to the MS subject without alpha EEG sleep (53.47 $\pm$ 6.87 vs. 63.06 $\pm$ 9.0, $t(13.09)= 2.4$, $p<.05$). Two-tailed t-test analysis revealed no significant differences between the alpha EEG sleep subsample and the other MS subjects in latencies to stage one sleep on the five MSLT nap opportunities.

PLMs

Fifty percent of the MS sample showed PLMs during nocturnal sleep. Three subjects of this PLM subsample were in the F group as opposed to five subjects from the NF group. Two-tailed t-test analysis revealed no significant differences between the F and NF groups on the PLM index (mean number of PLMs per hour) or PLM arousal index (mean number of arousals related to PLMs per hour) parameters. In addition, no significant differences between the PLM subsample and the other MS subjects were seen in latencies to stage one sleep on the five MSLT nap opportunities. Table 10 summaries PLM subsample characteristics.

Seven of the eight subjects in the PLM subsample (88 percent) were men. NPSG recording analysis revealed a mean PLM total of 236.5 movements with a mean PLM index of 39.07 movements per hour of sleep. Two-tailed t-test results revealed no significant difference in age between the mean age of this PLM subsample (41 years) and the MS sample as a whole (37.5 years). Four subjects (50 percent of the PLM subsample) experienced PLMs during NREM and REM sleep. Seven subjects of the PLM subsample also experienced arousals consequential to these movements. However, in those subjects experiencing PLMs, not all movements led to arousals as the mean PLM arousal index was 7.85 arousals per hour of sleep, which is considerably lower (80 percent) than the number of movements seen per hour. Two-tailed t-test analysis showed no significant differences between the PLM subsample and the other MS subjects in percentage of sleep efficiency, stage one sleep, stage three

sleep, stage four sleep, SWS, or REM sleep on NPSG recording. However, stage two sleep for the PLM subsample was significantly increased when compared to the MS subject without PLMs (63.8 $\pm$ 8.56 vs. 52.74 $\pm$ 6.13, $t(12.68) = -2.97$, $p<.01$).

The PLM subsample age mean (41 years) was not significantly greater than that of the alpha EEG sleep anomaly (34.44 years). T-test analysis revealed the alpha EEG sleep subsample to have a significantly reduced percentage of stage two sleep on NPSG recordings than the PLM subsample (52.29 $\pm$ 6.47 vs. 64.09 $\pm$ 9.2, $t(10.77) = -2.77$, $p<.05$). In addition, only one MS subject experienced both PLMs and alpha EEG sleep. On Fisher's Exact Test, a significant disparity was seen between the alpha EEG subsample and the PLM subsample. In addition, correlational analysis revealed a significant negative two-tailed correlation between the presence of PLMs and alpha EEG sleep. Only one subject of the MS sample did not have either PLMs or alpha EEG sleep on NPSG evaluation. Figure 5 illustrates these findings.

Respiratory Parameters

Hypopnea events, defined as a 50 percent reduction of airflow based on the analog output to the polygraph, were seen in six of the sixteen MS subjects, representing 37.5 percent of the sample. However, the greatest number of hypopnea events in any individual subject was fifteen. The mean incidence was nine events per NPSG recording. Sleep apnea events were detected in five of the sixteen MS subjects. Four subjects had both obstructive and non-obstructive sleep apnea, and one subject had only non-obstructive sleep apnea.

Only four subjects had obstructive apnea events and none had more than one. In contrast, the total number of non-obstructive apnea events did not exceed nine per subject. Because of the low frequency of respiratory events, in two-tailed t-test analysis respiratory difficulties were considered generally. When the presence of any respiratory difficulties was analyzed between the F and NF group, two-tailed t-test revealed no significant differences between groups.

Blood Drawings

Blood drawings were attempted in twelve of the sixteen MS subjects: seven subjects with fatigue and five without. Ten subjects experienced at least one arousal due to blood drawings, but none experienced more than five related arousals (mean: 2.9). Two-tailed t-test analysis revealed no significant blood-related arousal differences between the F and NF groups or the blood sampling and non-blood sampling groups. When all forms of nocturnal arousals (non-explained arousals, arousals due to PLMs, and arousals due to blood drawings) were compiled, no significant differences were seen between the F and NF groups or the blood sampling and non-blood sampling groups.

MS Sample Compared to Normal Population

NPSG Findings

The normal curve ratio test was used to compare the MS, F, and NF groups to published age and sex-matched norms (Williams et al., 1974). Comparisons of the z-ratios (ZR) are delineated in Table 10. Total sleep time ZR (TST.ZR) on the NPSG recording was significantly below normal expectations in six (32.5 percent) MS subjects (3 F and 3 NF group subjects)

and above expectation in one NF group subject (ZR = 3.12). In addition, the four (50 percent) out of eight NF group ratio was also significantly deviant from the expected norms (ZR = 2.54). However, the three out of eight F group ratio was not significantly different. Sleep efficiency ZR (SLPEFF.ZR) was below expectation in eleven (69 percent) of the MS subjects (4 F and 7 NF group subjects). Results on the normal curve ratio test indicated that this ratio was significantly deviant from expected norms for the MS (ZR = 5.5), F (ZR = 7.06), and NF (ZR = 2.55) group subjects.

Percentage of REM sleep ZR (REMPER.ZR) were below expectations in four (50 percent) of the MS subjects (2 F and 2 NF group subjects) and above expectations in two (12.5 percent) F group subjects. Results on the normal curve ratio test indicated that this six (32.5 percent) out of sixteen MS group ratio and four out of eight F group ratio were significantly deviant from expected norms for the MS (ZR = 2.68) and F (ZR = 2.54). The two out of eight NF group proportion was not significantly different.

Other sleep parameter variables that were compared to normative data were not found to have significantly deviant proportions for the MS, F, or NF groups. Latency to sleep onset ZR (SLAT.ZR) were deviant from expectations in three of the MS subjects (2 F and 1 NF group subjects). Percentage of stage 1 sleep ZR (S1PER.ZR) were deviant from expectations in three of the NF group subjects. Percentage of stage 2 sleep ZR (S2PER.ZR) were from deviant expectations in two of the NF group subjects. Percentage of stage 3 sleep ZR (S3PER.ZR) were also deviant from expectations in two of the NF group

subjects. Percentage of stage 4 sleep ZR (S4PER.ZR) were deviant from expectations in two of the MS group subjects (1 F and 1 NF group subjects).

Alpha Corrections

Since numerous tests of significance were conducted, Bonferroni corrections were considered relative to the three hypotheses examined. The first hypothesis, comparing the F and NF groups, was analyzed using 338 tests of significance. Eighty significant comparisons ($p<.05$) and ten trends ($p<.1$) were found. Applying the adjusted Bonferroni alpha of $p<.00015$ would render all findings insignificant. In addition, the probability of getting a type I error would be one out of 20 findings. Therefore, of the 80 significant findings, approximately 17 would be expected by chance.

The second hypothesis, examining sleep disruption and brain wave abnormalities between the MS sample and normative expectations, was analyzed using 14 tests of significance. Three tests were significant at the $p<.05$ level. Applying the adjusted Bonferroni alpha of $p<.0036$ would render only the Fisher's Exact Test comparison between the presence of PLM and alpha EEG sleep significant. Probability would predict less than one result being significant at the $p<.05$ level. Therefore, of the three significant findings, less than one would be expected by chance.

The third hypothesis, comparing sleep stage percentages and sleep architecture changes between the MS sample and normative data, was analyzed using 27 tests of significance. Seven tests were significant at the $p<.05$ level. Applying the adjusted Bonferroni alpha of $p<.0018$ would still

render the findings of reduced sleep efficiency for the MS and NF groups significant. Probability would predict approximately one result being significant at the $p<.05$ level. Therefore, of the seven significant findings, approximately one would be expected by chance.

Figure 3

Data Comparison Made Between the Multiple Sclerosis (MS) , Fatigued (F), Non-Fatigued (NF) Group, and Published Sex and Age - Matched Norms

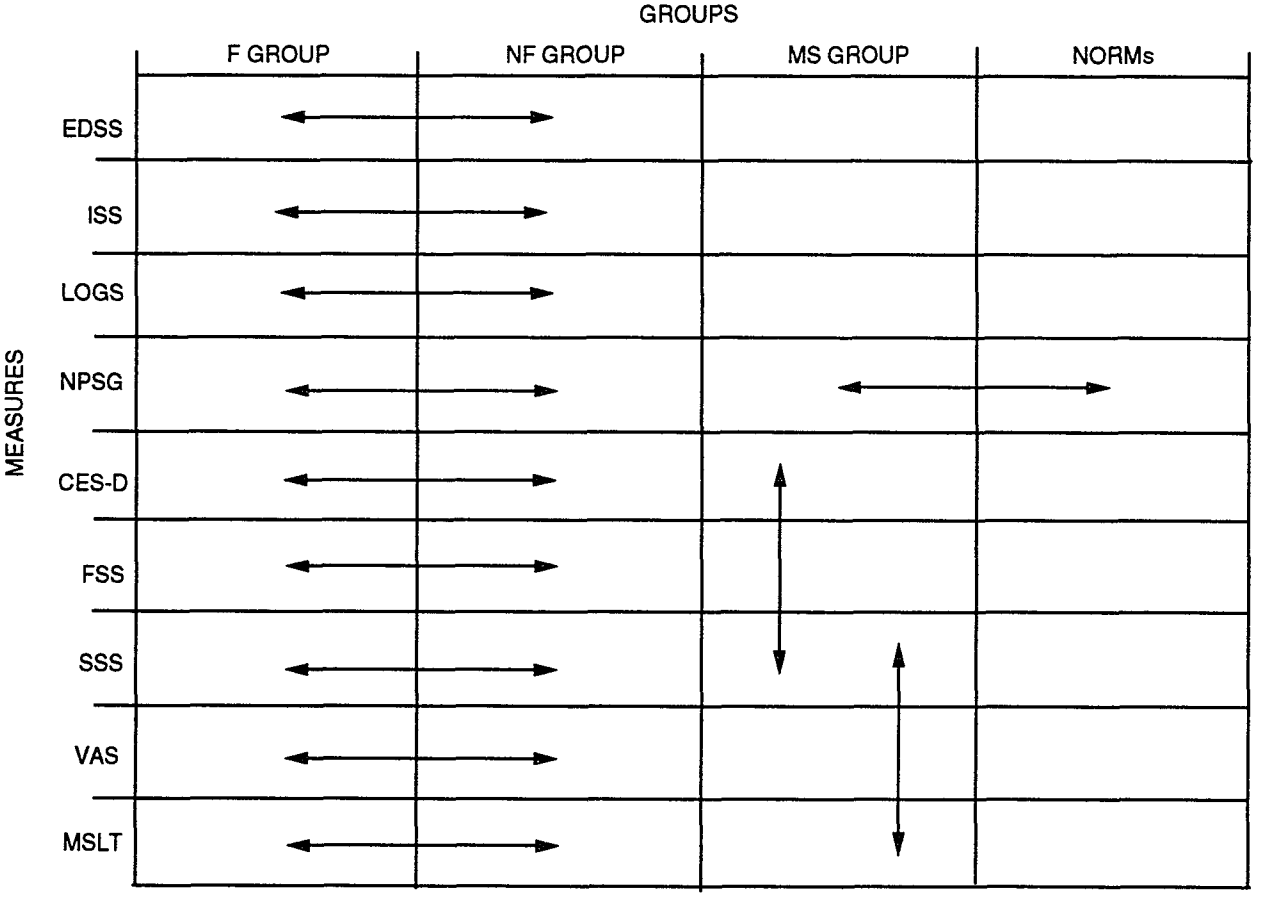


Table 5

FSS, CES-D, SSS, and VAS Mood Scale Responses for Fatigued (F) and Non-Fatigued (NF) Groups: Mann-Whitney - Wilcoxon Rank Sum Test (MW-WRST) Results

	F Group		NF Group		
Scale	Mean Rank	N	Mean Rank	N	MW-WRST
EDSS	7.06	8	9.99	8	n.s.
FSS	12.13	8	4.88	8	**
CES-D	11.88	8	5.13	8	**
SSS (BE)	10.00	8	4.17	6	**
SSS (AF)	9.38	8	5.00	6	*
SSS (AV)	9.88	8	4.33	6	*
ALERT(BE)	5.00	8	10.20	5	*
ALERT(AF)	6.13	8	9.33	6	n.s.
ALERT(AV)	5.50	8	9.40	5	t
CALM(BE)	6.00	8	8.6	5	n.s.
CALM(AF)	6.19	8	9.25	6	n.s.
CALM(AV)	6.25	8	8.20	5	n.s.
EFFORT(BE)	7.50	8	4.50	4	n.s.
EFFORT(AF)	9.38	8	5.00	6	*
EFFORT(AV)	7.38	8	4.75	4	n.s.
HAPPY(BE)	5.38	8	9.60	5	t
HAPPY(AF)	5.88	8	9.67	6	t
HAPPY(AV)	5.50	8	9.40	5	t

Table 5 (continued)

	F Group		NF Group		
Scale	Mean Rank	N	Mean Rank	N	MW-WRST
OVERALL(BE)	5.63	8	9.20	5	t
OVERALL(AF)	5.50	8	10.17	6	*
OVERALL(AV)	5.63	8	9.20	5	n.s.
SAD(BE)	8.00	8	5.40	5	n.s.
SAD(AF)	8.25	8	6.50	6	n.s.
SAD(AV)	7.63	8	6.00	5	n.s.
SLEEPY(BE)	8.50	8	4.60	5	t
SLEEPY(AF)	9.75	8	4.50	6	*
SLEEPY(AV)	8.63	8	4.40	5	t
TENSE(BE)	8.38	8	4.80	5	n.s.
TENSE(AF)	8.88	8	5.67	6	n.s.
TENSE(AV)	8.00	8	5.40	5	n.s.
WEARY(BE)	8.38	8	4.80	5	n.s.
WEARY(AF)	10.13	8	4.00	6	**
WEARY(AV)	9.00	8	3.80	5	*

t Trend at the $p<.1$ level

* Two-tailed significance at the $p<.05$ level

** Two-tailed significance at the $p<.01$ level

Table 6

Correlation Coefficients: Select VAS Mood Scale Responses by FSS Score, CES-D Score, and SSS Score

	FSS	CES-D	SSS(BE)	SSS(AF)	SSS(AV)
FSS	1.00	.66**	.66**	.41	.55**
CES-D	.66**	1.00	.47	.40	.46
ALERT(BE)	-.73**	-.48	-.88**	-.59*	-.76**
ALERT(AF)	-.39	-.27	-.71**	-.86**	-.87**
ALERT(AV)	-.69**	-.48	-.85**	-.81**	-.90**
CALM(BE)	-.28	-.39	-.28	-.25	-.29
CALM(AF)	-.01	-.27	-.37	-.17	-.27
CALM(AV)	-.16	-.31	-.30	-.17	-.24
EFFORT(BE)	.63*	.62*	.71*	.51	.63*
EFFORT(AF)	.55*	.56*	.74**	.82**	.86**
EFFORT(AV)	.62*	.57	.74**	.75**	.82**
HAPPY(BE)	-.56*	-.60*	-.38	-.27	-.34
HAPPY(AF)	-.42	-.36	-.63*	-.44	-.56*
HAPPY(AV)	-.59*	-.49	-.47	-.32	-.41
OVERALL(BE)	-.56*	-.39	-.54	-.51	-.57
OVERALL(AF)	-.51	-.47	-.63*	-.55*	-.63*
OVERALL(AV)	-.61*	-.41	-.55*	-.51	-.58*
SAD(BE)	.40	.43	.04	-.11	.04
SAD(AF)	.27	.35	.34	-.11	.07
SAD(AV)	.37	.38	.30	-.15	.02
SLEEPY(BE)	.69**	.63*	.72**	.51	.64*

Table 6 (continued)

	FSS	CES-D	SSS(BE)	SSS(AF)	SSS(AV)
SLEEPY(AF)	.47	.57*	.73**	.77**	.82**
SLEEPY(AV)	.69**	.62*	.75**	.67*	.77**
TENSE(BE)	.48	.69**	.36	.23	.36
TENSE(AF)	.42	.65*	.45	.25	.36
TENSE(AV)	.48	.66*	.39	.21	.31
WEARY(BE)	.53	.68*	.66*	.59*	.68*
WEARY(AF)	.63	.59*	.83**	.83**	.90**
WEARY(AV)	.69**	.65*	.79**	.77**	.85**

* Two-tailed significance at the $p<.05$ level

** Two-tailed significance at the $p<.01$ level

Table 7

Mean (M), Standard Deviation (SD), and Two-Tailed T-Test Results (T) for MSLT Nap Opportunities: Fatigued (F) versus Non-Fatigued (NF) Groups

	F Group (n=8)		NF Group (n=8)		
Nap #	M	SD	M	SD	T
1	12.06	5.32	13.62	7.10	n.s.
2	7.75	3.15	12.44	6.59	t
3	11.81	6.40	13.44	5.28	n.s.
4	11.44	6.90	11.38	4.60	n.s.
5	14.44	6.17	16.50*	6.12*	n.s.
Mean (Naps 1 - 5)	11.12	4.01	13.48	4.70	n.s.

* n =6 subjects

t Trendat the p<.1 level

Table 8

Spearman Correlations Between SSS, VAS Mood Scale, and CES-D Responses by Sleep Latency on MSLT Nap Opportunities (N =16)

	NAP 1	NAP 2	NAP 3	NAP 4	NAP 5
SSS	-.10	-.57*	.01	-.05	.37
ALERT	-.24	.27	.04	-.04	-.33
SLEEPY	.02	-.25	-.20	-.13	.05
WEARY	.10	-.40	-.11	-.01	.08
EFFORT	.46t	-.36	-.07	.06	.12
TENSE	.14	-.13	-.11	-.02	-.50t
CES-D	-.28	-.28	-.46	.19	.21

t Trend in correlation at $p<.1$ level

* Significant correlation at $p<.05$ level

Figure 4

Fatigued (F) versus Non-Fatigued (NF) Subject Responses on the SSS Before Nap Two by MSLT Sleep Latency on Nap Two

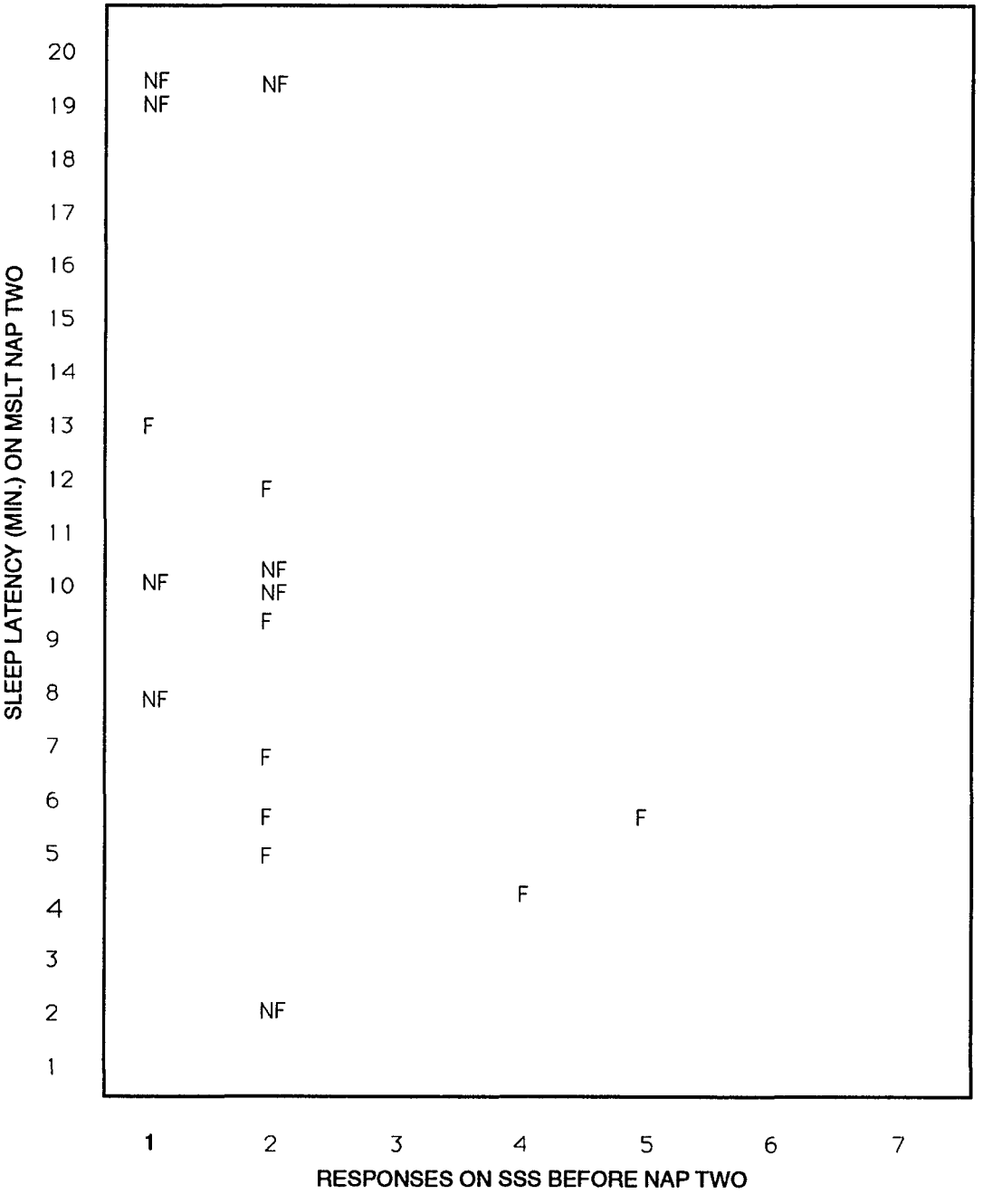
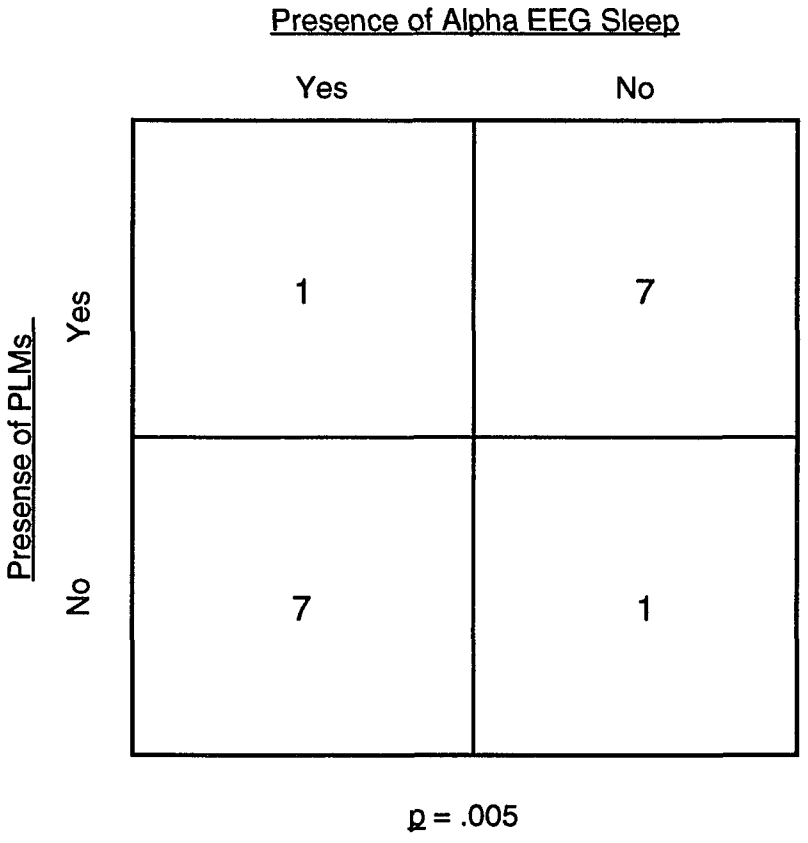


Figure 5

Fisher's Exact Test Results Comparing the Presence of the Alpha EEG Sleep Anomaly and Periodic Limb Movements (PLM) During the Nocturnal Sleep of the MS Sample (N = 16)



$p = .005$

Pearson Correlation : r (14) = -.75, p <.001

Table 9

Mean(M), Standard Deviation(SD), and Two-Tailed T-Test Results(T) for NPSG Sleep Architecture Parameters: Fatigued(F) versus Non-Fatigued(NF) Groups

Parameter[a]	Group	M	SD	T
TWT	F	63.88	44.23	n.s.
	NF	88.31	53.61	
TST	F	378.31	58.44	n.s.
	NF	374.88	80.02	
WASO	F	50.62	39.37	n.s.
	NF	63.44	55.24	
SLPEFF	F	0.86	0.1	n.s.
	NF	0.81	0.1	
WANS	F	0.06	0.18	t
	NF	7.56	9.64	
SLAT	F	14.50	9.16	n.s.
	NF	14.38	8.66	
REMLAT	F	82.75	55.75	n.s.
	NF	75.88	28.67	
TOTAWK	F	23.25	10.62	n.s.
	NF	30.38	14.31	
ARO30	F	24.00	18.88	n.s.
	NF	39.14	19.96	
S1PER	F	4.46	2.01	n.s.
	NF	5.73	5.28	

Table 9 (continued)

Parameter	Group	M	SD	T
S2PER	F	56.71	8.28	n.s.
	NF	59.82	10.33	
S3PER	F	7.02	3.18	n.s.
	NF	8.23	4.66	
S4PER	F	8.16	7.83	n.s.
	NF	7.15	7.24	
NREMPER	F	71.89	8.97	n.s.
	NF	75.20	6.61	
SWSPER	F	15.18	10.31	n.s.
	NF	15.38	6.85	
REMPER	F	23.66	8.47	n.s.
	NF	19.07	6.3	
S1EPLAT	F	12.00	7.49	n.s.
	NF	21.69	29.65	
S2EPLAT	F	16.25	8.41	n.s.
	NF	15.69	10.15	
S3EPLAT	F	42.50	32.68	n.s.
	NF	54.75	35.49	
S4EPLAT	F	78.42	98.17	n.s.
	NF	52.00	29.36	
REMEPLAT	F	115.12	75.12	n.s.
	NF	106.56	43.58	

t Trend at the $p<.1$ level

a For parameter definitions see pages 76 & 77

Table 10

Occurrence of Periodic Limb Movements (PLMs) in 8 Subjects with MS

Subject #	Sex	Age	Fatigue	# of PLMs	PLM Index	PLM Arousal Index	NREM/REM
1	M	27	no	41	8.15	2.98	NREM
2	M	36	no	321	52.41	4.9	NREM/REM
4	M	29	no	189	27.49	8.73	NREM/REM
6	F	59	no	373	65.63	7.57	NREM
8	M	40	yes	416	64.66	11.66	NREM/REM
9	M	49	yes	107	17.59	0	NREM
12	M	46	no	341	60.53	24.14	NREM/REM
13	M	43	yes	104	16.12	2.79	NREM

* MI = Myoclonus Index (number of movements per hours of sleep)

**MAI = Myoclonus Arousal Index (number of PLM-related arousals per hours of sleep)

Table 11

Normal Curve Ratio Test Results for the Multiple Sclerosis (MS), Fatigued (F), and Non-Fatigued (NF) Groups on Nocturnal Polysomnographic (NPSG) Recordings

NPSG Sleep Parameter	Ratio			Z-Ratio		
	MS	F	NF	MS	F	NF
TST.ZR[a]	7/16	3/8	4/8	3.12**	1.90	2.54*
SLPEFF.ZR[a]	11/16	4/8	7/8	5.5***	2.54*	7.06***
SLAT.ZR[a]	3/16	2/8	1/8	1.41	1.31	0.64
S1PER.ZR[a]	3/16	0/8	3/8	1.41	n/a	1.90
S2PER.ZR[a]	2/16	0/8	2/8	0.91	n/a	1.31
S3PER.ZR[a]	2/16	0/8	2/8	0.91	n/a	1.31
S4PER.ZR[a]	2/16	1/8	1/8	0.91	0.64	0.64
REMPER.ZR[a]	6/16	4/8	2/8	2.68**	2.54*	1.31
REMLAT.ZR[a]	2/16	2/8	0/8	0.91	1.31	n/a

* $p<.05$
** $p<.01$
*** $p<.001$
a For parameter definition see pages 80 & 81

Discussion

Fatigued versus Non-Fatigued Group Comparisons

The study results partially support the first hypothesis that persons with MS complaining of excessive fatigue have higher indices of daytime sleepiness (on subjective and objective measures) and experience more sleep-disruptive behaviors (i.e., PLMs, respiratory difficulties) and brain wave abnormalities (i.e., alpha EEG sleep) during nocturnal sleep than those persons with MS who do not report excessive fatigue. On subjective self-reports, the F subjects indicated significantly greater levels of sleepiness (on SSS and VAS mood scale responses) before and after nap opportunities throughout the daytime measures than did the NF subjects. In contrast, objective measures of sleepiness (i.e., MSLT results) did not support a F versus NF group differentiation. In addition, no significant differences in amounts of sleep disruptive behaviors or presence of brain wave abnormalities were found between the F and NF groups on NPSG recording. Of the eight subjects experiencing PLMs during nocturnal sleep, three were from the F group and five were from the NF group. No significant respiratory difficulties were found for any of the F or NF subjects. Of the eight subjects having alpha EEG sleep, five were from the F group and three were from the NF group. While suggesting an inverse relationship for PLMs and alpha EEG sleep in the F and NF groups, secondary analyses did not demonstrate a significant difference in prevalence rates between groups.

Subjective and Objective Measures of Sleepiness as Indicators of MS Fatigue

On subjective self-reports (SSS and VAS mood scale responses), the F subjects indicated significantly greater levels of sleepiness before and after nap opportunities throughout the daytime measures than did the NF subjects. In addition, self-report results also indicated that MS fatigue cannot be solely described by sleepiness; mood scale response comparisons between groups reveal that the F subjects also reported more instances of psychological distress, greater amounts of weariness throughout the day, and greater amounts of effort needed to do anything during the day. In addition, they reported being less alert, feeling less happy, and generally not feeling as great a sensation of overall well-being as did the NF subjects.

Secondary analyses revealed fatigue scores to be significantly related to mood scale reports. Significant positive correlations were seen between fatigue scores and scores on the CES-D, SSS, and VAS for levels of sleepiness, effort, and weariness. Therefore, as levels of reported fatigue were seen to increase, so were levels of sleepiness, sense of effort, weariness, and psychological distress. In contrast, fatigue scores were negatively correlated with alertness, happiness, and overall sense of well being. Hence, as reported fatigue was seen to increase, reported level of alertness throughout the day, sense of happiness, and overall sense of well being were seen to decrease.

These strong associations between fatigue and mood scales would indicate that fatigue might best be described by a combination of factors.

Based on the commonality seen in SSS, VAS sleepiness, and VAS weariness responses, and the substantial lack of coincidence in VAS alertness responses, sleepiness was chosen as a plausible component of reported fatigue. Similarly, since psychological distress is prevalent in the MS population, and sleep surveys have shown that sleep complaints and depression are often concurrently reported in persons with MS (Leo et al., 1991; Saunders et al., 1991; & Clark et al., 1992), CES-D responses were also considered. Through regression analysis, sleepiness and psychological distress accounted for thirty-eight percent of the variance found in reported fatigue. However, apart from concluding that both factors should be considered when examining fatigue, further interpretation remains unclear.

One possible explanation is that fatigue remains too vague in both the minds of the subject and the examiner. As discussed in the introduction, Hartman (1973), described two patterns of tiredness: 1) physical tiredness associated with prolonged activity; and 2) mental tiredness associated with prolonged intellectual and/or emotional activity. Perhaps a similar delineation between physical fatigue, which may be more akin to sleepiness, and mental fatigue, which may be more associated with psychological distress, needs to be made. On the other hand, it may be that persons who complain of excessive fatigue, are more prone to complaining in general or are attempting to direct attention towards themselves. With fatigue being a major concomitant of MS, the dearth of psychosocial research in this area is problematic and needs to be addressed in future studies.

Additional evidence that fatigue cannot be solely defined by sleepiness was seen in the lack of objective polysomnographic support for the claims of subjective sleepiness. Comparisons of MSLT sleep latencies between groups showed a tendency for the F subjects to fall asleep faster on the second nap opportunity than the NF subjects. Although this indicates an objective level of increased sleepiness for the F group, other nap opportunities did not show this tendency. Therefore, this finding remains inconclusive and needs to be re-examined in future studies.

Secondary analyses also revealed some significant associations between subjective self-report responses and MSLT sleep latencies. Sleepiness, as indicated by the SSS, was seen to be significantly associated with sleep latencies on nap two of the MSLT. As subjects reported increased sleepiness levels on the SSS prior to nap two, latency for sleep onset on nap two decreased. This effect was pronounced in the F subjects, who reported significantly higher levels of sleepiness prior to nap two and showed a trend toward falling asleep faster on nap two than did NF subjects. Similarly, a trend was seen for increases in level of effort prior to nap one to be associated with decreases in sleep latency on nap one of the MSLT. A trend was also seen for increases in level of tension prior to nap five to be associated with decreases in sleep latency on nap five of the MSLT. Significantly elevated psychological distress in the F subjects (as measured by the CES-D) was seen to be associated with shortened sleep latencies on nap three on the MSLT.

Although these relationships may be indicative of a relationship between

self-report responses and polygraphic findings, they are not consistent across nap opportunities and may denote a time of day effect. Nap one was scheduled two hours after the subjects were awakened. Having recently gotten out of bed, it is reasonable that the subjects may have perceived returning to bed as an effort. In addition, the subjects may not have been fully awake at the beginning of nap one, and therefore, fell back to sleep more readily. Similarly, nap two was scheduled four hours after the subjects were awakened and were given a late, caffeine-free, breakfast. Therefore, the subjects, especially the F group, may have experienced a "post-lunch dip" at that time, producing a shorten sleep latency. The fifth and last nap, was scheduled ten hours after the subjects were awakened. Therefore, the pronounced increase in tension seen prior to nap five may have been related to the ending of the study and returning home, while the decrease in sleep latency on nap five may have been associated with a late afternoon circadian downshift and dissociation with tense mood state.

Time of day effects (i.e., "post-lunch dip") have been readily demonstrated in performance and objective (MSLT sleep latencies) measures (Blake, 1967; Carskadon, et al., 1979; Richardson et al., 1978), while subjective alertness (VAS) and sleepiness (SSS and VAS) responses are more closely linked to body temperature rhythms (Colquhoun, 1971; Froberg, 1977). Monk (1989) concluded that there are certain "gates to sleep" at particular times of day that are independent of subjective feelings of sleepiness. However, further research is necessary to delineate the circadian fluctuations in self-report

responses, and to determine whether these response fluctuations are reflected in polysomnographic findings.

Sleep-Disruptive Behaviors, Brain Wave Abnormalities, and Other NPSG Findings

As mentioned earlier, no significant differences between the F and NF group in the frequency of disruptive sleep behaviors (i.e., PLMs, respiratory difficulties) or presence of brain wave abnormalities (i.e., alpha EEG sleep) were found. Further analysis of NPSG recordings did not reveal any significant differences between the F and NF groups on sleep stage percentages or sleep architecture parameters. However, wake time after nocturnal sleep and before the scheduled morning arise time was seen in six subjects. Interestingly, five of those were NF subjects and only one was a F subject. Since the morning wake-up time was determined by the subject's own self-report, it appears that the NF subjects are either over-estimating their sleep need or are hyperaroused and awakening sooner than desired. Although hyperarousal, as has been noted in the insomnia population (Kuisk et al., 1989; & Regestein et al., 1993), has not been demonstrated in the present study of NF MS subjects, their self-report of low sleepiness, low weariness, and high alertness levels are suggestive. In addition, although no significant differences in objective sleepiness (MSLT) were found, the mean latency to stage one sleep was higher for the NF subjects on four out of five nap opportunities.

The present findings do not support our previously reported findings of increased movement activity in the nocturnal sleep of MS persons with

complaints of excessive fatigue (Caruso et al., 1991). However, those results were based on actigraphy monitoring of non-dominant wrist activity. Due to the dearth of polygraphic studies and the need for comparable baseline nocturnal sleep data in the MS population, a standard NPSG montage was chosen for this study in favor of a montage with separate limb electrode placements.

MS Sample versus Normative Expectations: Sleep Disruptions and Brain Wave Abnormalities

Comparisons between the MS sample findings and studies in other populations support the second hypothesis that persons with MS have more sleep-disruptive behaviors (i.e., PLMs, respiratory disruptions) and brain wave abnormalities (i.e., alpha EEG sleep) during nocturnal sleep than are expected for persons without neurologic or psychiatric disorders. Fifty percent of the MS sample (8 subjects: 3 F and 5 NF) experienced PLMs during NPSG recordings indicating a higher than expected prevalence rate for the sample. However, no significant respiratory difficulties were found. In addition, 50 percent of the MS sample (8 subjects: 5 F and 3 NF) had alpha EEG sleep on NPSG recordings indicating a higher than expected prevalence rate for the sample. Although not part of the original hypothesis, periodic blood sampling is discussed as a possible sleep-disruptive variable.

PLM Findings

Similar to the present finding of a 50 percent prevalence rate, in another study, Potolicchio et al. (1991) found that 64 percent of eleven MS subjects

experienced PLMs during nocturnal sleep. These percentages of PLMs in MS are exceptionally high when considering that the prevalence of PLMs in normal adults has been estimated at five to six percent (Bixler et al., 1982), and 18 percent in sleep disorder clinic samples (Coleman et al., 1983). In addition, when compared to Ancoli-Israel et al.'s (1991) sample of 420 elderly persons (65 to 99 years), our MS sample with a mean age of 37.5 years still had a five percent higher prevalence rate for PLMs. As also seen in the aforementioned studies, PLMs were more prevalent in men; seven (87.5%) of the eight subjects in the MS PLM subsample were men.

Although the etiology of PLMs remains unknown, several motor system-based hypotheses have been presented. Behrman (1958) and Bornstein (1961) have hypothesized than PLMs are derived from a dysfunctional descending reticular activating system. Lugaresi et al. (1972) proposed that PLMs may result from the rhythmical fluctuations of reticular excitability in response to humoral interaction as seen in the periodic fluctuations of respiration and blood pressure. In a study of somatosensory and brainstem auditory evoked responses, Mosko and Nudlemen (1986) found a lack of measurable change in either modality. As was previously proposed by Behrman (1958) and Bornstein (1961), Mosko and Nudlemen concluded this to be supportive of a primary dysfunction in the descending motor system resulting in the disinhibition of the reticular activating system, and the consequential release of the episodic movements. Mosko and Nudlemen's conclusions are also consistent with Smith's (1985) hypothesis that PLMs, in their motoric resemblance to the

normally occurring Babinski response, are caused by a disinhibition of descending impulses on pyramidal tract function.

In a more recent study, Yokota et al. (1991) examined the relationship of PLMs and spinal cord lesions. The sample consisted of three persons with MS, three persons with cervical spondylosis, two persons with spinal cord injuries, and two persons with spinal vascular attacks. Since two subjects had transected spinal cords, and as MS related optic and spinal cord lesions subsided a decrease in PLMs was observed, they concluded that PLMs could be generated in the spinal cord. Due to EMG similarities between the flexor withdrawal reflex found in spinal automatism and PLMs, Yokota et al. concluded that the underling mechanisms may be similar, or that PLMs may also be a symptom of spinal automatism. However, in contrast to the reports of pyramidal tract involvement and motor weakness being typically seen in spinal automatism, the lack of motor weakness in their sample led Yokota et al. to concur with other findings (Eccles and Lundberg, 1959; & Lance and Mcleod, 1981) that spinal automatism derives from the disruption of the dorsal reticulospinal tract, running dorsolateral of the corticospinal tract.

From the present data, both the descending pyramidal tract or the dorsal reticulospinal tract are plausible etiologies of PLMs in MS. Several of our MS PLM subsample experienced lower limb weaknesses while others did not. It would appear that the addition of magnetic resonance imaging (MRI) studies in future research might help further delineate this discrepancy.

Secondary analyses revealed no significant differences in percentage of

stage one sleep, SWS, REM sleep, and sleep efficiency parameters on NPSG recordings between the PLM subsample and those who were not experiencing PLMs. However, in the PLM subsample, stage two sleep was significantly increased when compared to the non-PLM subsample. Coleman (1982) concluded that PLMs were most active during stage one and two sleep, less frequent during SWS, and almost absent during REM sleep. It is possible that this increase in stage two sleep in the PLM subsample may result from: 1) more subtle changes in SWS parameters than can be seen in the present data; 2) an underlying driving mechanism that serves to maintain stage two sleep, thereby discharging PLM motor activity; or 3) maintenance of stage two sleep by some PLM-related physiological "drive" or "pressure."

In contrast to most reports that PLMs are almost absent in REM sleep (Coleman et al., 1982; Saskin et al., 1985; Lugaresi et al., 1986; & Pollmacher and Schulz, 1993), four subjects (50% of the PLM subsample) experienced PLMs in REM as well as NREM sleep. Of the four persons with PLMs in REM sleep, two experienced REM naps on subsequent MSLTs. When compared to normative data (Williams et al., 1974), the first subject also showed an increase of REM percent and a decrease of REM latency on NPSG recordings, while the second subject showed a decrease of REM percent. In addition, several studies (van de Hoed et al., 1979; Coleman et al., 1980; & Mosko et al., 1984) have found a high incidence of PLMs in the narcoleptic population. Although highly speculative, failure to suppress PLMs in REM sleep, the lack of consistent PLM related arousals in REM sleep, the presence of REM sleep on

nap opportunities (3 subjects, 2 with PLMs), changes in NPSG REM sleep parameters, and the presence of PLMs in narcolepsy may suggest the presence of some underlying REM dysregulation and/or changes in REM arousal thresholds reminiscent of those seen in narcolepsy. Table 12 summarizes REM findings in all 3 subjects with REM naps.

In addition, the possibility of spinal cord involvement must be considered. Yokota et al. (1991) found two spinal cord patients out of the ten subjects studied to have PLMs in REM sleep. Since the spinal cord was transected in one subject, it suggests that these movements may have been of spinal origin and indicative of a dissociation from the atonia typical of REM sleep.

It is also interesting that in the present PLM subsample, five of the eight subjects were not complaining of fatigue or sleep disruption. In a study of PLMs in insomniacs and persons with excessive daytime sleepiness, Rosenthal et al. (1984) concluded that sleep complaints were associated with PLM arousals. However, the present sample showed an opposite tendency. A similar discordance was seen between sleep related complaints and PLMS in an elderly-based study (Coleman, et al., 1981). Possible explanations remain unclear, and perhaps may be characterologically-based or revealed by specifically designed arousal threshold analysis.

Respiratory Disturbances

Severe respiratory complications have been documented in persons with advanced MS (Howard et al., 1992). Therefore, NPSG respiratory monitoring

was conducted on all sixteen MS subjects. Although hypoxic events were seen in six subjects and sleep apnea was seen in five, all indices were within normal limits. However, most of our sample were young, employed, medication-free, and had less disabling disease. It is probable that more respiratory difficulties would be seen in MS subjects with more advanced disease.

Alpha EEG Sleep Findings and Relationship to PLMs

Alpha EEG sleep was found in 50 percent (8 subjects: 5 F subjects and 3 NF subjects) of the MS sample. In contrast to the PLM subsample, the alpha EEG subsample was comprised of seven women (87.5%) and one male. In addition, PLMs and alpha EEG sleep appeared to be almost mutually exclusive. Only one subject had PLMs and alpha EEG sleep on NPSG recording. However, the etiology of alpha EEG sleep remains unknown, and unlike PLMs, has not been studied as extensively. Although studies of alpha EEG sleep (Hauri and Hawkins, 1973; & Moldofsky and Lue, 1980) have noted changes in REM sleep parameters, secondary analyes revealed no reductions in REM sleep parameters between the alpha EEG subsample and the non-alpha EEG sleep subsample. As found in the present PLM subsample, no significant differences in the percentage of stage one sleep, SWS, REM sleep, and sleep efficiency were seen on NPSG recordings between the subjects in the alpha EEG sleep subsample and those that did not experience alpha EEG sleep. However, in contrast to the PLM subsample, the alpha EEG subsample showed a significant decrease in percentage of stage two sleep when compared to the non-alpha EEG subsample. Further secondary analyses demonstrated a

significant difference in the percentage of stage two sleep between the PLM subsample and the alpha EEG sleep subsample. Therefore, in addition to their nearly mutually exclusive presence on NPSG recording, alpha EEG sleep and PLMs appear to have opposing effects on stage two sleep suggestive of differential affects on some common underlying mechanisms.

Hauri and Hawkins (1973) found that a disturbed or immature brain metabolism was strongly suggested in some subjects with alpha EEG sleep and could not be ruled out in others. Consequently, they speculated that alpha EEG sleep may result from some common underlying CNS dysfunction and that the level of associated complaints was related more to the individual's coping style than the disease itself. In fact, although fatigue and general malaise typify alpha EEG sleep symptomatology, alpha EEG sleep was not found to be significantly more prevalent in the present MS F sample. It would appear that further studies of alpha EEG sleep should examine CNS mechanisms involved in the production of NREM sleep, and perhaps, more specifically, the possible underlying mechanisms that could work to suppress PLMs.

In addition, a review of the literature suggests that, as seen in this sample, alpha EEG sleep occurs predominantly in women. In Hauri and Hawkin's (1973) study of psychiatric patients, six (66.67%) of the nine subjects having alpha EEG sleep were women. Similarly, in Moldofsky and Lue's (1980) study of fibrositis, ten (66.67%) of the fifteen subjects having alpha EEG sleep were women. Finally, in Saskin et al.'s (1986) study of posttraumatic

rheumatic pain disorder, all eleven subjects (100%) were women.

Furthermore, only one person in the MS sample did not experience either PLMs or alpha EEG sleep. Although not descriptive of alpha EEG sleep or PLMs individually, it does describe the diversity of symptomatology seen in MS. Because plaque placement can vary greatly in each individual, some monitoring factor (i.e., MRI) would be helpful in delineating plaque formation patterns and predicting models of possible underlying pathophysiology of brain wave abnormalities and motoric sleep-disruptive phenomenon.

Blood Sampling

Although periodic blood sampling was attempted in this MS sample, few arousals (mean: 2.9) were found to be related to the blood drawings. This was in contrast with Adam's (1982) study of indwelling venous catheter blood sampling in which total sleep time, sleep efficiency, and REM sleep were significantly reduced, and wakefulness was significantly increased. In order to minimize sleep-disruption in the present MS sample, blood drawings were attempted while monitoring cortical EEG for any related changes, and were immediately abandoned if any preliminary changes were seen in cortical activity. Secondary analyses revealed no significant sleep architecture changes (i.e., sleep efficiency, number of arousals) between the blood sampling and non-blood sampling subsamples.

MS Sample versus Normative Data: Sleep Stage Percentages and Architectural Changes

Comparisons between the MS sample and age and sex-matched

normative data (Williams et al., 1974) support the third hypothesis that persons with MS manifest more variation in percentage of specific sleep stages (i.e., changes in percentage of stage 1, stage 2, stage 3, stage 4, and REM sleep) and changes in sleep architecture (i.e., sleep efficiency, total sleep time) than would be predicted by age and sex-appropriate norms for persons without neurological or psychiatric disorders. In the present study significant changes in percentage of REM sleep, sleep efficiency, and total sleep time were seen in the MS sample when compared to the normative data (Williams et al., 1974).

Percentage of REM Sleep

Significant changes in REM sleep parameters were seen in 32.5 percent of the MS sample. Four (25%) of the subjects had decreases in REM percent (2 F and 2 NF subjects), while two F subjects showed significant increases. As mentioned earlier in discussing PLMs and summarized in Table 12, three subjects (2 with PLMs and 1 without) had REM sleep on their fourth MSLT nap opportunity. As described in the introduction, several studies have sought to genetically link MS and narcolepsy (Ekbom, 1966; Piorier, et al., 1980; Schrader et al., 1980; Rumbach et al., 1989; & Younger et al., 1991). However, although associations have been implicated, none have been conclusive. Similarly, in the present study, the instability of nocturnal REM sleep percentage and the appearance of REM sleep on nap opportunities, suggest the presence of some narcolepsy related processes.

In Younger et al.'s (1991) case studies, both subjects had MS and narcolepsy and were positive for the HLA-DR2 antigen, suggesting a similar

genetic basis. In addition, in one subject the onset of narcolepsy preceded that of MS by approximately 13 years, while in the other subject MS preceded narcolepsy by approximately 32 years. This suggests that, although tendencies may be present earlier, both in narcolepsy and MS the manifestation of symptoms can occur much later in life or possibly not at all. Perhaps, in the present study, the subjects experiencing changes in REM sleep parameters have narcoleptic tendencies that may or may not be manifested later in life. Additional research manipulating REM sleep parameters, similar to that seen in Spielman et al.'s (1986) study in narcolepsy, and HLA typing prospective MS subjects may lead to more conclusive findings.

Decreases in the percentage of nocturnal REM sleep have been documented in the elderly population (Prinz, 1977; Williams et al.,1974; Hayashi and Endo, 1982; & Benca et al., 1992). Other studies have not reproduced this decline (Jovanovic, 1976; Gillin et al., 1981; & Spiegel, 1981). However, Bliwise and Bergman (1987), point out that, unless the studies are performed in a time isolation protocol, REM sleep percentage can be manipulated by allowing different sleep lengths (i.e., adjusting wake-up times) and by the laboratory environment. Therefore, two time isolation studies conducted in the elderly were reviewed. Both studies showed significant reductions in nocturnal REM sleep percentage, suggesting that REM need or ability to maintain REM sleep declines with age.

Several studies have shown nocturnal REM sleep percentage to increase in association with aging and depression (Vogel et al., 1980; Hayashi and Endo,

1982; & Beersma et al., 1984). In the present study, the two MS subjects that had increased REM sleep percentage, were both in the F group. As discussed earlier, MS fatigue was highly associated with psychological distress. It is possible that for these subjects, changes in REM sleep percentage is related to their emotional status at the time of the study. Since depressive symptoms and depressive episodes are common in MS (Joffe et al., 1987), additional research is needed to further examine the possible effects of MS related psychological distress on REM sleep parameters.

The pontine tegmentum nuclei have been associated with REM sleep generation (Siegel, 1990). In a recent study (Valldeoriola et al., 1993), a lesion in the pontine tegmentum was seen to obliterate REM and alter NREM sleep. Given that pontine lesions are common in MS (Baum et al., 1988), the possibility of MS lesions effecting REM sleep also needs to be considered. Additional studies using MRI, or other brain imaging technology, to group MS subjects may serve to clarify this possibility.

Sleep Efficiency

Significant declines in sleep efficiency were seen for 11 (69%) of the MS subjects: four (50%) F and seven (87.5%) NF subjects. Six subjects (2 F and 4 NF) experienced PLMs, but not all had significant amounts of PLM related arousals. Two subjects had PLM indexes less than 20 with PLM arousal indexes less than five. The remaining four subjects had PLM indexes greater than 20, but only two subjects had PLM arousal indexes greater than 10. This difference between PLM indexes and PLM arousal indexes shows that 20

percent of PLMs led to arousals and subsequent declines in sleep efficiency. Although adversely effecting sleep efficiency, the percentage also suggests the presence of some protective sleep mechanism serving to maintain sleep continuity. Further research into the etiology and motoric inhibition and disinhibition patterns of PLMs is needed to describe the mechanisms involved in PLMs and related arousals. Table 13 summarizes the PLM index and PLM arousal index results.

PLMs have also been documented in other conditions with related sleep changes: narcolepsy (van de Hoed et al., 1979; Coleman et al., 1980; & Mosko et al., 1984), CFS (Krupp et al., 1993), sleep apnea (Lugaresi et al., 1972; & Coleman et al., 1980), nocturnal epilepsy (Martinelli et al., 1981; & Coleman et al., 1980), delayed sleep phase syndrome (Coleman et al., 1980), and hypersomnolence (Zorick et al., 1978; Coleman et al., 1980). In addition, PLMs are frequently seen in the elderly population (Ancoli-Israel et al., 1991) suggesting that PLMs may also be a function of the breakdown of sleep normally associated with the aging process.

Declines in sleep efficiency were observed in five subjects (62.5%) with alpha EEG sleep: three F subjects without PLMs, one NF subject without PLMs, and one NF subject with PLMs. Although alpha EEG sleep has been associated with non-restorative sleep (Moldofsky and Lue, 1980), related arousals and declines in sleep efficiency have not been documented in other populations. However, the possibility of alpha EEG sleep having arousing or disruptive affects in the sleep of persons with MS cannot be excluded. Further research

is needed to examine the etiology of alpha EEG sleep in MS.

In the four subjects with declines in sleep efficiency, with alpha EEG sleep, and without PLMs, three had complaints of fatigue. In studies of CFS (Krupp et al., 1993), RA (Mahowald et al., 1989), fibromyalgia (Moldofsky, 1993), and fibrositis (Moldofsky, 1989), the presence of alpha EEG sleep has been associated with complaints of fatigue. Although the present study was unable to statistically support a relationship between alpha EEG sleep and fatigue, alpha EEG sleep cannot be excluded as a possible contributing factor in complaints of fatigue.

Sleep efficiency declines in MS may also be related to disturbances in the sleep-wake cycle. As discussed in the introduction, numerous studies on the chronic decerebrate cat (Bazett & Penfield, 1922; Head, 1923; Hobson, 1965; Villablanca, 1966; & Jouvet, 1967) have shown the brain stem's (especially the pons and the medulla) role in maintaining the sleep-wake cycle. Baum et al.'s (1988) study of MS lesion location in the brain stem showed 60.5 percent of the 43 subjects studied exhibited pathologically high signal intensities in the brain stem region. Specifically, 27.9 percent showed lesions in the rostral pons, 14 percent in the caudal pons, 9.3 percent in the mesencephalon, and 9.3 percent in the medulla oblongata. Therefore, 51.2 percent of the MS subjects showed lesions in the pons and/or medulla which could disrupt the sleep-wake cycle and sleep continuity. Additional research employing MRI or other brain imaging techniques is needed to further explore the relationship between MS brainstem lesions and the sleep-wake cycle.

A similar increase in number of awakenings and decrease in sleep efficiency has also been found in elderly samples (Williams et al., 1974; & Webb, 1982). However, the etiology and possible role of brain stem structures has not been described. It would be interesting to compare the causes of arousals in the elderly and the atrophic process related to the aging brain with MS related arousals and the more accelerated brain matter deterioration related to MS lesion formation.

Total Sleep Time

Total sleep time was significantly above expectations in one NF subject and below expectations in 32.5 percent of the MS sample (three F and three NF subjects). However, since total recording time was determined by the average total sleep time reported on two-week sleep logs, total sleep time on the NPSG recording did not reflect free-running sleep. It is possible that the subjects could have underestimated their sleep needs or that the NPSG recording night was not an "average" night. Therefore, these findings are based on subjective reports, and comparisons to normative data are questionable.

Final Conclusions

The present study shows that reported fatigue in persons with MS is best described as a combination of sleepiness and psychological distress. On objective measures of sleepiness and sleep parameters, few significant differences were found between the F and NF groups. This suggests that either the effects were more subtle than the study design was able to detect or that complaints of fatigue have significant emotional and characterological components that also need to be addressed.

The preceding results also indicate that PLMs and alpha EEG sleep are prevalent in the sleep of persons with MS. In addition it appears that PLMs and alpha EEG sleep are almost mutually exclusive, differentially effect stage two sleep, and are gender related with the prevalence of PLMs being greater in male subjects and alpha EEG sleep being seen more often in female subjects. Further research employing MRI, or other brain imaging technology, could be useful in describing the possible neuropathology of each as seen by patterns of MS lesion formations.

When compared to normative data, significant changes were seen in REM sleep parameters. Three subjects experienced REM sleep on MSLT nap opportunities. In addition, comparisons to normative data showed increases in REM sleep percentages in four subjects and decreases in two. These changes in REM sleep parameters may suggest the presence of narcolepsy related processes, and HLA typing of MS subjects as well as REM manipulation is suggested in future studies. The decrease in REM sleep percentage in two F

subjects also raises the question of the effects of MS related psychological distress on REM sleep.

Declines in sleep efficiency were also seen in the MS sample. Although a percentage of these declines can be attributed to PLM related arousals, and perhaps the presence of alpha EEG sleep, other physiologically based possibilities need to be examined. The propensity for MS lesion formation in different areas of the pons and medulla suggests the possibility of disturbances in the sleep-wake cycle. MRI, or other brain imaging techniques, in conjunction with further sleep studies are needed to clarify this possibility.

MS is a generally progressive neurological disease that shows sleep disruptions similar to those seen in other disorders (i.e., narcolepsy, CFS, RA, fibrositis). It also shows an accelerated (by lesion formation) similarity to the progressive breakdown or reduced need for sleep seen in the aging process. Therefore, in studying the sleep of persons with MS, examining its relationship to other related disorders (i.e., narcolepsy) and the aging process is important. In addition, manipulations of sleep parameters (i.e., REM) and grouping subjects by lesion location and HLA typing would be instrumental in further understanding mechanisms of the sleep process and the nature of sleep in MS. Additional research in MS sleep is needed.

Table 12

REM Sleep Parameters on NPSG Recordings Compared to Normative Data* for 3 MS Subjects with REM Naps on MSLT

	NPSG Findings			MSLT Findings	
Subject #	REM Latency	REM Percent	PLMs in REM	REM Nap #	REM Latency
2	40.5 min. (below norms)	28.98 (above norms)	yes	4	13 min.
12	51.5 min. (w.n.l.)	17.6 (below norms)	yes	4	11 min.
13	40.5 min. (below norms)	27.15 (w.n.l.)	no	4	12 min.

* Williams et al., 1974

Table 13

Comparisons of Presence of Alpha EEG Sleep, PLM Index, and PLM Arousal Index for Fatigued (F) and Non-Fatigued (NF) Subjects

Subject #	F or NF	Alpha EEG Sleep	PLM Index	PLM Arousal Index
1	NF	yes	8.2	3.0
2	NF	no	52.4	4.9
3	F	yes	n/a	n/a
4	NF	no	27.5	8.7
5	NF	no	65.6	7.6
6	F	yes	n/a	n/a
7	NF	yes	n/a	n/a
8	F	no	64.7	11.7
9	F	no	17.6	0
10	F	yes	n/a	n/a
11	F	yes	n/a	n/a
12	NF	no	60.5	24.2
13	F	yes	n/a	n/a
14	F	no	10.5	1.8
15	NF	no	n/a	n/a
16	NF	yes	n/a	n/a

Appendix 1

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY

JACK D.WEILER HOSPITAL
OF THE ALBERT EINSTEIN COLLEGE OF MEDICINE
A DIVISION OF MONTEFIORE MEDICAL CENTER

BRONX MUNICIPAL HOSPITAL CENTER
OF THE CITY OF NEW YORK

Individual's Consent for Participation as a
Subject in Clinical Research

By signing this form, I have agreed to participate as a subject in a medical research study entitled: Sleep Disruption in Multiple Sclerosis: Implications for Immune Dysregulation and Fatigue to be carried out under the supervision of Nicholas G. LaRocca, Ph.D., 1300 Morris Park Ave., Bronx, N.Y. 10461, (212) 824-6156.
(Official Address and Telephone Number)

Records of this study will be kept confidential, and I will not be identified in any written or verbal reports with the following possible exceptions. If this research involves an experimental drug or device, the U.S. Food and Drug Administration or the company that sponsors the research may inspect my records. These agencies have been requested to maintain confidentiality. My records may also be inspected by the Committee on Clinical Investigations at AECOM, WHAECOM and BMHC, and by The City College of New York, where one of the researchers is on faculty, and by the National Multiple Sclerosis Society, the agency which is funding this research.

(collaborating groups or agencies)

I understand that if I am physically injured as a result of this research, only immediate, essential, short-term medical treatment will be made available without charge to me personally. Monetary compensation for injury is not offered by any of the sponsoring institutions, organizations or companies.

If this study is carried out at the Jack Weiler Hospital of the Albert Einstein College of Medicine, I have been told that I may seek further advise from the Patient Relations Office, Room 2060, (telephone number 904-2395), Monday through Friday from 9 A.M. to 5 P.M.

In the event of a research-related injury or if any questions arise related to this project, I can call the supervisor of this study or Dr. Charles Smith at (212) 430-2682. I

have been given a copy of this form whether or not I have agreed to participate in this study. I have asked all the questions I want to ask, after reading and listening to an explanation of the five paragraphs on the next page which describe:

1. The Purpose of the research.
2. The Procedures involved and duration of my participation.
3. The Risks that I will be taking, if any.
4. The Benefits that may result, to me or to others.
5. Alternative procedures or treatment.

1. The Purpose of This Research: Fatigue is one of the major problems faced by people with MS. It is an overwhelming feeling of tiredness that may hinder everyday activities. In addition, difficulty sleeping is often reported by persons with MS. To date, no studies have investigated the possible relationship between sleep changes and reported fatigue. This study will examine the patterns, behaviors, and disruptions that may occur during sleep. Comparisons between reports of fatigue to those of sleepiness will also be made. Since immunological changes have been well documented in both MS and in sleep, blood samples will be drawn during the night.

2. The Study Procedures and Length of Time I will Participate: In order to determine if there are any sleep-related differences between persons with complaints of fatigue and those without, this study will involve both persons with fatigue and those for whom fatigue is not a problem. Once I have entered the study, my participation will last a total of 16 days. I will make one visit to the MS care center for screening purposes and, after 2 weeks have past and I have completed my sleep logs, I will make 2 visits to the sleep laboratory involving 2 nights and one day. On the first day, I will arrive at the center at about 9 A.M. and leave at approximately 1 P.M. The first night at the sleep laboratory, I will arrive 2 hours before my average bedtime, and leave shortly after getting out of bed in the morning. The second night, I will arrive at the sleep laboratory at the same time as the first night but upon awakening in the morning I will remain at the laboratory until approximately 5 P.M. that same day.

Day at MS Care Center - *Screening:* On the first day I will answer a number of questions concerning my health and general information about myself relating to fatigue, work, family, and past health and illnesses. The doctor will give me a brief physical examination and draw about 2 tablespoons of blood from a vein in my arm for routine blood tests. A neuropsychologist will give me several short tests of memory, attention, concentration and reasoning which should not require more than 45 minutes. A psychologist will then ask me questions concerning my thoughts and emotions which should require approximately 2 hours. I understand that if I have recently (within approximately the last 6 months) undergone the blood tests, neuropsychological tests and the psychological interview for another study at the center, I will not be required to take them again. Before leaving the center, 2 weeks worth of sleep logs (2 pages) will be fully explained and given to me. The sleep logs require that each morning, when I wake up, I answer a number of questions concerning my sleep the night before and as well as my activities the previous day. I understand that these logs have to be completed before I can continue in the study. I understand that the 2 week long sleep logs constitute 14 days of the study, after which I will spend the 15th and 16th days of the

study in the sleep lab.

First Night at Sleep Laboratory - *Adaptation to sleep laboratory:* The first night at the sleep laboratory will be on a Sunday night and will only involve my "getting used to" the new surroundings. I understand that a few non-invasive skin electrodes, that will not penetrate my skin, will be placed, by a psychologist /sleep technician, on my face, scalp and arm so that I can get used to how they feel. I will not drink any caffeinated beverages for at least 6 hrs prior to going to bed. I will then go to bed at my regular bedtime with the bedroom's microphone turned on so that I can speak to the psychologist, who will be present throughout the night. If I need to get up at any time during the night, I will call to the psychologist, who will help me up. In the morning the psychologist/sleep technician will remove the electrodes. At this time I am free to go until later that night when I will return to the sleep laboratory.

Second Night at Sleep Laboratory - *Polysomnographic recording night:* The second night at the sleep laboratory will be on a Monday night. Although very similar to the first night, it will be slightly different in that electrodes will be placed on my scalp, face, leg, chest and around my nose, and they will be connected (via a "plug") to a large recording machine outside my bedroom. Two belts will be placed around my chest and stomach, and a finger piece will be put on one index finger. In addition, a physician will place an indwelling catheter in a vein of the arm I tend to use less (e.g., if I am right-handed, it will be my left arm) so that blood samples can be drawn every 20 minutes for the first four hours of the night. I understand that a total of approximately one cup of blood will be taken by the time I get up in the morning. I will not drink any caffeinated beverages for at least 6 hrs prior to going to bed. The psychologist and a sleep technician will be with me throughout the night. In the morning the psychologist will awaken me at my scheduled wake up time and I will start my day at the sleep lab.

Day at Sleep Laboratory - *Multiple Sleep Latency Testing:* The Multiple Sleep Latency Test is a standard test that is used in sleep laboratories to assess levels of sleepiness. In this study I will undergo a modified version consisting of 5, 20 minute nap opportunities for which the electrodes around my nose, the belts around my body, and the finger piece will be removed. The first nap will be 2 hours after my scheduled wake up time. The second nap will be 2 hours after the first; the third nap will be 2 hours after the second; the fourth nap will be 2 hours after the third; and the fifth will be 2 hours after the fourth. I will be given 2 brief questionnaires concerning my sensations of sleepiness, if any, before and after each of my nap opportunities. After answering the questionnaires at the end of nap 5, all the electrodes will be removed and I can go home. Breakfast will be provided before Nap 1, and lunch will be provided after Nap 2 or 3 depending on my preference. No caffeinated beverages will be allowed throughout the day. If I have any specific dietary requirements, I will inform the psychologist at the beginning of the study.

The Cost of the Procedures - I understand that there will be no cost to me for any of the procedures connected with this study.

3. The Risks that I Will be Taking: I understand that there are no significant physical risks involved in the study. However, I also understand that there is a small risk of a

slight bruise forming whenever blood is taken for prolonged periods of time, but that this is not serious and will go away within a few days. Due to the length of time that I will be spending in the sleep laboratory, I realize that at times I may be bored. Since the evaluations will be undertaken within a hospital facility where space is at a premium, I realize that the rooms are small and that I may feel a "closed-in" feeling at times. I also understand that although non-invasive electrodes will be used, I may experience minor skin irritations from electrode placement.

4. The Benefits of the Study: There will be few direct benefits to me as a result of the study. I will receive psychological, neuropsychological, neurological, immunological, and polysomnographic (sleep recording) evaluations at no cost to me. These tests could provide information that my doctor could use in my medical care, especially for fatigue. I will indirectly benefit by contributing to a better understanding of the experience of fatigue commonly reported in MS, the underlying immunological processes inherent in MS, and the nature of sleep and its function in specific disease states. There is also a small chance that these studies could help identify treatable sleep problems.

5. Alternative Procedures: This study includes most of the methods currently used to assess "sleepiness", examines changes that commonly occur in the immune system during sleep, and provides testing before and after nap opportunities. However, I may choose not to participate.

I have been told by the doctor or other persons performing this research that I may be a subject only if I wish, and that I may withdraw from the study at any time. I have also been assured that my treatment by doctors and staff at the Albert Einstein College of Medicine (AECOM), The Jack D. Weiler Hospital of the Albert Einstein College of Medicine (WHAECOM), and the Bronx Municipal Hospital Center (BMHC), now and in the future, will not be affected in any way if I refuse to participate or if I enter the program and withdraw later.

_____ _____

Signature of Patient Date

_____ _____

Signature of Physician Date

Appendix 2

SLEEP IN MULTIPLE SCLEROSIS
Patient Protocol

Sleep Lab scheduling for patients:

Patient's name: _____

Address: _____

_____

Date of birth: _____ Sex: _____

Telephone: (H) _____ (W) _____

Fatigue status: Fatigued Non-fatigued

Date of last clinc visit: _____

Major complaints: _____

_____

EDSS score: _____

MS course: _____

Date of telephone interview _____

Current medications _____

_____

Approximate current sleep schedule _____

_____

Naps? _____

Date of run at sleep lab _____

Date two-week sleep logs need to be sent out _____

Special dietary requirements _____

_____

Other relevant information _____

_____

Appendix 3

PROGRESS NOTE

NAME:_____ ID #: _ _ _ _ _ _ _ (1-8)

CARD #: _ _ (7-8) REC: _ _ (9-10) DATE: _ _/ _ _/ _ _ (11-16) RATER: _ _ _ (17-19)

EDSS: _ _ _ _ _ (20-23)

FUNCTIONAL SYSTEMS:	SCORE	EXTRA DIGIT	
1. PYRAMIDAL:	_	_	(24-25)
2. CEREBELLAR:	_	_	(26-27)
3. BRAINSTEM:	_	_	(28-29)
4. SENSORY:	_	_	(30-31)
5. BOWEL & BLADDER:	_	_	(32-33)
6. VISUAL:	_	_	(34-35)
7. MENTAL:	_	_	(36-37)
8. SPASTICITY:	_	_	(38-39)

INCAPACITY STATUS:		
1. STAIR CLIMBING:	_	(42)
2. AMBULATION:	_	(43)
3. TRANSFERS:	_	(44)
4. BOWEL FUNCTION:	_	(45)
5. BLADDER FUNCTION:	_	(46)
6. BATHING:	_	(47)
7. DRESSING:	_	(48)
8. GROOMING:	_	(49)
9. FEEDING:	_	(50)
10. VISION:	_	(51)
11. SPEECH AND HEARING:	_	(52)
12. MEDICAL PROBLEMS:	_	(53)
13. MOOD AND THOUGHT:	_	(54)
14. MENTATION:	_	(55)
15. FATIGUE:	_	(56)
16. SEXUAL FUNCTION:	_	(57)

ENVIRONMENTAL STATUS:		
1. WORK:	_	(61)
2. FINANCIAL:	_	(62)
3. HOME:	_	(63)
4. PERSONAL ASSISTANCE:	_	(64)
5. TRANSPORTATION:	_	(65)
6. COMMUNITY ASSISTANCE:	_	(66)
7. SOCIAL ACTIVITY:	_	(67)

CURRENT MANAGEMENT: CHANGES:

COMMENTS:

SIGNATURE: _____

Appendix 4

WEEKLY SLEEP LOG

NAME : _____

Directions: Each morning when you awake answer questions 1-10 concerning your sleep last night & questions 11-17 describing how you felt yesterday

	DAY						
	DATE						
1) Were you in bed before going to sleep (eg. watching TV, reading) ? ------ ---------- If YES, the time you got into bed							
2) The time you turned the lights out or ---------- began trying to fall asleep							
3) How long it took you to fall asleep ----------							
4) The time you finally got out of bed ---------- in the morning							
5) Your estimate of the total amount of ---------- time you were asleep							
6) The number of times you woke-up ----------	#						
a) Because you had to go to the bathroom ------	a)						
b) Because of spasms ----------	b)						
c) Because of other reasons ----------	c)						
7) The time you last woke-up and didn't ---------- go back to sleep							
8) The total time you were physically out of bed and awake during the night ----------							
9) List the type and dosage of medicines taken in last 24 hrs. ----------							
10) Rate how difficult it was waking-up and getting yourself going this morning 1-------2-------3-------4-------5-------6-------7 not difficult very difficult							
11) Number of naps or number of brief ---------- episodes of dozing during the day							
12) Total amount of sleep while ---------- napping or dozing							
13) Total number of cups of coffee plus number of cans of caffeinated beverages --------							
14) Total number of ounces of liquor plus ------- glasses of wine plus glasses of beer							
15) Amount of exercise ---------- Time of day was: Morn / Midday / Eve							
16) Rate your overall ALERTNESS 1-------2-------3-------4-------5-------6-------7 least alert most alert							
17) Rate your overall FATIGUE 1-------2-------3-------4-------5-------6-------7 least fatigued most fatigued							

Appendix 5

ABK 7/26/83 4.

II. CES-D

INSTRUCTIONS - I will be reading a number of statements about ways you might have felt or behaved. Please tell me how often you have felt this way, DURING THE PAST WEEK. Feel free not to answer any of the questions if you so wish, without any consequences or penalty. All of your responses will be kept strictly confidential. (HAND CARD TO RESPONDENT)

CODE:
0. Rarely or None of the Time (Less than 1 Day)
1. Some or a Little of the Time (1-2 Days)
2. Occasionally or a Moderate Amount of Time (3-4 Days)
3. Most or All of the Time (5-7 Days)
9. No answer

During the past week:	Score	Columns
1. I was bothered by things that usually don't bother me.....	____	/31
2. I did not feel like eating; my appetite was poor.....	____	/32
3. I felt that I could not shake off the blues even with help from my family or friends.....	____	/33
4. I felt that I was just as good as other people.....	____*	/34
5. I had trouble keeping my mind on what I was doing.....	____	/35
6. I felt depressed.....	____	/36
7. I felt that everything I did was an effort.....	____	/37
8. I felt hopeful about the future.....	____*	/38
9. I thought my life had been a failure.....	____	/39
10. I felt fearful.....	____	/40
11. My sleep was restless.....	____	/41
12. I was happy.....	____*	/42
13. I talked less than usual.....	____	/43
14. I felt lonely.....	____	/44
15. People were unfriendly.....	____	/45
16. I enjoyed life.....	____*	/46
17. I had crying spells.....	____	/47
18. I felt sad.....	____	/48
19. I felt that people dislike me.....	____	/49
20. I could not get "going".....	____	/50

*Scoring to be reversed.

Appendix 6

INSTRUCTIONS

Below are a series of statements regarding your Fatigue. By Fatigue, we mean a sense of tiredness, lack of energy or total body give-out. Please read each statements and choose a number from 1 to 7, where #1 indicates you completely disagree with the statement and #7 indicates you completely agree.

****

Circle the appropriate number on the answer sheet!

Questions:

	Completely Disagree						Completely Agree
1. I feel drowsy when I am fatigued.	1	2	3	4	5	6	7
2. When I am fatigued, I lose my patience.	1	2	3	4	5	6	7
3. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
4. When I am fatigued, I have difficulty concentrating.	1	2	3	4	5	6	7
5. Exercise brings on my fatigue.	1	2	3	4	5	6	7
6. Heat brings on my fatigue.	1	2	3	4	5	6	7
7. Long periods of inactivity brings on my fatigue.	1	2	3	4	5	6	7
8. Stress brings on my fatigue.	1	2	3	4	5	6	7
9. Depression brings on my fatigue.	1	2	3	4	5	6	7
10. Work brings on fatigue.	1	2	3	4	5	6	7
11. My fatigue is worse in the afternoon.	1	2	3	4	5	6	7
12. My fatigue is worse in the morning.	1	2	3	4	5	6	7
13. My fatigue is better during or after sex.	1	2	3	4	5	6	7
14. Resting improves my fatigue.	1	2	3	4	5	6	7

	Completely Disagree						Completely Agree
15. Sleeping improves my fatigue.	1	2	3	4	5	6	7
16. Cool temperatures improve my fatigue.	1	2	3	4	5	6	7
17. Positive experiences improve my fatigue.	1	2	3	4	5	6	7
18. I am easily fatigued.	1	2	3	4	5	6	7
19. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
20. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
21. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
22. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
23. Fatigue predated other symptoms of MS.	1	2	3	4	5	6	7
24. Fatigue is my most disabling symptom.	1	2	3	4	5	6	7
25. Fatigue is among my 3 most disabling symptoms.	1	2	3	4	5	6	7
26. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7
27. Fatigue makes other MS symptoms worse.	1	2	3	4	5	6	7
28. Fatigue that I now experience is different in quality or severity than the fatigue I experienced before I developed MS.	1	2	3	4	5	6	7

Appendix 7

MS Sleep Study
POLYGRAPH MONTAGE
Nocturnal Polysomnographic Study (NPSG)

Subject # _____

Polygraph _____

Room # _____

Date _____

Note any changes to montage on this sheet!

channel	derivatn	LOW	HIGH	sensitivity	pin#s
1	C4/A1,A2 central EEG alt: C3	0.3	60	7.5 uV/mm	1/A1,A2
2	O2/A!,A2 occipital EEG	0.3	60	7.5 uV/mm	3/A1,A2
3	C4/O2	0.3	60	7.5uV/mm	1/3
4	ROC/A1,A2	0.3	60	7.5 uV/mm	5A1,A2
5	LOC/A1,A2	0.3	60	7.5 uV/mm	6/A1,A2
6	chin EMG	10	90	1.0 uV/mm	7/8/9
7	RAT/LAT	10	90	1.0 uV/mm	10/11 alt: 12/13
8	RNA/LNA	0.1	30	5.0 mV/cm (adjust)	19/20
9	OA	0.1	30	5.0 mV/cm	19/21
10	EKG	0.1	90	50 uV/mm(adjust)	
11	DC respiratory effort (bellows): adjust sensitivity & balance voltage				
12	DC oximeter (no adjustments to polygraph)				

Appendix 8

MS Sleep Study
POLYGRAPH MONTAGE
MULTIPLE SLEEP LATENCY TEST (MSLT)

Subject # _____

Polygraph _____

Room # _____

Date _____

Note any changes to montage on this sheet!

channel	derivatn	LOW	HIGH	sensitivity	pin#s
1	C4/A1,A2 central EEG alt: C3	0.3	60	7.5 uV/mm	1A1,A2
2	O2/A!,A2 occipitai EEG	0.3	60	7.5 uV/mm	3/A1,A2
3	C4/O2	0.3	60	7.5uV/mm	1/3
4	ROC/A1,A2	0.3	60	7.5 uV/mm	5/A1,A2
5	LOC/A1,A2	0.3	60	7.5 uV/mm	6/A1,A2
6	LOC/ROC	3.0	60	7.5 uV/mm	5/6
7	chin EMG	10	90	1.0 uV/mm	7/8/9
8	EKG (adjust)	0.1	90	50 uV/mm	

Appendix 9

SLEEP STUDY MSLT PROTOCOL

Each nap will be 2 hours apart with the first nap starting exactly 2 hours after the person's arise time that morning. The standard 20 minute MSLT protocol is to be used with EXACTLY 15 minutes of accrued sleep being allowed per nap. It is important that these parameters be as precise as possible because this is RESEARCH and slight changes increase the number of variable that need to be considered!!!!

Please ask the person to fill out both sides of the 1 page questionnaire (SSS and Visual Analog Scales) before and after each nap for a grand total of 10 times!!

Name: _____

Nap Number:	Lights Out Time:
1	_____
2	_____
3	_____
4	_____
5	_____

Appendix 10

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY

Medical Rehabilitation Research & Training Center for Multiple Sclerosis

Stanford Sleepiness Scale (SSS)

Name: _____

Day & Date: _____

Time right now: _____:_____ AM PM (circle one)

Please answer this question by circling one answer:

This is the 1st 2nd 3rd 4th 5th 6th 7th 8th 9th 10th time today that I have answered this questionnaire.

Please choose the number of the statement which best describes how you feel right now.

1. Alert. Wide awake. Energetic.
2. Functioning at a high level, but not at peak. Able to concentrate.
3. Awake, but not fully alert.
4. A little foggy, let down.
5. Foggy. Beginning to loose interest in remaining awake. Slowed down.
6. Sleepy. Prefer to be lying down. Woozy.
7. Cannot stay awake. Sleep onset soon.

(over, please)

Appendix 11

Mood Scales

Please put a vertical mark, bisecting each line below, at the place which best describes how you feel right now.

How alert do you feel?

very little _____ very much

How sad do you feel?

very little _____ very much

How tense do you feel?

very little _____ very much

How much of an effort is it to do anything?

very little _____ very much

How happy do you feel?

very little _____ very much

How weary do you feel?

very little _____ very much

How calm do you feel?

very little _____ very much

How sleepy do you feel?

very little _____ very much

Overall, how do you feel?

very little _____ very much

References

Adam, K. (1982). Sleep is changed by blood sampling through an indwelling venous catheter. *Sleep*, **5**, 154-158.

Ahles, T. A., Yunus, M. B., Riley, S. A., Bradley, J. M. & Masi, A. T. (1984). Psychological factors associated with primary fibromyalgia syndrome. *Arthritis and Rheumatism*, **27**, 1101-1106.

Akerstedt, T. & Gillberg, M. (1981). The circadian variation of experimentally displaced sleep. *Sleep*, **4**, 159-169.

Akerstedt, T., Torsvall, L. & Gillberg, M. (1982). Sleepiness and shift work: Field studies. *Sleep*, **5**, S95-S106.

Alter, M., Zhen-xin, Z., Davanipour, Z., Sobel, E., Zibulewski, J., Schwartz, G. & Friday, G. (1986). Multiple sclerosis and childhood infections. *Neurology*, **36**, 1386-1389.

Ancoli-Israel, S. (1989). Epidemiology of sleep disorders. In T. Roth (Ed.), *Clinics in Geriatric Medicine* (pp. 347-362). Philadelphia: W.B. Saunders Company.

Ancoli-Israel, S., Kripke, D., Mason, W. & Messin, S. (1981). Sleep apnea and nocturnal myoclonus in a senior population. *Sleep*, **4**, 349-358.

Ancoli-Israel, S., Kripke, D. F., Klauber, M. R., Mason, W. J., Fell, R. & Kaplan, O. (1991). Sleep-disordered breathing in community-dwelling elderly. *Sleep*, **14**, 486-495.

Ancoli-Israel, S., Kripke, D. F., Klauber, M. R., Mason, W. J., Fell, R. & Kaplan, O. (1991). Periodic limb movements in sleep in community-dwelling elderly. *Sleep*, **14**, 496-500.

Anderson, D. W., Ellenberg, J. H., Leventhal, C. M., Reingold, S. C., Rodriguez, M. & Silberberg, D. H. (1992). Revised estimate of the prevalence of multiple sclerosis in the United States. *Annals of Neurology*, **31**, 333-336.

Association of Sleep Disorders Centers (1979). Diagnostic classification of sleep and arousal disorders. *Sleep*, **2**, 1-137.

Bajada, S., Mastagria, F., Black, J. & Collins, D. (1980). Effects of induced hyperthermia on visual evoked potentials and saccade parameters in normal subjects and multiple sclerosis patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **43**, 849-852.

Bauer, J. J. & Firnhaber, W. (1965). Prognostic criteria in multiple sclerosis. *Annals of the New York Academy of Sciences*, **122**, 542-551.

Baum, H. M. & Rothschild, B. B. (1981). The incidence and prevalence of reported multiple sclerosis. *Annals of Neurology*, **5**, 420-428.

Bazett, H. C. & Penfield, W. G. (1922). A study of Sherrington decerebrate animal in the chronic as well as the acute condition. *Brain*, **45**, 185-265.

Beersma, D. G. M., Daan, S. & Van den Hoofdakker, R. H. (1987). Distribution of REM latencies and other sleep phenomena in depression as explained by a single ultradian rhythm disturbance. *Sleep*, **7**, 126-136.

Behrman, S. (1958). Disturbed relaxation of limbs. *British Medical Journal*, **1**, 1454-1457.

Benca, R. M., Obermeyer, W. H., Thisted, R. A. & Gillin, J. C. (1992). Sleep and psychiatric disorders: A meta-analysis. *Archives of General Psychiatry*, **49**, 651-668.

Berger, R. J. (1975). Bioenergetic functions of sleep and activity rhythms and their possible relevance to aging. *Federal Proceedings*, **34**, 97-102.

Berger, R. J. (1984). Slow wave sleep, shallow torpor and hibernation: Homologous states of diminished metabolism and body temperature. *Biological Psychiatry*, **19**, 305-326.

Berger, R. J. & Phillips, N. H. (1988). Comparative aspects of energy metabolism, body temperature and sleep. *Acta Physiologica Scandinavica*, **133 (suppl 574)**, 21-27.

Bixler, E. O., Kales, A., Soldatos, C. R., Kales, J. D. & Healy, S. (1979). Prevalence of sleep disorders in the Los Angeles metropolitan area. *American Journal of Psychiatry*, **136**, 1257-1262.

Bixler, E. O., Kales, A., Vela-Bueno, A., Jacoby, J. A., Scarone, S. & Soldatos, C. R. (1982). Nocturnal myoclonus and nocturnal myoclonic activity in a normal population. *Research Communications in Chemical Pathology and Pharmacology*, **36**, 129-140.

Blake, M. J. F. (1967). Time of day effects on performance in a range of tasks. *Psychonologic Science*, **9**, 349-350.

Blessed, G., Tomlinson, B. E. & Roth, M. (1968). The association between quantitative measures of dementia and of senile changes in the cerebral grey matter of elderly subjects. *British Journal of Psychiatry*, **114**, 797-811.

Bliwise, D. L. & Bergmann, B. M. (1987). Individual differences in stages 3 and 4 sleep. *Psychophysiology*, **34**, 35-40.

Bobowick, A. R., Kurtzke, J. F., Brody, J. A., Hrubec, Z. & Gillespie, M. (1978). Twin study of multiple sclersis: An epidemiologic inquiry. *Neurology*, **28**, 978-987.

Bonnet, M. H. (1985). The effect of sleep disruption on performance, sleep and mood. *Sleep*, **8**, 11-19.

Bonnet, M. H. (1986). Performance and sleepiness as a function of the frequency and placement of sleep disruption. *Psychophysiology*, **23**, 263-271.

Bornstein, B. (1961). Restless legs. *Psychiatric Neurology*, **141**, 165-201.

Bremer, F. (1970). Preoptic hypnogenic focus and mesencephalic reticular formation. *Brain Research*, **21**, 132-134.

Broughton, R. (1972). Sleep and Clinical Pathological States. In M.H. Chase (Ed.), *The Sleeping Brain* (pp. 363-431). Los Angeles: Brain Information Service - Brain Research Institute.

Broughton, R., Ghanem, Q., Hishikawa, Y., Sugita, Y., Nevsimalova S., & Roth, B. (1981). Life effects of narcolepsy in 180 patients from North America, Asia and Europe compared to matched controls. *Canadian Journal of Neurological Sciences*, **8(4)**, 299-304.

Brownell, B. & Hughes, J. T. (1962). The distribution of plaques in the cerebrum in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **25**, 315-320.

Buschke, H. & Fuld, P. A. (1974). Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology*, **11**, 1019-1025.

Campbell, S. M., Clark, S., Tindall, E. A., Forehand, M. E. & Bennett, R. M. (1983). Clinical characteristics of fibrositis. I. A "blinded" control study of symptoms and tender points. *Arthritis and Rheumatism*, **26**, 817-824.

Carskadon, M. A. (1985). Sleep tendency on a constant routine. *Sleep Research*, **14**, 292.

Carskadon, M. A., Brown, E. & Dement, W. C. (1982). Sleep fragmentation in the elderly: Relationship to daytime sleep tendency. *Neurobiology of Aging*, **3**, 321-327.

Carskadon, M. A. & Dement, W. C. (1977). Sleep tendency: An objective measure of sleep loss. *Sleep Research*, **6**, 200-200.

Carskadon, M. A. & Dement, W. C. (1979). Sleepiness during extension of nocturnal sleep. *Sleep Research*, **8**, 147.

Carskadon, M. A. & Dement, W. C. (1981). Respiration during sleep in the aged human. *Journal of Gerontology*, **36**, 420-425.

Carskadon, M. A. & Dement, W. C. (1981). Cumulative effects of sleep restriction on daytime sleepiness. *Psychophysiology*, **18**, 107-113.

Carskadon, M. A. & Dement, W. C. (1982). Nocturnal determinants of daytime sleepiness. *Sleep*, **5(S)**, 73-81.

Carskadon, M. A. & Dement, W. C. (1982). Nocturnal determinants of daytime sleepiness. *Sleep*, **5**, S73-S81.

Carskadon, M. A. & Dement, W. C. (1982). The multiple sleep latency test: what does it measure?. *Sleep*, **2**, S67-S72.

Carskadon, M. A. & Dement, W. C. (1987). Daytime sleepiness: Quantification of a behavioral state. *Neuroscience and Biobehavioral Review*, **11**, 307-317.

Carskadon, M. A., Dement, W. C., Mitler, M. M., Roth, T., Westbrook, P. R. & Keenan, S. (1986). Guidelines for the multiple sleep latency test (MSLT): A standard measure of sleepinesss. *Sleep*, **9**, 519-524.

Carskadon, M. A., Seidel, W. F., Greenblatt, D. J. & Dement, W. C. (1982). Daytime carry-over effects of triazolam and flurazepam in elderly insomniacs. *Sleep*, **5**, 361-371.

Carskadon, M. C. & Dement, W. C. (1979). Sleep tendency during extension of nocturnal sleep. *Sleep Research*, **8**, 147.

Caruso, L. S., LaRocca, N. G., Tryon, W., Robbins, K., Foley, F. W. & Smith, C. R. (1991). Activity monitoring of fatigued and non-fatigues persons with multiple sclerosis. *Sleep Research*, **20**, 368-368.

Chiarello, R. J. & Cole, J. O. (1987). The use of psychostimulants in general psychiatry. *Archives of General Psychiatry*, **44**, 286-295.

Clark, C. M., Fleming, J. A., Li, D., Oger, J., Klonoff, H. & Paty, D. (1992). Sleep disturbance, depression, and lesion site in patients with multiple sclerosis. *Archives of General Psychiatry*, **49**, 641-643.

Clemente, C. D. & Sterman, M. B. (1963). Cortical synchronization and sleep patterns in acute restrained and chronic behaving cats induced by basal forebrain stimulation. *Clinical Neurophysiology*, **24**, 172-187.

Clemente, C.D. & Sterman, M.B. (1967). Basal forebrain mechanisms for internal inhibition and sleep. In S.S. Kety, E.V. Evarts & H.L. Williams (Eds.), *Sleep and Altered States of Consciousness* (pp. 127-147). Baltimore: Association of Research in Nervous and Mental Disorders.

Coleman, P. M., Pollak, C. P. & Weitzman, E. D. (1980). Periodic movements in sleep (nocturnal myoclonus): Relation to sleep disorders. *Annals of Neurology*, **8**, 416-421.

Coleman, R.M. (1982). Periodic leg movements in sleep (nocturnal myoclonus) and restless legs syndrome. In C. Guilleminault (Ed.), *Sleeping and Waking Disorders, Indications and Techniques* (pp. 265-296). Menlo Park: Addison-Wesley.

Coleman, R.M. (1983). Diagnosis, treatment, and followup of about 8,000 sleep-wake disorder patients. In C. Guilleminault & E. Lugaresi (Eds.), *Sleep/Wake Disorders: Natural History, Epidemiology, and Long-Term Evolution* (pp. 87-98). New York: Raven Press.

Coleman, R.M., Bliwise, D.L. & Sabjen, N. (1983). Epidemiology of periodic movements during sleep. In C. Guilleminault & E. Lugaresi (Eds.), *Sleep/Wake Disorders: Natural History, Epidemiology, and Long Term Evolution* (pp. 217-229). New York: Raven Press.

Coleman, R. M., Laughton, E. M., Guilleminault, C. C., Zarcone, V. P., van den Hoed, J. M. & Dement, W. C. (1981). Sleep-wake disorders in the elderly: A polysomnographic analysis. *Journal of American Geriatrics Society*, **29**, 289-296.

Colquhoun, W.P. (1971). Circadian variations in mental efficiency. In W.P. Colquhoun (Ed.), *Biological Rhythms in Human Performance* (pp. 39-107). London: Academic Press.

Crosby, L. J. (1991). Factors which contribute to fatigue associated with rheumatoid arthritis. *Journal of Advanced Nursing*, **16**, 974-981.

Dejong, R.N. (1979). Reflexes spinal automatism. In *The Neurologic Examination* (pp. 464-467). Baltimore, MD: Harper and Row.

Doty, R. W. (1969). Electrical stimulation of the brain in behavioral context. *Annual Review of Psychology*, **20**, 289-320.

Dublin, L.I., Lotka, A.J. & Spiegelman, M. (1949). *Length of Life.* New York: Ronald Press.

Dunwiddie, T. V. (1985). The physiological role of adenosine in the central nervous system. *International Review of Neurobiology*, **27**, 63-139.

Ebers, G. C., Bulman, D. E., Sadovnick, A. D., Paty, D. W., Warren, S., Hader, W., Murray, T. J., Seland, T. P., Duquette, P., Grey, T., Nelson, R., Nicolle, M. & Brunet, D. (1986). A population-based study of multiple sclerosis in twins. *New England Journal of Medicine*, **315**, 1638-1642.

Eccles, R. M. & Lundberg, A. (1959). Supraspinal control of interneurons mediating spinal reflexes. *Journal of Physiology*, **147**, 565-574.

Ekbom, K. (1966). Familial multiple sclerosis associated with narcolepsy. *Archives of Neurology*, **15**, 337-344.

Erman, M. K., Beckham, B., Gardner, D. A. & Roffwarg, H. P. (1987). The modified assessment of sleepiness test (MAST). *Sleep Research*, **16**, 550.

Feinberg, I., Koresko, R. L. & Heller, N. (1967). EEG sleep patterns as a function of normal and pathological aging in man. *Psychiatry Research*, **5**, 107-144.

Feinberg, I., March, J. D., Fein, G., Floyd, T. C., Walker, J. M. & Price, L. (1978). Period and amplitude analysis of 0.5-3 c/sec acitivity in NREM sleep of young patients. *Electroencephalography and Clinical Neurophysiology*, **44**, 202-213.

Folkard, S. (1979). Time of day and level of processing. *Memory and Cognition*, **7**, 247-252.

Folstein, M. F. & Luria, R. (1973). Reliability, validity and clinical application of visual analogue mood scale. *Psychological Medicine*, **3**, 479-486.

Foster, F. G., Kupfer, D. J. & Coble, P. (1976). Rapid eyemovement sleep density. *Archives of General Psychiatry*, **33**, 1119-1123.

Freal, J. E., Kraft, G. H. & Coryell, J. K. (1984). Symptomatic fatigue in multiple sclerosis. *Archives of Physical Medicine and Rehabilitation*, **65**, 135-138.

Friedman, L., Bergmann, B. M. & Rechtschaffen, A. (1979). Effects of sleep deprivation on sleepiness, sleep intensity, and subsequenty sleep in the rat. *Sleep*, **1**, 369-391.

Froberg, J., Karlsson, C. G., Levi, L. & Lindbeg, L. (1972). Circadian variations in performance, psychological ratings, catecholamine excretion and diuresis during prolonged sleep deprivation. *International Journal of Psychobiology*, **2**, 23-36.

Froberg, J. E. (1977). Twenty-four-hour patterns in human performance, subjective and physiological variables and differences between morning and evening active subjects. *Biological Psychiatry*, **5**, 119-134.

Gallager, D. W. (1982). Benzodazepines and gamma-aminobutyric acid. *Sleep*, **5**, S3-S11.

Garma, L. & Bouard, G. (1981). Nocturnal awakenings as a function of age in insomniacs. *Reviews in Neurology*, **137**, 677-692.

Genovesi, U., Moruzzi, G., Palestini, M., Rossi, G. F. & Zanchetti, A. (1956). EEG and behavioral patterns following lesions of the mesencephalic reticular formation in chronic cats with implanted electrodes. *Abtracts Committee of the XXth international Physiology Congress Bruxelles*, **20**, 335-336.

Gillin, J. C., Duncan, W. C., Murphy, D. L., Post, R. M., Wehr, T. A., Goodwin, F. K., Wyatt, R. J., Bunney, W.E. (1981). Age-related changes in sleep in depressed and normal subjects. *Psychiatry Research*, **4**, 73-78.

Guilleminault, C. & Flagg, W. (1984). Effect of baclofen on sleep-related periodic leg movements. *Annals of Neurology*, **15**, 234-239.

Guilleminault, C., Raynal, D., Takahashi, S., Carskadon, M. & Dement, W. (1976). Evaluation of short-term and long-term treatment of the narcolpesy syndrome with chlorimipramine hydrochloride. *Acta Neurologica Scandinavica*, **54**, 71-78.

Guler, M., Kirnap, M., Bekaroglu, M., Uremek, G. & Onder, C. (1992). Clinical characteristics of patients with fibromyalgia. *Isreal Journal of Medical Sciences*, **28**, 20-23.

Haber, A. & LaRocca, N.G. (1985). *Minimal Record of Disability for Multiple Sclerosis*. New York: National Multiple Sclerosis Society.

Harper, R.M. & McGinty, D.J. (1973). A technique for recording single neurons from unrestrained animals. In M.I. Phillips (Ed.), *Brain Unit Activity During Behavior* (pp. 82-104). Springfield, Illinois: Thomas.

Hartmann, E. (1973). *The Functions of Sleep*. New Haven: Yale University Press.

Hartse, K. M., Roth, T. & Zorick, F. J. (1982). Daytime sleepiness and daytime wakefulness: The effects of instruction. *Sleep*, **5(S)**, 107-118.

Hartung, H. P., Will, R. G., Francis, D., Grosse-Wilde, H., Rudge, P., Scaravilli, F., Hennerici, M. & McDonald, W. I. (1988). Familial multiple sclerosis. *Journal of the Neurological Sciences*, **83**, 259-268.

Hauri, P. & Hawkins, D. R. (1973). Alpha delta sleep. *Electroencephalography and Clinical Neurophysiology*, **34**, 233-237.

Hayashi, Y. & Endo, S. (1982). All-night sleep polygraphic recordings of healthy aged persons: REM and slow wave sleep. *Sleep*, **5**, 277-283.

Head, H. (1923). The conception of nervous and mental (II). *British Journal of Psychology*, **14**, 126-147.

Herndon, R. B. & Rudick, R. (1981). Fatigue in M.S. *M.S. Quarterly*, **Summer**, 4-14.

Hobson, J. A. (1965). The effects of chronic brain-stem lesions on cortical and muscular activity during sleep and waking in the cat. *Electroencephalography and Clinical Neurophysiology*, **19**, 41-62.

Hoddes, E., Dement, W. C. & Zarcone, V. (1972). The development and use of the Stanford sleepiness scale (SSS). *Psychophysiology*, **9**, 150.

Hoddes, E., Zarcone, V. P., Smythe, H., Phillips, R. & Dement, W. C. (1973). Quantification of sleepiness: A new approach. *Psychophysiology*, **10**, 431-436.

Howard, R. S., Wiles, C. M., Hirsh, N. P., Loh, L. & Spencer, G. T. (1992). Respiratory involvement in multiple sclerosis. *Brain*, **115**, 479-494.

Inoue, S. (1985). Sleep substances: Their roles and evolution. In S. Inoue & A.A. Borbely (Eds.), *Endogenous Sleep Substances and Sleep Regulation* (pp. 3-12). Toyko: Japan Scientific Societies Press.

Javanovic, U. J. (1976). The sleep waking cycle in healthy test subjects. *Waking and Sleeping*, **1**, 7-26.

Joffe, R. T., Lippert, G. P., Gray, T. A., Sawa, G. & Horvath, Z. (1987). Mood disorder and multiple sclerosis. *Archives of Neurology*, **44**, 376-378.

Jouvet, M. (1963). The rhombencephalic phase of sleep. *Progress in Brain Research*, **1**, 406-424.

Jouvet, M. (1965). Behavioural and EEG effects of paradoxical sleep deprivation in the cat. *Proceedings of the International Congress of Physiological Science*, **4**, 344-355.

Jouvet, M. (1965). Paradoxical sleep - A study of its nature and mechanisms. *Progress in Brain Research*, **18**, 20-57.

Jouvet, M. (1967). Neurophysiology of the states of sleep. *Physiological Review*, **47**, 117-177.

Jouvet, M. (1969). Biogenic amines and the states of sleep. *Science*, **163**, 32-41.

Jouvet, M. (1969). Neurophysiological and biochemical mechanisms of sleep. In A. Kales (Ed.), *Physiology and Pathology* (pp. 89-100). Philadelphia: Lippincott.

Kapen, S., Saad, J. & Koshorek, G. (1989). A polysomnographic study of multiple sclerosis. *Sleep Research*, **18**, 340.

Kilduff, T. S., Bowersox, S. S., Kaitin, K. I., Baker, T. L., Ciaranello, R. D. & Dement, W. C. (1986). Muscarinic cholinergic receptors and the canine model of narcolepsy. *Sleep*, **9**, 102-106.

Kinnunen, E., Koskenvuo, M., Kaprio, J. & Aho, K. (1987). Multiple sclerosis in a nationwide series of twins. *Neurology*, **1987**, 1627-1629.

Kleitman, N. (1963). *Sleep and Wakefulness*. Chicago: University of Chicago Press.

Kleitman, N. (1967). Phylogenetic, ontogenetic and environmental determinants in the evolution of sleep-wakefulness cycles. *Research in Nervous and Mental Disorders*, **45**, 30-38.

Kripke, D. F., Simons, N. R., Garfinkel, L. & Hammond, E. C. (1979). Short and long sleep and sleeping pills. Is increased mortality associated?. *Archives of General Psychiatry*, **36**, 103-116.

Krupp, L. B., Alvarez, L. A., LaRocca, N. G. & Scheinberg, L. C. (1988). Fatigue in multiple sclerosis. *Archives of Neurology*, **45**, 435-437.

Krupp, L. B., Jandorf, L., Coyle, P. K. & Mendelson, W. B. (1993). Sleep disturbance in chronic fatigue syndrome. *Journal of Psychosomatic Research*, **37**, 325-331.

Krupp, L. B., LaRocca, N. G., Muir-Nash, J. & Steinberg, A. D. (1989). The fatigue severity scale. *Archives of Neurology*, **46**, 1121-1123.

Krupp, L. B. & Mendelson, W. B. (1990). Sleep in chronic fatigue syndrome. *Sleep*, **(suppl)**, 261-263.

Krupp, L. B., Mendelson, W. B. & Friedman, R. (1991). An overview of chronic fatigue syndrome. *Journal of Clinical Psychiatry*, **52**, 403-410.

Kuisk, L. A., Bertelson, A. D. & Walsh, J. K. (1989). Presleep cognitive hyperarousal and affect as factors in objective and subjective insomnia. *Perceptual and Motor Skills*, **69**, 1219-1225.

Kurtzke, J. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*, **33**, 1444-1452.

Kurtzke, J. F., Beebe, G. W., Nagler, B., Nefzger, M. D., Auth, T. L. & Kurland, L. T. (1970). Studies on the natural history of multiple sclerosis. *Archives of Neurology*, **22**, 215-225.

Kurtzke, J. F., Beebe, G. W. & Norman, J. E. (1979). Epidemiology of multiple sclerosis in U.S. veterans: 1. race, sex, and geographic distribution. *Neurology*, **29**, 1228-1235.

Kurtzke, J. F. & Hyllested, K. (1987). Multiple sclerosis in the Faroe Islands III. An alternative assessment of the three epidemics. *Acta Neurologica Scandinavica*, **76**, 317-339.

Lance, J.W. & Mcleod, J.G. (1981). A physiological approach to clinical neurology. In (pp. 80-81). Bessles, London: William Clomes (Beccles) Ltd..

Lansbury, J. (1968). Clinical appraisal of the activity index as a measure of rheumatoid activity. *Arthritis and Rheumatism*, **11**, 599-604.

LaRocca, N. G., Scheinberg, L. C., Slater, R. J., Giesser, B., Smith, C. R., Traugott, U., Schapiro, R. T., Paty, D. W., Franklin, G. M., Cobble, N., Petajan, J. H., Kraft, G. H., Frankel, D., Catanzaro, M., Poser, C. M., Tourtellotte, W. W. & Baumhefner, R. W. (1984). Field testing of a minimal record of disability in multiple sclerosis: The United States and Canada. *Acta Neurologica Scandinavica*, **70**, 126-138.

Lavie, P. (1981). Sleep habits and sleep disturbances in industrial workers in Israel: Main findings and some characteristics of workers complaining of excessive daytime sleepiness. *Sleep*, **4**, 147-158.

Lee, K. A., Hicks, G. & Nino-Murcia, G. (1991). Validity and reliability of a scale to assess fatigue. *Psychiatry Research*, **36**, 291-298.

Leo, G. J., Rao, S. M. & Bernardin, L. (1991). Sleep disturbance in multiple sclerosis. *Neurology*, **41**, 727.

Levine, B., Roehrs, T., Stepanski, E., Lamphere, J., Zorick, F. & Roth, T. (1987). Fragmenting sleep diminishes its recuperative value. *Sleep*, **10**, 590-599.

Lucas, E. A. & Sterman, M. B. (1972). Effects of performance and forebrain lesions on sleep-wake (SW) and REM cycles in the cat. *Anatomical Record*, **172**, 357.

Lugaresi, E., Coccagna, G., Ceroni, G.B. & Ambrosetto, C. (1968). Restless legs syndrome and nocturnal myoclonus. In H. Gastaut (Ed.), *The Abnormalities of Sleep in Man* (pp. 285-294). Bologna, Italy: Aulo Gaggi Editore.

Lugaresi, E., Coccagna, G., Montovani, M. & Lebrun, R. (1972). Some periodic phenomena arising during drowsiness and sleep in man. *Electroencephalography and Clinical Neurophysiology*, **32**, 701-705.

Lugaresi, E.F., Cirignotta, G., Coccagna, G. & Montagna, P. (1986). Nocturnal myoclonus and restless leg syndrome. In S. Fahn, C.D. Marsden & V.M. Woert (Eds.), *Advance in Neurology: Myoclonus* (pp. 295-307). New York: Raven Press.

MacKay, R. P. & Hirano, A. (1967). Forms of benign multiple sclerosis. *Archives of Neurology*, **17**, 588-592.

MacKay, R. P. & Myrianthopoulos, N. C. (1966). Multiple sclerosis in twins and their relatives. *Archives of Neurology*, **15**, 449-462.

Mahoney, F. L. & Barthel, D. W. (1965). Functional evaluation: The Barthel index. *Maryland State Medical Journal*, **14**, 61-65.

Mahowald, M. W., Mahowald, M. L., Bundlie, S. R. & Ytterberg, S. R. (1989). Sleep Fragmentation in Rheumatoid Arthritis. *Arthritis and Rheumatism*, **32**, 974-983.

Martinelli, P., Montagna, P., Pazzaglia, P. & Coccagna, G. (1978). Stiff-man syndrome associated with nocturnal myoclonus and epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry*, **41**, 458-462.

Matsuzaki, M., Takagi, H. & Tokizane, T. (1964). Paradoxical phase of sleep: Its artificial induction inthe cat by sodium butyrate. *Science*, **146**, 1328-1329.

Matthews, W., Read, D. & Pountney, E. (1977). Effects of raising body temperature on visual and somatosensory evoked potentials in patients with multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **42**, 250-255.

McDonald, W. & Sears, T. (1970). The effects of experimental demyelination on conduction in the central nervous system. *Brain*, **93**, 583-598.

McGinty, D. J. & Sterman, M. B. (1968). Sleep suppression after basal forebrain lesions in the cat. *Science*, **160**, 1253-1255.

Meenan, R. F., Gertman, P. M. & Mason, J. H. (1980). Measuring health status in arthritis: the arthritis impact measurement scales. *Arthritis and Rheumatism*, **23**, 146-152.

Michael, J. & Davis, F. (1973). Effects of induced hyperthermia in multiple sclerosis: Differences in visual acuity during heating and recovery phases. *Acta Neurologica Scandinavica*, **49**, 141-151.

Miles, L. E. & Dement, W. C. (1980). Objective sleep parameters in elderly men and women. *Sleep*, **3**, 131-149.

Miller, R. G., Carson, P. J., Moussavi, R. S., Green, A. T., Baker, A. J. & Weiner, M. W. (1991). Fatigue and myalgia in AIDS patients. *Neurology*, **41**, 1603-1607.

Mitler, M. M., Gujavarty, S. & Browman, C. P. (1982). Maintenance of wakefulness test: A polysomnographic technique for evaluating treatment efficacy in patients with excessive somnolence. *Electroencephalography and Clinical Neurophysiology*, **53**, 658-661.

Mitler, M. M., van den Hoed, J., Carskadon, M. A., Richardson, G., Park, R., Guilleminault, C. & Dement, W. C. (1979). REM sleep episodes during the multiple sleep latency test in narcoleptic patients. *Electroencephalography and Clinical Neurophysiology*, **46**, 479-481.

Mizuno, N., Clemente, C. D. & Sauerland, K. (1969). Fiber projections from rostral basal forebrains structures in the cat. *Journal of Comparative Neurology*, **136**, 127-142.

Moldofsky, H. (1976). "Psychogenic rheumatism" or the "fibrositis syndrome". In O. Hill (Ed.), *Modern Trends in Psychosomatic Medicine* (pp. 187-195). Boston: Butterworths and Co.

Moldofsky, H. (1989). Nonrestorative sleep and symptoms after a febrile illness in patients with fibrositis and chronic fatigue syndromes. *Journal of Rheumatology Supplement*, **19**, 150-153.

Moldofsky, H. (1989). Sleep and fibrositis syndrome. In R.M. Bennet & D.L. Goldenberg (Eds.), *Rheumatic Diseases of North America* (pp. 91-103). Philadelphia: W.B. Saunders Company.

Moldofsky, H. (1993). Fibromyalgia, sleep disorder and chronic fatigue syndrome. *Ciba Foundation Symposium*, **173**, 262-279.

Moldofsky, H. & Chester, W. J. (1970). Pain and mood patterns in patients with rheumatoid arthritis. *Psychsomatic Medicine*, **32**, 309-318.

Moldofsky, H. & Lue, F. A. (1980). The relationship of alpha and delta EEG frequencies to pain and mood in "fibrositis" patients treated with chlorpromazine and L-tryptophan. *Electroencephalography and Clinical Neurophysiology*, **50**, 71-80.

Moldofsky, H., Lue, F. A. & Smythe, H. (1979). Alpha NREM sleep and morning symptoms in rheumatoid arthritis. *Sleep Research*, **8**, 236.

Moldofsky, H., Lue, F. A. & Smythe, H. (1983). Alpha EEG sleep and morning symptoms in rheumatoid arthritis. *Psychsomatic Medicine*, **10**, 373-379.

Moldofsky, H. & Scarisbrick, P. (1976). Introduction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. *Psychsomatic Medicine*, **38**, 35-44.

Moldofsky, H., Scarisbrick, P., England, R. & Smythe, H. (1975). Musculoskeletal symptoms and nonREM sleep disturbance in patients with "fibrositis" syndrome and healthy subjects. *Psychosomatic Medicine*, **37**, 341-351.

Moldofsky, H., Tullis, C., Lue, F. A., Quance, G. & Davidson, J. (1984). Sleep-related myoclonus in rheumatic pain modulation disorders (fibrositis syndrome) and in excessive daytime somnolence. *Psychsomatic Medicine*, **46**, 145-151.

Monk, T. H. (1987). A visual analogue scale technique to measure global vigor and affect. *Psychiatry Research*, **27**, 89-99.

Monk, T. H. & Moline, M. L. (1988). Removal of temporal constraints in the middle aged and elderly: Effect on sleep and sleepiness. *Sleep*, **11**, 513-520.

Monnier, M. & Gaillard, J. M. (1980). Biochemical regulation of sleep. *Experientia*, **36**, 21-24.

Montplaisir, J. & Godbout, R. (1989). Restless legs syndrome and periodic movements during sleep. In M.H. Kryger, T. Roth & W.C. Dement (Eds.), *Principles and Practice of Sleep Medicine* (pp. 402-409). Philadelphia: W.B. Saunders Company.

Moruzzi, G. (1974). Neural mechanisms of the sleep-waking cycle. In O. Petre-Quadens & J.D. Schlag (Eds.), *Basic Sleep Mechanisms* (pp. 13-31). New York: Academic Press.

Mosko, S. S. & Nudelman, K. L. (1986). Somatosensory and brainstem auditory evoked responses in sleep-related periodic leg movements. *Sleep*, **9**, 399-404.

Mosko, S. S., Shampain, D. S. & Sassin, J. F. (1984). Nocturnal REM latency and sleep disturbance in narcolepsy. *Sleep*, **7**, 115-125.

Moskowitz, E. & McCann, C. (1957). Classification of disability in the chronically ill and aging. *Journal of Chronic Diseases*, **5**, 342-346.

Murray, T. J. (1985). Amantadine therapy for fatigue in multiple sclerosis. *Canadian Journal of Neurological Science*, **12**, 251-254.

Nicholson, A. N., Pascoe, P. A., Spencer, M. B., Stone, B. M., Roehrs, T. & Roth, T. (1986). Sleep after transmeridian flights. *Lancet*, **2**, 1205-1208.

Norman, S. E., Chediak, A. D., Kiel, M. & Cohn, M. A. (1990). Sleep disturbances in HIV-infected homosexual men. *AIDS*, **4**, 775-781.

Olgiati, R., Jacquet, J. & DiPrampero, P. (1986). Energy cost of walking and exertional dyspnea in multiple sclerosis. *American Review of Respiratory Diseases*, **134**, 1005-1010.

Oswald, I. (1980). Sleep as a restorative process: Human clues. *Progress in Brain Research*, **53**, 279-288.

Pansky, B. & Allen, D. (1980). *Review of Neuroscience*. New York: Macmillan Publishing Co Inc..

Pinals, R. S., Masi, A. T., Larsen, R. A. & The Subcommittee for Criteria of Remission in Rheumatoid Arthritis of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee (1981). Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis and Rheumatism*, **24**, 1308-1315.

Poirer, G., Montplaisir, J., Dumont, M., Duquette, P., Decary, F., Pleines, J. & Lamoureux, G. (1987). Clinical and sleep laboratory study of narcoleptic symptoms in multiple sclerosis. *Neurology*, **37**, 693-695.

Pollard, H. & Schwartz, J. C. (1987). Histamine neuronal pathways and their functions. *Trends in Neuroscience*, **10**, 86-89.

Pollmacher, T. & Schulz, H. (1993). Periodic leg movements (PLM): Their relationship to sleep stages. *Sleep*, **16**, 572-577.

Poser, C.M., Paty, D.W., Scheinberg, L., Mc Donald, W.I., Davis, F.A., Ebers, G.C., Johnson, K.P., Sibley, W.A., Silberberg, D.H. & Tourtellotte, W.W. (1984). New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. In C.M. Poser (Ed.), *Diagnosis of Multiple Sclerosis* (pp. 225-229). New York: Thieme-Stratton.

Poser, C. M., Paty, D. W., Scheinberg, L. C., Mc Donald, W. I., Davis, F. A., Ebers, G. C., Johnson, K. P., Sibley, W. A., Silberberg, D. H. & Tourtellotte, W. W. (1983). New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. *Annals of Neurology*, **13**, 227-231.

Potolicchio, S. J., Calderon, E. T. & Richert, J. (1991). Periodic limb movements of sleep and chronic fatigue in multiple sclerosis: Correlation between diagnosis and treatment. *Neurology*, **41 (Suppl 1)**, 320-321.

Prinz, P. N. (1977). Sleep patterns in the healthy aged: relationship with intellectual function. *Journal of Gerontology*, **32**, 179.

Purpura, D.P. (1974). Intracellular studies of thalamic synaptic mechanisms in evoked synchronization and desynchronization of electrocortical activity. In O. Petre-Quadens & J.D. Schlag (Eds.), *Basic Sleep Mechanisms* (pp. 99-125). New York: Academic Press.

Purpura, D. P. & Shofer, R. J. (1963). Intracellular recordings from thalamic neurons during reticulocortical activation. *Neurophysiology*, **26**, 494-505.

Rabins, P. V., Brooks, B. R., O'Donnel, P., Pearlson, G.D., Moberg, P., Jubelt, B., Coyle, P., Dalos, N. & Folstein, M.F. (1986). Structural brain correlates of emotional disorder in multiple sclerosis. *Brain*, **109**, 585-587.

Radloff, L. S. (1977). CES-D scale: a self-report depression scale for research in the general population. *Psychological Measurement*, **1**, 385-401.

Raine, C.S. (1990). Neuropathology. In S.M. Rao (Ed.), *Neurobehavioral Aspects of Multiple Sclerosis* (pp. 15-36). New York: Oxford University Press.

Rao, S. (1986). Neuropsychology of multiple sclerosis: A critical review. *Journal of Clinical and Experimental Neuropsychology*, **8**, 503-542.

Rasminsky, M. (1973). The effects of temperature on conduction in demyelinated single nerve fibers. *Archives of Neurology*, **28**, 287-292.

Rechtshaffen, A. & Kales, A. (1968). *A Manual of Standardized Terminology Techniques and Scoring System for Sleep Stages of Human Subjects.* Government Printing Office, Washington D.C.: National Institute of Health Publications 204.

Regan, D., Murray, T. & Silver, R. (1977). Effects of body temperature on visual evoked potiental delay and visual perception in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **4083**, 1083-1091.

Regestein, Q. R., Dambrosia, J., Hallett, M., Murawski, B. & Paine, M. (1993). Daytime alertness in patients with primary insomnia. *American Journal of Psychiatry*, **150**, 1529-1534.

Reynolds, C. F., Kupfer, D. J., Hoch, C. C., Stack, J. A., Houck, P. R. & Sewitch, D. E. (1986). Two year followup of elderly patients with mixed depression and dementia: Clinical and EEG sleep findings. *Journal of American Geriatrics Society*, **34**, 793.

Reynolds, C. F., Kupfer, D. J., Taska, L. S., Hoch, C. C., Sewitch, D. E. & Spiker, D . G. (1985). Sleep of healthy seniors: A revisit. *Sleep*, **8**, 20-29.

Reynolds, C. F., Kupfer, D. J., Taska, L. S., Hoch, C. C., Spiker, D. G., Sewitch, D. E., Zimmer, B., Marin, R. S., Nelson, J. P., Martin, D. & Morycz, R. (1985). EEG sleep in elderly, depressed, demented and healthy subjects. *Biological Psychiatry*, **20**, 431-442.

Richardson, G. S., Carskadon, M. A., Flagg, W., Van den Hoed, J., Dement, W. C. & Mitler, M. M. (1978). Excessive daytime sleepiness in man: Multiple sleep latency measurement in narcoleptic and control subjects. *Electroencephalography and Clinical Neurophysiology*, **45**, 621-627.

Richardson, G. S., Carskadon, M. A., Orav, E. J. & Dement, W. C. (1982). Circadian variation of sleep tendency in elderly and young adult subjects. *Sleep*, **5**, S82-S94.

Roberts, W. W. & Robinson, T. C. L. (1969). Relaxation and sleep induced by warming of preoptic region and anterior hypothalamus in cats. *Experimental Neurology*, **25**, 282-294.

Roehrs, T., Zorick, F., Wittig, R. & Roth, T. (1985). Efficacy of reduced triazolam dose in elderly insomniacs. *Neurobiology of Aging*, **6**, 293-296.

Rosenthal, L., Roehrs, T., Sicklesteel, J., Zorick, F., Wittig, R. & Roth, T. (1984). Periodic movements during sleep, sleep fragmentation, and sleep-wake complaints. *Sleep*, **7**, 326-330.

Roth, T., Roehrs, T., Carskadon, M. & Dement, W. (1989). Daytime sleepiness and alertness. In M.H. Kryger, T. Roth & W.C. Dement (Eds.), *Principles and Practice of Sleep Medicine* (pp. 14-23). Philadelphia: W.B. Saunders Company.

Rumbach, L., Tongiio, M. M., Warter, J. M., Collard, M. & Kurtz, D. (1989). Multiple sclerosis, sleep latencies and HLA antigens. *Journal of Neurology*, **236**, 309-310.

Sadovnick, A. D. & Baird, P. A. (1988). The familial nature of multiple sclerosis: Age-corrective empiric recurrence risks for children and siblings of patients. *Neurology*, **38**, 990.

Sadovnick, A. D. & MacLeod, P. M. J. (1981). The familial nature of multiple sclerosis: empiric recurrence risk for first-, second-, and third-degree relatives of patients. *Neurology*, **31**, 1039-1041.

Sandroni, P., Starr, A., Walker, C. & van den Noort, S. (1991). Physiology of 'fatigue' in multiple sclerosis. *Neurology*, **41**, 729.

Sandy, K. R. (1983). Anergia and depression as early features of multiple sclerosis. *South Africian Medical Journal*, **61**, 732.

Saskin, P., Moldofsky, H. & Lue, F. A. (1985). Periodic movements in sleep and sleep-wake complaint. *Sleep*, **8**, 319-324.

Saskin, P., Moldofsky, H. & Lue, F. A. (1986). Sleep and posttraumatic pain modulation disorder (fibrositis syndrome). *Psychosomatic Medicine*, **48**, 319-323.

Saskin, P., Moldofsky, H., Salem, L., Anch, M. & Lue, F.A. (1987). Sleep and symptoms in psychophysiologic insomnia and fibrositis. *Sleep Research*, **16**, 421.

Saunders, J., Whitham, R. & Schaumann, B. (1991). Sleep disturbance, fatigue, and depression in multiple schlerosis. *Neurology*, **41**, 728.

Schauf, C. L. & Davis, F. A. (1974). Impulse conduction in multiple sclerosis: A theoretical basis for modification by temperature and pharmacological agents. *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 152-161.

Schiffer, R. B. (1987). The spectrum of depression in multiple sclerosis. *Archives of Neurology*, **44**, 596-599.

Schneider-Helmert, D. (1985). Multiple relaxation test (MRT): An investigation into pathophysiology of chronic insomnia. *Sleep Research*, **14**, 211.

Schrader, H., Gotlibsen, O. B. & Skomedal, G. N. (1980). Multiple sclerosis and narcolepsy/cataplexy in a monozygotic twin. *Neurology*, **30**, 105-108.

Schumacher, G. A, Beebe, G. & Kibler, R. F. (1965). Problems of experimental trials of therapy in multiple sclerosis: Report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Annals of the New York Academy of Sciences*, **122**, 552-568.

Seidel, W. F., Roth, T., Roehrs, T., Zorick, F. & Dement, W.C. (1984). Treatment of a 12-hour shift of sleep schedule with benzodiazepines. *Science*, **224**, 1262-1264.

Sibley, W.A. (1990). Diagnosis and course of multiple sclerosis. In S.M. Rao (Ed.), *Neurobehavioral Aspects of Multiple Sclerosis* (pp. 5-14). New York: Oxford University Press.

Slosarska, M. & Zernicki, B. (1969). Synchronized sleep in the chronic pretrigeminal cat. *Acta Biologiae Experimentalis*, **29**, 175-184.

Smith, R. C. (1985). Relationship of periodic movements in sleep (nocturnal myoclonus) and the Babinski sign. *Sleep*, **8**, 239-243.

Snyder, S.H. & Taylor, K.M. (1972). Histamine in the brain: A neurotransmitter?. In S.H. Snyder (Ed.), *Perspectives in Neuropharmacology: A Tribute to Julius Axelrod* (pp. 43-74). New York: Oxford University Press.

Spiegel, R. (1981). *Sleep and Sleepiness in Advanced Age.* New York: SP Medical.

Spielman, A. J., Adler, J. M., Glovinsky, P. B., Pressman, M. R., Thorpy, M. J., Ellman, S. J. & Ackerman, K. D. (1986). Dynamics of REM sleep in narcolepsy. *Sleep*, **9**, 175-182.

Spitzer, R. L., Endicott, J. & Robins, E. (1978). Research diagnostic criteria: Rational reliability. *Archives of General Psychiatry*, **35**, 773-782.

Stepanski, E., Lamphere, J., Badia, P., Zorick, F. & Roth, T. (1984). Sleep fragmentation and daytime sleepiness. *Sleep*, **7**, 18-26.

Stepanski, E., Salava, W., Lamphere, J., Roehrs, T., Zorick, F., Badia, P. & Roth, T. (1984). Experimental sleep fragmentation and sleepiness in normal subjects: A preliminary report. *Sleep Research*, **13**, 193.

Sterman, M. B. & Clemente, C. D. (1962). Forebrain inhibitory mechanisms: Cortical synchronization induced by basal forebrain stimulation. *Experimental Neurology*, **6**, 91-102.

Sterman, M. B. & Clemente, C. D. (1962). Forebrain inhibitory mechanisms: sleep patterns induced by basal forebrain stimulation in the behaving cat. *Experimental Neurology*, **6**, 103-117.

Sterman, M.B. & Clemente, C.D. (1974). Forebrain mechanisms for the onset of sleep. In O. Petre-Quadens & J.D. Schlag (Eds.), *Basic Sleep Mechanisms* (pp. 83-97). New York: Academic Press.

Sterman, M. B., Knauss, T. K., Lehmann, D. & Clemente, C. D. (1964). Alteration of sleep patterns following basal forebrain lesions. *Federal Proceedings*, **23**, 209.

Strogatz, S.H. (1986). *The Mathematical Structure of the Human Sleep Wake Cycle.* New York: Springer-Verlag.

Symonds, C. P. (1953). Nocturnal myoclonus. *Journal of Neurology, Neurosurgery and Psychiatry*, **16**, 166-171.

Timms, R. M., Shaforenko, R., Hajdukovic, R. M. & Mitler, M. M. (1985). Sleep apnea syndrome: Quantitative studies of nighttime measures and daytime alertness. *Sleep Research*, **14**, 222.

Ulrich, R., Shaw, D. H. & Kupfer, D. J. (1980). The effects of aging in sleep. *Sleep*, **3**, 131-141.

Valldeoriola, F., Santamaria, J., Graus, F. & Tolosa, E. (1993). Absence of REM sleep, altered NREM sleep and supranuclear horizontal gaze palsy caused by a lesion of the pontine tegmentum. *Sleep*, **16**, 184-188.

van den Hoed, J., Kraemer, H., Guilleminault, C., Zarcone, V. P., Miles, L. E. & Dement, W. C. (1981). Disorders of excessive daytime somnolence: Polygraphic and clinical data for 100 patients. *Sleep*, **4**, 23-37.

van den Hoed, J., Lucas, E. A. & Dement, W. C. (1979). Hallucinatory experiences during cataplexy in patients with narcolepsy. *American Journal of Psychiatry*, **136**, 1210-1211.

Villablanca, J. (1962). Electroencephalogram in the permanently isolated forebrain of the cat. *Science*, **138**, 44-46.

Villablanca, J. (1965). The electrocorticogram in the chronic "cerveau isole" cat. *Clinical Neurophysiology*, **19**, 576-586.

Villablanca, J. (1966). Ocular behavior in the chronic "cerveau isole" cat. *Brain Research*, **2**, 99-102.

Villablanca, J. (1966). Behavioral and polygraphic study of "sleep" and "wakefulness" in chronic decerebrate cats. *Electroencephalography and Clinical Neurophysiology*, **21**, 562-577.

Vogel, G. W., Vogel, F., McAbee, R. S. & Thurmond, A. J. (1980). Improvement of depression by REM sleep deprivation. *Archives of General Psychiatry*, **37**, 247-253.

Webb, W.B. (1972). Sleep deprivation: Total, partial and selective. In M.H. Chase (Ed.), *The Sleeping Brain* (pp. 323-362). Los Angelos: BIS/BRS.

Webb, W. B. (1982). The measurement and characteristic of sleep in older persons. *Neurobiology of Aging*, **3**, 311-319.

Wechsler, D. (1945). A standardized memory scale for clinical use. *Journal of Psychology*, **19**, 87-95.

Weitzman, E. D., Moline, M. L., Czeisler, C. A. & Zimmerman, J. C. (1982). Chronobiology of aging: Temperature, sleep-wake rhythms and entrainment. *Neurobiology of Aging*, **3**, 299-309.

Whitlock, F. A. & Siskind, M. M. (1980). Depression as a major symptom of multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **43**, 861-865.

Wilkinson, R.T. (1968). Sleep deprivation: Performance tests for partial and selective sleep deprivation. In L.E. Abt & B.F. Riess (Eds.), *Progress in Clinical Psychology* (pp. 28-43). New York: Grune and Stratton.

Williams, A., Eldridge, R., McFarland, H., Houff, S., Krebs, H. & McFarlin, D. (1980). Multiple sclerosis in twins. *Neurology*, **30**, 1139-1147.

Williams, R.L., Karacan, I. & Hursch, C.J. (1974). *EEG of Human Sleep Clinical Applications*. New York: John Wiley & Sons.

Willoughby, E.W. & Paty, D.W. (1990). Brain imaging in multiple sclerosis. In S.M. Rao (Ed.), *Neurobehavioral Aspects of Multiple Sclerosis* (pp. 37-62). New York: Oxford University Press.

Wolfe, F., Cathey, M. A., Kleinheksel, S. M., Amos, S. P., Hoffman, R. G., Young, D. Y. & Hawley, D. J. (1984). Psychological status in primary fibrositis and fibrositis associated with rheumatoid arthritis. *The Journal of Rheumatology*, **11**, 500-506.

Wolfe, F., Hawley, D. J., Cathey, M. A., Caro, X. & Russell, I.J. (1985). Fibrositis: Symptom frequency and criteria for diagnosis. *Journal of Rheumatology*, **12**, 1159-1163.

Yokota, T., Hirose, K., Tanabe, H. & Tsukagoshi, H. (1991). Sleep-related periodic leg movements (nochturnal myoclonus) due to spinal cord lesion. *Journal of the Neurological Sciences*, **104**, 13-18.

Younger, D. S., Pedley, T. A. & Thorpy, M. J. (1991). Multiple sclerosis and narcolepsy: Possible similar genetic susceptibility. *Neurology*, **41**, 447-448.

Yunus, M. B., Ahles, T. A., Aldag, J. C. & Masi, A. T. (1991). Relationship of clinical features with psychological status in primary fibromyalgia. *Arthritis and Rheumatism*, **34**, 15-21.

Yunus, M. B. & Masi, A. T. (1985). Juvenile primary fibromyalgia syndrome. *Arthritis and Rheumatism*, **28**, 138-145.

Zorick, F., Roehrs, T., Conway, W., Fujita, S., Wittig, R. & Roth, T. (1983). Effects of uvulopalatopharyngoplasty on the daytime sleepiness associated with sleep apnea syndrome. *Bulletin of European Pathophysiological Research*, **19**, 600-603.

Zorick, F., Roehrs, T., Wittig, R., Lamphere, J., Sicklesteel, J. & Roth, T. (1986). Sleep-wake abnormalities in narcolepsy. *Sleep*, **9**, 189-193.

Zorick, F., Roth, T., Salis, P., Kramer, M. & Lutz, T. (1978). Insomnia and daytime excessive sleepiness as presenting symptoms in nocturnal myoclonus. *Sleep Research*, **7**, 256.

Zulley, J. & Campbell, S. S. (1985). Napping behavior during "spontaneous internal desynchronization": Sleep remains in synchrony with body temperature. *Human Neurobiology*, **4**, 123-126.