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Review

Sleep in Normal Aging and Dementia

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SLEEP IN NORMAL AGING

A review of sleep patterns as a function of age highlights a difficult issue: "What is normal?" "Normal" can be paraphrased in a variety of ways (1) and investigators often use the term to connote a variety of meanings. Frequent confusion occurs because the term is used descriptively, to indicate representativeness, as well as clinically, to indicate absence of disease. Often the definitions conflict because the knowledge base in one area greatly outweighs available information in the other. In the case of sleep, for example, an enormous amount of excellent data exists concerning the representative amounts of sleep-related respiratory disturbance (SRRD) in a variety of nonclinical geriatric populations, but far less is known about whether the SRRD in these populations is injurious and signifies disease.

"Aging" is also subject to semantic confusion. Repeatedly, chronological age has been shown to only approximate physiological age. The decline in slow wave sleep, for example, may occur at a chronological age far earlier than most age-related declines in other biological functions. Some researchers in gerontology have noted that distance from death may be a far better approximation of the aging process, but too few longitudinal sleep studies exist to yield these types of findings (2). In addition to the issue of physiological age, subjective age must be considered. Because the practice of sleep disorders medicine in geriatrics relies heavily on the increased self-reports of sleep disturbance seen in aging, subjective appraisal of the older person's symptoms must be considered. Whether an aged individual views his or her 75% sleep efficiency as insomnia or merely accepts this as a normal part of aging may depend largely on that individual's perspective on growing old and what that means to him or her. Buysse et al. (3) have suggested that it may well be that although extremely healthy elderly individuals still incur numerous age-related changes in sleep, they adapt their perception of such sleep. They also have noted that self-reports of polysomnographically measured sleep are inherently less accurate and valid in older relative to younger subjects (3). Evidence for such age differences in other studies, however, is decidedly mixed and varies by the variables under consideration and/or the subject's gender (4–8).

An equally important counterpoint to normal aging is "successful" aging (9). Successful aging can be viewed as an optimization of existing biopsychosocial function, beyond the limitations of specific genetic predisposition or sociocultural milieu. Our knowledge of sleep and sleep disorders in aging has seldom progressed to the point that we know what constitutes such optimization of function and quality of life, although considerable heterogeneity in various aspects of sleep and rhythms across individuals almost certainly guarantees that growing old need not be accompanied by the inevitability of decline.

Finally, normal aging must be viewed relative to dementia, or so-called pathological aging. Although the high prevalence of dementing illnesses is high in late life, determination of the number of normal elderly persons who may be in incipient stages of dementia has seldom been addressed. Unlike sleep studies in dementia, in which diagnostic procedures typically have been used to rule out causes of reversible dementia, few sleep studies of normal aging rely on extensive diagnostic work to eliminate individuals in the earliest stages of mental impairment.

The point here is not to dismiss all that is known about sleep patterns in normal aging as inadequate, but rather to point out the complexities of defining "normal aging" in an overly simplistic manner. "Normal aging" can never be defined without some arbitrary criteria. In most of the work we summarize, we will define sleep in normal aging in humans as those representative sleep characteristics occurring in the presumed nondemented population over the age of 60. It

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is also important to recognize that the age-related alterations in sleep described below may have a minimal relationship to age changes in sleep processes per se and may simply be secondary manifestations of senescence. Because age changes must be placed in the framework of evolutionary history and are at least partially based at the genomic level (10), this review will include, where relevant, age-related changes in other mammalian species as well. Studies of sleep and rhythms in older animals also offer the advantage of removing the effects of confounding variables, which may not be easily accomplished in humans.

Waking EEG waveforms in normal aging

Age related changes in waking electroencephalographic (EEG) activity are well documented and have been reviewed in detail elsewhere (11). In brief, focal slow activity (including delta, 0–3 Hz, and theta, 4–7 Hz, activity) is common in the nondemented aged and may occur primarily in the left temporal region, but with minimal pathological significance (12–15). Diffuse delta activity is much more typical of dementia, although at least two reports noted some diffuse slowing in 20–40% of apparently nondemented individuals over age 70 (16,17). Age-related decreases in alpha frequency have been noted (17–19), but newer studies have not always found alpha slowing in old age (13,20). Alpha amplitude also decreases with age (21). The occurrence of beta, or fast (14–30 Hz), activity may increase with normal aging without obvious pathological significance (16,22,23).

More recently, EEG analyses with automated signal processing has yielded somewhat contradictory results. Spectral analysis with sophisticated brain electrical activity mapping (BEAM), for example, yielded minimum relationships between spontaneous alpha frequency and power and age (24). Work using other techniques (zero-crossing processing with band pass filtering) showed age differences in waking alpha frequency only when 3–5-year-old children were compared with all other age groups (up to age 79) (25). Significant negative correlations between age and slow wave activity in waking have been noted with BEAM (24). Using Fast Fourier Transforms (FFT's), Breslau et al. (26) reported age-related declines in delta, theta, alpha and beta power, although topographic factors may have played a role.

Sleep characteristics and associated factors in aging

Most surveys inquiring about sleep and including geriatric subjects have reported increased nocturnal awakenings in aging (27–55), although sleep latency may show only equivocal changes with age (35,38,39,42,47,51,54–56). Hypnotic medication usage increases with age, and elderly women are proportionally higher users of sedative/hypnotics relative to elderly men (33,35,37,40–42,47,51,57–62). Morgan (61) has reported a median prevalence of hypnotic drug usage across studies of about 10% for men and about 15% for women. In studies limited to a restricted age range in middle-aged and elderly persons, however, chronological age pe se often does not correlate with higher prevalence of poor sleep (63–67), which is consistent with the role of other health or psychological factors in the poor sleep of advanced age. A few early studies (40,68,69) and much recent evidence now point to the role of medical diseases and chronic illness in much of the poor sleep seen in old age (32,39,67,70–82). As examples of such research, several studies by Morgan et al. (67,73) reported that the usage of medications for a variety of health conditions (excluding hypnotics) differentiated good and poor sleepers and noted that the number of physician visits and self-ratings of health also distinguished the groups. Gislason and Almqvist (78) reported that when somatic diseases were controlled multivariately, some types of insomnia complaints showed no age-related increase, and some even showed a decrease with age. Hanson and Ostergren (75) noted that, among a representative sample of 68-year-old men, users of the health care system were more likely to suffer from insomnia. Finally, Ford and Kamerow's (32) recent study showed that when individuals with poor sleep accompanying physical illness, medication use or drug/alcohol use were not included in a definition for insomnia, age-related prevalence rates of poor sleep were far less striking than in most previous studies. In fact, no age-related increase was detected unless insomnia was present on two separate interviews separated by 1 year.

More specifically, conditions such as nocturia (33,56,61,83,84), headache (85), gastrointestinal illness (33,86), bronchitis and asthma (36,78,86), cardiovascular symptoms (78,87), type I diabetes (78) (c.f. type II) (87) and menopausal status (49,88) have also been shown to differentially impact upon the sleep of older subjects. Conditions involving chronic pain, such as osteoarthritis, rheumatoid arthritis and fibromyalgia, have been shown to be particularly disruptive to sleep in the elderly (78,89–93), and animal models for such sleep disruption have been developed (94,95). Drug and alcohol-dependent insomnia have also been shown to be more common in elderly individuals in a case series of clinic patients (76).

In addition to these factors, there are many alterations specific to sleep itself that change in aging. Factors such as elevated autonomic activity (96–98) may predispose elderly persons to poor sleep. This has been

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hypothesized to be due to elevated activity in the sympathetic nervous system (99), although attempts to modify sympathetic tone in healthy elderly subjects may result in elevated plasma norepinephrine without corresponding alterations in sleep quality (100). A greater susceptibility to external arousal (101–105) [confirmed in animal models (106) but not always at the population level (28)] may also predispose the aged person to poor sleep. Additionally, putative changes in circadian rhythm amplitude (see section below), as evidenced by age-related increases in daytime napping and fatigue (3,8,33,40,43–45,50,53,55,63,65,107–110) and, possibly, increased daytime sleep tendency on the multiple sleep latency test (MSLT) or other daytime nap tests (111–122), may predispose to poor quality of sleep. However, Aber and Webb (119) showed that naps were not related to poorer sleep at night in the elderly, and younger populations may often report napping as well (123–126). Simple inactivity and bed rest, so common in the more infirm geriatric population, have been shown to disrupt sleep in younger subjects (127), and curtailment of daytime napping and bed rest may improve sleep in the elderly (128–133). Conditioning factors may be as important in perpetuating the insomnia of old age as in the insomnia of younger individuals (134,135). Levels of outdoor light exposure in elderly subjects, although not always significantly less than in younger subjects (136), have been speculated to predispose elderly subjects to poor sleep, and preliminary data suggest bright light as an effective treatment for poor sleep in the elderly (137). Finally, the roles of breathing disturbance and periodic leg movements (PLMS) in the disturbed sleep of the elderly are highly controversial and are discussed more fully in the section below.

It is tempting, given the host of medical and sleep-specific factors leading to poor sleep in old age (see also Sleep architecture, below), to dismiss the role of psychological influences in the sleep of the aged. This perspective, however, tends to ignore the increased salience of late-life psychological issues in the genesis of sleep disturbance. Factors relevant for geriatric populations such as bereavement (138–141), retirement (142), holocaust trauma (143) and fear of death in sleep (144) can disrupt sleep, as can anxiety (145–147) and depression (27,32,67,147–151). In addition, there is only mixed evidence that the associations between psychopathology and disturbed sleep, so well demonstrated in younger patients, are in any way abated in geriatrics (87,145–147,152–154). This issue can be quite complex, however, as elderly individuals without psychiatric history undergoing bereavement may develop depression that, on the basis of polysomnographic findings, may appear very much like major depression (141). Habte-Gabr et al.'s (82) data suggest that in an elderly rural population, physical diseases were associated with poor sleep, but club membership, active involvement in religion and having a close friend were all associated with better-quality sleep. Finally, in a longitudinal epidemiologic study, Rodin et al. (149) have reported that although poor physical health predicted a wide variety of disturbed sleep symptoms, depressive mood was at least a powerful predictor. Taken together, these data even suggest the development of potential causal models in which illness, disease and life events may not directly affect sleep, but rather induce dysphoria, which then may result in sleep disturbance (141). To the extent that adequate social supports may be available, these may serve to buffer the effects of disease on sleep. Tests of such causal models with path analysis have not proved fruitful to date in middle-aged women (155).

Sleep architecture

Over the years, a large number of studies have reported on age-related changes in polysomnographically defined sleep architecture in the elderly (74,76,156–183). Many of the earlier studies have not reported on (or, in some cases, recorded) respiration and leg movements in these subjects, thus raising the possibility that any or all of the changes in sleep architecture could be secondary to the SRRD and PLMS highly prevalent in the elderly. This is understandable given the relative recency of the discoveries involving breathing disruption and periodic movements in sleep. Even in those newer normative studies excluding elderly subjects with these conditions (often on the basis of single-night screenings), the highly variable nature of both SRRD and PLMS in the elderly (184–191) and their virtual omnipresence in at least mild forms (116,117,192–199) leaves open the possibility that many sleep architecture changes in old age could be reflecting such intermittent events (116,192,193,200–202), although not all data concur (117,203). Moreover, the interaction between sleep architecture and breathing disturbances and leg movements may be complex, and causality cannot be assumed to be unidirectional, i.e. intermittent events causing sleep disruptions. It may well be that disturbed sleep predisposes the aged individual to such apparently pathophysiological events. For example, stages 3 and 4 sleep are associated with the occurrence of fewer breathing disruptions (202,204–209) and periodic leg movements (PLMs) (206,210), and instability of sleep/wakefulness has been speculated to be the mechanism underlying SRRD in the aged (204,211). The possibility thus exists that the presence of slow wave sleep in the elderly might even be protective in some sense, although there is no evidence to support this hypothesis at this time.

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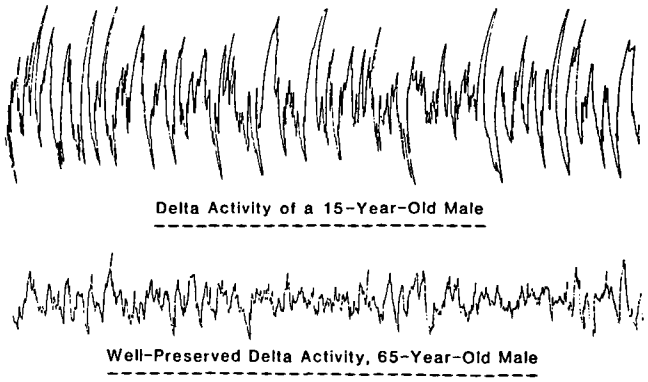

FIG. 1. Example of age differences in delta activity amplitude. Note decline in delta amplitude in the 65-year-old relative to the adolescent. (From reference 785.)

Although it can be misleading to generalize figures across studies because of known differences among laboratories and scorers, there is general uniformity on age differences in most polysomnographic measures of sleep disturbance. Nocturnal sleep efficiency decreases to approximately 70–80%, and the percentage of stage 1 increases to about 8–15% in the elderly, although both sets of figures vary to some degree with the age and sex of the subjects. A recent meta-analysis of polysomnographic data showed that older women, for example, may sleep somewhat better than older men (212), which contrasts with the self-report data mentioned above in which elderly women typically report more sleep complaints than elderly men. In addition to these measures of sleep disruption, transient arousals (111), consisting of brief episodes of alpha intrusion in sleep lasting between 2 and 15 seconds, may occur very frequently both in association with SRRD and PLMs as well as independently, although they may be difficult to score reliably (213). Newly developed templates for brief arousal scoring may be helpful in this regard (214). Nocturnal sleep latency may not be greatly prolonged in the elderly (161,162,168–170,175,215), which could be related to the slightly increased sleep tendency seen in geriatric subjects in some (111,112), but not all (122), studies with the MSLT. Animal studies have generally confirmed these age-related changes in sleep fragmentation (216). In addition to these changes in humans, spindling amplitude, duration and amount all decrease with aging (217,218).

The most easily recognized age-related change in a sleep stage is the decrease in slow wave (stage 3 and 4) sleep, which Feinberg's early data (177) suggested to occur primarily in the first nonrapid eye movement (NREM) cycle, a finding now confirmed in other analyses (165,166,219–221). The precise age at which slow wave sleep declines has yet to be determined conclusively, although some studies suggest a decline may be seen by age 20 (see section below, Maturation and aging). In extreme old age (over 90), stages 3 and 4 may disappear completely (222), and computer analysis of delta activity suggest age-related declines can be seen when comparing individuals in their 70s and 80s (166). A recent meta-analysis found little evidence of an age-related decline in visually scored slow wave sleep above age 20, although interlaboratory and interscorer differences probably affected these results more than for other visually scored sleep architecture measures (156). Computer analyses have suggested that the decline in delta is best characterized as a decrease in the amplitude of the slow wave activity (Fig. 1), although a slightly higher frequency of delta may be seen as well (220,221,223,224). Some researchers have proposed that the usual (75 μV) amplitude criterion for delta activity be abolished for old age (225), thus correcting for the absence of delta by scoring only for frequency. To more easily accomplish this, the visual appearance of delta could be altered by increasing amplifier sensitivity. Studies adopting such a definition have effectively eliminated age differences in slow wave sleep both cross-sectionally (226) and longitudinally (227). The potential merit of such alterations in conventional scoring and recording procedures would be the greater validity of such age-corrected slow wave sleep data. However, because the functional significance and mechanism of delta activity remains obscure, such normalization procedures remain premature. At any rate, it has been suggested that because the greatest age differences in delta amplitude occur at low amplitude (5–20 μV), abolishment of a minimal amplitude criterion may not only inflate the quantity of stages 3 and 4 sleep in older persons, but also inflate these stages in younger persons (223,228). A number of studies have shown that older women have better-preserved slow wave sleep than men (158,159,166, 168,169,229,230), and although not all studies show this (160,171,172,176), recent computer EEG analysis has confirmed this finding (166,231). Dijk et al. (232) have contended that the gender difference in slow wave sleep in the elderly is also discernible in younger persons as well and predominantly reflects extracerebral factors, such as skull thickness.

Despite the uncertainty regarding gender differences in delta activity in old age, age effects per se in delta have been confirmed in other species. The age-related decline in slow wave sleep has been shown for other mammalian species, such as the mouse (233), cat (234–236), rhesus monkey (228,237) and baboon (228,238). Because the EEG in these animals is recorded from the dura, these findings indicate that extracerebral factors are probably not involved in the age-related decline in delta activity. Additionally, in the aged cat the female predominance in delta activity has also been noted (235,236), arguing against skull thickness as the exclu-

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sive mechanism for gender differences in delta activity. Delta activity may not decrease with age in rats (239–243), perhaps reflecting the relative stability of the cortical neuron pool (244). However, in some species of rats the decline may still be seen (245), implying that strain differences may influence expression of delta activity in sleep (216,243).

Disagreement exists regarding whether the proportion of nocturnal sleep spent in rapid eye movement (REM) sleep (i.e. REM percentage) varies with aging. Many studies have reported data indicating that REM percentage does not vary appreciably with aging (157,161,169,231,246,247), but other studies have suggested relatively low REM percentages in the aged (160,168,170,176,178,215,248) or negative relationships between REM percentage and age (171). Benca et al.'s (156) recent meta-analysis shows some evidence of a decline in REM time and a lengthening in the duration of the first REM period with aging. Even when age differences are observed, the magnitude of the findings is certainly not impressive. Perhaps some of the disagreement involves the fact that REM percentage can be manipulated in a quasiartificial manner by allowing different lengths of sleep (i.e. adjusting wake-up times). Because the laboratory environment can never mimic a true ad libitum sleep situation (unless the studies are performed in a time isolation protocol), REM percentage may simply be an inherently less stable parameter (249). Thus, if REM percentage declines with normal aging, the effect is not of sufficient magnitude to overpower these confounds across studies. It is of interest, however, that for six elderly subjects studied in a time isolation facility, REM percentages were reduced (248), although in a later report entrainment and free-run conditions resulted in similar REM fractions in older subjects (250). Gender differences in REM percentage in old age are inconsistent (212).

Laboratory studies of REM sleep amounts in other mammalian species also yield equivocal results. Although reductions in REM sleep (as a function of 24-hour recordings) have been shown for the aged cat (234,236), rat (240,242,245,251) and mouse (233), contradictory evidence also exists for the last two species (239,252,253). Again, interactions between age and strain of animals suggest a genetic component in the manifestation of age patterns in sleep (216,233, 242,243,245).

Age differences in the duration of NREM sleep prior to the first REM period of the night (REM latency), with older subjects showing shorter latencies than younger subjects, have been shown in some studies of normals and depressed patients (156,157,161,171, 172,177,219,231,248,254–256). However, some find the effect only in the latter (257,258) (Fig. 2), and the result may be a function of the decreased stages 3 and 4 sleep within that cycle as a function of aging (219,259). Consistent with this, REM latencies are usually longer in older women than older men (212). One additional possibility in explaining short REM latencies in aged individuals is an age-related change in the circadian timing system. Specifically, if the core body temperature curve is phase-advanced relative to sleep onset, an early onset REM might be predicted. A study by Weitzman et al. (248) comparing young and old individuals in time isolation provides some support for this. They observed a shift of REM sleep earlier in the night, with less REM occurring later in the night concurrent with a shorter period of the temperature cycle in older subjects.

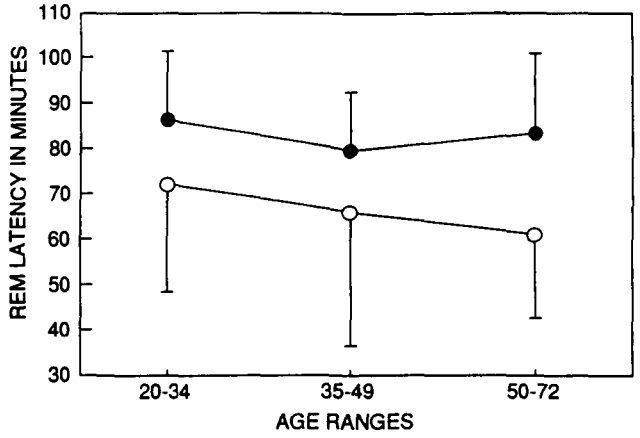

FIG. 2. Means and standard deviations for REM latency as a function of age in control subjects (closed circles) and depressed patients (open circles). In this study, age effects were significant only for the depressed patients. REM latency was defined as the time from beginning of persistent sleep (10 consecutive minutes) to first epoch of REM, including wakefulness. (From reference 257.)

Based on Reynolds et al.'s (260) contention that differences in sleep parameters between normals and depressives should be more pronounced in the elderly, several recent meta-analyses have attempted to examine standardized differences between such groups as a function of age when studied (156,261). [Age of illness onset would not appear to have pronounced effects (262).] The results of these studies suggest that aged depressives show relatively lower sleep efficiencies than aged controls and that those differences are more pronounced than in younger patients and controls. Findings with REM parameters (including REM latencies) are somewhat more ambiguous, whereas results with visually scored slow wave sleep show no evidence of differential age effects across depressives and controls, perhaps due to a "floor" effect (156,261) or inter-laboratory scoring differences (263,264). As a final note on this issue, Vitiello et al. have suggested that if elderly normals and depressives are recruited from the community rather than clinical referrals, there are few differences in sleep patterns (81).

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Maturation and aging

The point at which age-related decline in delta activity actually begins has been subject to controversy. The normative values reported by Williams et al. (168) show significant differences between ages 16–19 and 20–29 in women and between 20–29 and 30–39 in men for percentage of stages 3 and 4 sleep. In addition, other studies have shown apparent age differences in stages 3 and 4 sleep when comparing 19–21-year-olds with 22–24-year-olds (265) or 15–24-year-olds to 25–34-year-olds (161). Feinberg (177) showed that 11.8–16.2- and 17.6–23.8-year-olds differed significantly in stages 3 and 4, regardless of sleep cycle. Later studies using automated analysis showed negative relationships between age and the number of delta zero-crossings (266) and delta amplitude (266,267) in young adults in their 20s, although a replication by Feinberg et al. (268) found only the former. Delta wave counts showed a 50% reduction when men 21–30 were compared to men ages 31–40 (165), and Smith et al.'s (223) data showed a significant difference in delta amplitude in males on the order of 30% between childhood and age 13 and 65% between childhood and 30 years of age. Using spectral analysis Astrom and Jochumsen (269) reported negative correlations between delta power and age in an 18–28-year-old group. Perhaps even more provocative are results suggesting declines across adolescence per se (270–272), including Tanner stage I–V (273). Because some of these data were longitudinal, extracerebral factors (232) were probably not major factors in accounting for these age differences, although slight changes in cranial thickness during final stages of pubescent growth might conceivably have played some role. Additionally, at least some data suggest that age and head size predict delta activity independently within young adults of restricted age range (267). As a corollary to this, the enormous individual differences in slow wave sleep seen in some studies of young adults (249,274–276) probably reflect both extracerebral and age-related factors.

Assuming the validity of such age-related changes, the question then arises as to the interpretation of these results. Feinberg et al. (277) have contended that such changes are likely to reflect normal maturational processes, reflecting declining cortical metabolic rate, increased dendritic pruning and decreased cortical synaptic density, which may, in some cases, become aberrant and lead to psychiatric disorder. An equally plausible, and perhaps more parsimonious, assumption is that such changes represent an extremely early biomarker of aging within the central nervous system. This would link aging processes to attainment of reproductive maturity, a model supported by a body of evidence in a number of mammalian species (10,278,279). When viewed from the historical window of human evolutionary history, evidence of aging at such a young chronological age is not nearly as incongruous as it appears. From the standpoint of physiological age, it is important to bear in mind that human life expectancy prior to the development of modern civilization was on the order of 20–30 years (280). Declines in delta activity across adolescence may thus very well be an evolutionary remnant of the initiation of senescent processes.

Changes in sleep need with age

One of the common "myths" regarding aging and sleep that, depending on one's point of view, has been variously espoused or maligned, is that the need for sleep does not change with age. Arguments for and against this notion have waxed and waned over the years (158,177,228,281–289), often on the basis of single findings one way or the other. Rechtschaffen (290) has argued cogently that the construct of sleep need must be configured from a converging matrix of findings not limited to a particular method, type of study or type of subject. Methods yielding data regarding age-related changes in sleep need include both correlational and experimental approaches. Sources of data include descriptive studies of sleep amounts (sleep quotas) and studies of sleep deprivation effects and other experimental manipulations (e.g. exercise, sleep interruption). Elucidation of age-related sleep need can also be made using both human and animal data, albeit with the caveat that species differences may exist and limit generalization.

Among nonexperimental paradigms, the simplest approach to the construct of sleep need is simply to look at sleep quotas, the amount of sleep individuals typically obtain as they age. Although many polysomnographic studies (158,161,162,167–170,175) and some surveys (31,40,42) have shown reduced sleep times in the elderly, not all survey data concur. These surveys suggest no change, or even increases in sleep times with age (c.f. forementioned data on nocturnal awakenings with aging) (33,37,44,45,50,53–55,63,66, 82,228,291). Some of these studies include napping in their totals, thus implying a redistribution of sleep around the 24-hour day. If, in fact, net sleep amounts do not change with aging, the need for sleep may be just as strong in old age, but that need may be met differently. Napping in old age, however, cannot simply be equated with unfulfilled sleep need, because both cultural (53,292) and social (e.g. retirement) (293) factors as well as boredom (294) undoubtedly play a role. Physiological studies of daytime alertness in elderly subjects demonstrate enhanced pupillary miosis (295), possible decreased (parietal) P300 amplitude (296),

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indicative of sleepiness (297), and in some (111–113,119,121), but not all (114–118,120,122,298), studies, enhanced sleepiness on the MSLT or other daytime nap tests. All provide some additional support for the notion of a modified expression of sleep need. The presence of SRRD may provide a partial, but not complete, explanation of such increased sleepiness (see below). Despite these data, most animal studies suggest that total sleep time per 24 hours may decrease with aging (240,242,245,251), at least in rats in a 12:12 light/dark schedule, although these changes may be less apparent in aged mice or cats (236,252). Such evidence for a decreased need must be tempered by the known age-related redistribution of sleep around the 24-hour day in rats under 12:12 light–dark (240,242,245,251) but not constant conditions (299). Thus, the data from other species are not always consistent with the human data in implying no fundamental alteration of sleep need.

Among experimental paradigms, the most frequently used putative manipulation of sleep need in the elderly has been sleep deprivation (300–314). Deprivation effects on physical functioning appear similar in young and elderly subjects (310), although an early animal study (313) suggested greater effects in aged rodents. Although the focus of a number of the more recent studies has been the use of sleep loss to assist in the differential diagnosis and understanding of late-life psychopathological syndromes (302,303,305), these studies are also of interest because of their examination of sleep deprivation effects on sleep length and stages. Most studies show increases in total sleep times (TST) following 36–40 hours (301,303,305,306) or 64 hours (304,308) of sleep loss. In one study, elderly insomniacs undergoing 64 hours of sleep loss showed recovery increases in TST of over 90 minutes, which essentially made their postdeprivation sleep equivalent to good-sleeping elderly subjects (308). However, in another report of 36 hours of sleep loss, neither elderly depressives nor demented patients showed such a "renormalization" of sleep length. However, significant increases in TST were noted. As for slow wave sleep (SWS), several early studies of aged subjects (307,311,312) demonstrated increases in stages 3 and 4 sleep in postdeprivation recordings limited to the first part of the night. These have now been confirmed in whole night studies under conditions of 36–40 hours (301,303,305,306) and 64 hours (304,308) (Fig. 3) of total sleep loss, but not necessarily for REM deprivation per se (302). The rebound of SWS in the elderly is most clearly seen in the first, relative to the second and third, recovery night (Fig. 3) (308). Perhaps related to their higher baseline levels of SWS, women may show the SWS rebound effect more dramatically than men (306). REM sleep results are more complicated

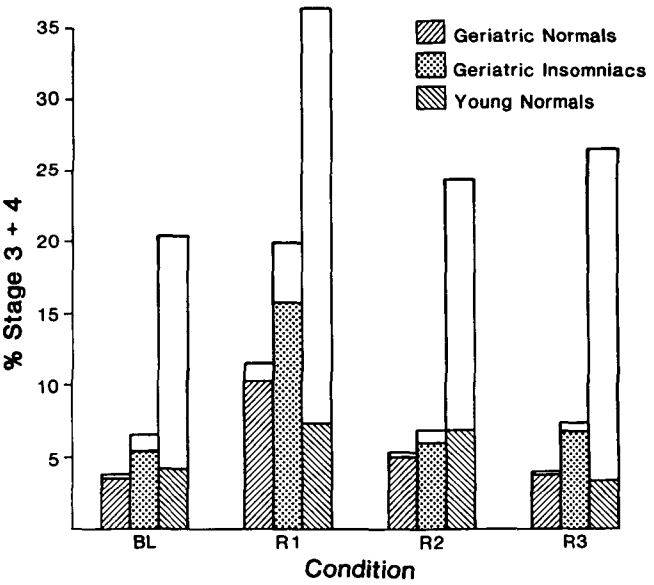

FIG. 3. Changes in slow wave sleep (stages 3 + 4 %) following 64 hours of sleep deprivation in young and elderly subjects. Code for nights is as follows: BL (Baseline); R1–3 (Recovery Nights 1–3); shaded area is percent stage 3; white area is percent stage 4. Note maximal increases in SWS occurring only on R1 for elderly subjects. (From reference 308.)

to interpret (315) because REM percentage has been reported to increase (301), decrease (303) or not change (305,306) following sleep deprivation. REM latency, however, has been shown to increase postdeprivation in both depression and dementia but decrease in controls (303,314). The latter result was also noted by Bonnet (304). In a later study of selective REM deprivation, Reynolds et al. (302) noted that during recovery sleep most REM measures showed predictable patterns of response (greater number of REM periods, higher REM %, reduced REM latencies, higher REM density), regardless of diagnostic group, although on the deprivation night some differential diagnostic group interactions were observed.

Taken as a whole, these studies of experimental sleep deprivation again suggest that, although some differences by diagnosis, gender, amount of sleep loss incurred or particular variable under consideration may exist, the fundamental homeostatic response to the sleep loss in elderly humans is preserved. However, this probably represents an oversimplification of the results. Carskadon and Dement (301) noted that most aspects of sleep architecture were modified only on the first night of postdeprivation recovery sleep in their elderly subjects, whereas in younger subjects the effects persist for several additional nights. Similar results were reported by Bonnet and Rosa (308). Age differences in MSLT-defined daytime sleepiness following sleep deprivation (301) or sleep interruption (105) also suggest more rapid recovery in this measure as well in older relative to younger subjects. Also, during sleep depri-

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vation elderly subjects appear to have fewer "microsleep" episodes than younger subjects (316). Furthermore, when the outcome under consideration is neither sleepiness nor nocturnal sleep architecture but rather performance measures, a number of studies have suggested that older subjects, particularly if they are poor sleepers (300), appear less affected by sleep loss than younger subjects. The older subjects also return to baseline levels of performance more quickly—or at least no more slowly (301,308,309,311,314,315,317)—than younger subjects, although some ambiguous evidence also exists (315,318–320). For example, Brendel et al. (314) noted that hit rates on the Mackworth clock test (a test of vigilance) were reduced about 20% post sleep deprivation in young adults, but were unaffected in the elderly. Additionally, there can be little doubt that in a baseline situation elderly persons perform more poorly on measures of vigilance (115,321–324).

Several other lines of experimental evidence suggest that sleep need may be altered in old age. For example, elderly individuals may be more susceptible to poor sleep on the first laboratory night, yet subsequent nights showed no more effects than younger subjects, arguing for a reduced effect on sleep stages (325). Again, other studies suggest that this is a controversial finding (170,326,327). Elderly subjects' sleep may also respond differently to exercise than that of younger subjects (328–330) in terms of sleep stages, although at least one study implied that exercise effects on sleep are more difficult to detect in fit elderly subjects (331) and existing self-report data imply similar effects in young and old subjects (332,333). Although they were unable to find exercise effects on sleep in fit or sedentary elderly volunteers, Edinger et al. (330) reported larger numbers of delta waves in fit elderly subjects in baseline conditions. Regardless of the results of these and all of the above-cited studies, it is clear that to speak of continued sleep need (or modification thereof) in old age is an overly simplistic concept, which is not consistently and unequivocally supported by the existing knowledge base. Studies generally show divergent results, which can be variously construed as evidence for an age-related decreased need, an unchanged need, an unchanged need but deficient mechanism or perhaps an alteration in type of need (286). The ability to sleep may remain unchanged. Moreover, many of the studies used to examine sleep need in relation to aging, particularly those involving the possible redistribution of sleep around the 24-hour day, fit as well with putative alterations in circadian rhythm-related processes as with age-related alterations in homeostatic mechanisms. Finally, it must be recognized that any examination of sleep need presupposes a thorough understanding of sleep function. Until the latter issue is more completely evaluated, it may be impossible to discuss age-related changes in sleep need.

Circadian rhythms in aging

Age-related changes in the redistribution of sleep–wakefulness alluded to in the preceding sections represent only a small piece of a complex array of age-related chronobiological changes in physiological functions, including body temperature, the endocrine system and numerous blood constituents. Some have even considered the temporal disorganization of physiology as the fundamental characterization of the aging process (334), and one early study reported marked asynchrony in diurnal variation among a wide number of physiological variables in aged humans (335). The studies reviewed in this section generally have derived from the well-known observations of about 20 years ago, in which experimentally induced lesions of the suprachiasmatic nucleus (SCN) of the anterior hypothalamus in animals resulted in arrhythmicity in a variety of physiological systems, including sleep–wakefulness (336–338), drinking and locomotor activity (339,340), temperature (338,340,341), corticosterone (342) and pineal activity (343). More recently, partial ablation of the SCN has been shown to result in decreases in rhythm amplitude and reduction in free-running periods (344–347). In humans, a region homologous to the SCN has been described (348) and has been shown to decrease in size with aging, at least above age 80 (349). Below this age, the effect may be more pronounced in women (350). The neuronal loss in both animals and humans is thought to be predominantly vasopressinergic (351). These data thus suggest that the aged human may undergo changes in circadian rhythms paralleling those alterations seen in animal models.

Inference of age-related changes in circadian rhythms in humans relies almost exclusively on indirect evidence. Endogenous circadian rhythms can only be studied in an environment free from time cues (i.e. under "free running" or "nonentrained" conditions) or under protocols of constant routine, where factors such as activity, posture, food intake and sleep itself are rigidly controlled (352,353). Under entrained conditions, masking effects obscure any appraisal of the presence or absence of underlying endogenous rhythms as well as introducing the possibility that the entrainment mechanism itself may vary with aging. Despite the inherent limitations of such data, a large number of studies examining age differences have occurred and some consistencies have emerged. For example, the apparent age-related redistribution of sleep/wakefulness across the 24-hour day, as inferred from increased napping, fatigue and perhaps daytime sleepiness men-

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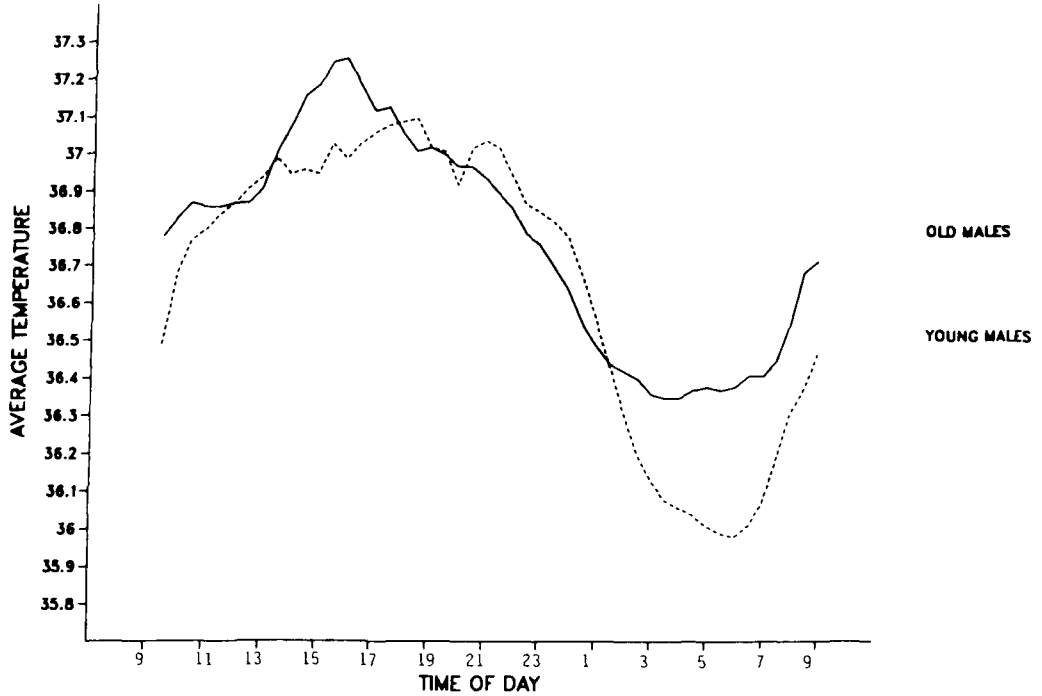

FIG. 4. Rectal temperatures in young (dotted line) and old (solid line) men showing apparent decreased amplitude and earlier phase in body temperature cycle as a function of aging under field (entrained) conditions. (From reference 356.)

tioned above, suggests a decline in the amplitude of this rhythm. This finding, under entrained conditions, has received some corroboration in different species as follows: in humans body temperature in most (248,335,354,355,356) (Fig. 4) but not all reports (357,358), urinary electrolytes (359), leukocytes and neutrophils (360), renin and aldosterone (361,362), plasma beta-endorphin (363,364), and, possibly, melatonin (365–372), thyroid-stimulating hormone (373,374), testosterone (375–378) and prolactin (366,379,380); in rodent species such as mice and rats—sleep/wakefulness (240,242,245,252,253), rest activity (381–384), body temperature (385–388), testosterone (389) and melatonin (390–392). These findings are not corroborated in cats, whose sleep/wake cycle may be more capricious (236). Wax's series of studies in aged mice (393–395) have not shown consistent age differences in the amplitude of activity, but older animals self-selected more changes in illumination. This could be construed as evidence of breakdown of the endogenous oscillator. Strain differences, however, interacted with age effects in these studies. The breakdown of rhythm amplitude in sleep and locomotor activity in aged female rats was related to postestrus status in several studies (383,396). Neither cortisol nor ACTH show marked declines in rhythm amplitudes in aged humans (397–403), although in animals the data are more equivocal (404–406). Human growth hormone also shows an age-related decrease (407), but this is usually considered to more closely reflect age-related changes in sleep than in circadian dysfunction (96). Although attenuation of the amplitude of any such rhythms in themselves could reflect diminished capacity of a given physiological system to respond to a central circadian signal, decreased amplitude of the endogenous oscillator is often considered to contribute, at least partially, to the observed findings (351,408,409).

Despite these results with other physiological variables, studies of human age differences in simple rest activity amplitude in entrained environments often show conflicting results suggesting both more robust (410) and less robust rhythm (411) amplitude. Similarly those few polysomnographic studies of sleep/wakefulness attempting to examine both nocturnal sleep and spontaneously occurring daytime sleep generally show that few elderly subjects elect to nap under these circumstances and that napping, when it does occur, occupies only an exceedingly small proportion of total sleep (215,229,230,247). These results thus imply fairly well-preserved rhythm amplitude of the sleep–wake cycle. Given the above-cited studies of most other physiological rhythms, age-related alterations in sleep/wake rhythm amplitude may be particularly susceptible to masking effects (see below).

In addition to data on putative rhythm amplitude under entrained conditions, a number of studies have yielded data on possible age-related alterations in phase relationships among physiological functions showing diurnal patterns. In parallel with studies suggesting earlier bedtimes and wake up times in the aged (3,33,

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44,45,50,53,63,65,82,107,110,410,412–414), some human studies have implied earlier acrophases for body temperature (98,248,354,356,415) (Fig. 4) (see also 355), TSH (379), protein-bound iodine (401) and cortisol (365,366,399,400,416). However, the evidence is mixed in studies of melatonin in humans (365,370) and body temperature rhythms in animals (388,417, 418). As mentioned previously, the decreases in REM latency (length of first NREM period) can also be interpreted to reflect such alterations in the body temperature cycle (419).

A possible sexual dimorphism in the shape of the human SCN and the possibility of a more pronounced age-related decline in females (350) raises the possibility that some aspects of circadian rhythms could be manifest differently in elderly men and women. Under entrained conditions, earlier acrophases in elderly women relative to elderly men have been noted in body temperature (98,420,421) and total and unbound cortisol (400) [although not in activity (410)], which may be related to the earlier bedtimes and/or wake up times in women seen in some (420) but not all studies (44,45,53,82). Similarly, larger rhythm amplitudes in body temperature (420,421) and prolactin (366) in elderly women relative to elderly men have been noted, although these results were again not seen in rest activity (410) or total protein (422). The temperature amplitude data are consistent with the somewhat stronger evidence that in many studies elderly men may show greater daytime levels of daytime tiredness and sleepiness than elderly women (3,8,109,118,412) (but see 230). However, this predominance of daytime tiredness in aged males could reflect the male predominance in SRRD (see below) and associated sleepiness. This serves again to illustrate the complex multidetermined nature of any particular sleep/wake symptom in the aged. Measures of general well-being and sleep quality have related inconsistently to cosinor-derived measures of circadian rhythms (358,420), but elderly depressed patients have been shown to have relatively later acrophases of activity relative to aged controls (423). In addition, an early study based on retrospective self-reports concluded that longevity itself may be associated with early bedtimes and wake up times (424), which again raises the issue of whether certain aspects of sleep and rhythms may lead to more "successful" aging (9). There is also evidence suggesting that increasing age is associated with more "lark" than "owl" tendencies (425,426). Monk et al. (426) reported greater homogeneity in bedtimes and wake-up times of elderly subjects relative to younger subjects.

Very few studies reflect age differences in human endogenous circadian rhythms recorded in free-running conditions. Wever (427) reported that seven of his 10 oldest subjects (ages 40–70) living in time isolation showed real internal desynchronization, compared to 22% of his younger subjects. It is unknown whether internal desynchronization, consisting of several independent oscillating rhythms (e.g. activity and temperature) with different periods in a steady state, may be related to the asynchrony of physiological measures seen in entrained conditions. As originally reported, this study found no evidence of age-related changes in period length of the free-running temperature rhythm. However, Monk (428) has reanalyzed Wever's data to suggest that in women over 40, a strong negative correlation between age and period length was present. Weitzman et al. (248) studied the sleep–wake and temperature rhythms of six young and six nondemented elderly men under temporal isolation. They reported no internal desynchronization. The free-running period of the sleep–wake cycle did not differentiate the young and old groups, although the period of the body temperature cycle was shorter in the elderly. Similar results were presented by Monk and Moline (250). The Weitzman et al. study (248) also reported that older subjects slept less than younger subjects, despite the fact that they chose more time for sleep (longer dark periods). Because subjects were instructed to avoid napping, however, these results may be less relevant for age-related changes in total sleep across the circadian day.

In animal studies made in constant conditions, the free-running period (tau) of locomotor activity was shown to shorten in relation to aging in the early longitudinal study of Pittendrigh and Daan (429) using hamsters and deer mice and later confirmed in the former species (430). Cross-sectional comparisons of young versus old animals showing age-related shortening of tau have also been reported (299,431,432). However not all cross-sectional data concur (351,383,409), and some studies in mice even suggest an increase in tau in aging (393–395). These data again raise the possibility of strain/species differences. However, differences in method across studies, including age of the particular species under study in relation to overall life span of that species as well as selective attrition (operating in cross-sectional data), could have played a role. These points are elucidated in greater detail by Richardson (351) and Brock (409). Also relevant for any discussion of aged-related changes in tau are the results of Edgar et al. (433–435), which suggest that in young mice, activity feedback serves to shorten the free-running period. Because absolute levels of locomotor activity decrease with aging in the mouse (393,394), activity restriction could differentially effect tau in older relative to younger animals.

More recently, Czeisler et al. have employed a "constant routine" protocol to unmask endogenous rhythms as a function of age without the confounds of light/

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dark, activity, posture, food intake and even sleep itself (352,353,436,437). Results from these studies confirm a phase advance of about 90 minutes and a reduced amplitude of about 30% in the body temperature rhythms of older relative to younger subjects (352,353,436–438). About 40% of the elderly subjects reached their temperature trough before 4:00 a.m., although wide intersubject variability was noted in the aged subjects (436). Appropriately timed (evening) bright light successfully delayed the rhythm (437). Preliminary data suggest that early morning awakening insomnia in the elderly was primarily associated with the phase advance in the temperature cycle, whereas multiple nocturnal awakenings were more closely related to decreases in amplitude (438). Somewhat different results have been shown by Monk et al. (356,428,439), whose data suggest that, under the constant routine protocol, young and elderly subjects differ very little on body temperature rhythm amplitude, whereas under entrained conditions the predictable differences in amplitude (young > old) existed. These results raise the possibility that age-related alterations in the mechanisms of entrainment and/or responses to zeitgebers may be different in young and elderly subjects. These changes account for the generally consistent differences in amplitude between young and old subjects seen in many of the above-mentioned studies under entrained conditions.

Evidence for age-related decrements related to entrainment comes from a variety of sources, including both naturalistic and experimental studies of phase-shifting tolerance. Naturalistic studies of shift work and jet lag suggest that older subjects have disproportionate sleep disturbance relative to younger subjects (440–445). This has been confirmed polysomnographically (446), although one laboratory simulation could not produce the effect (447). Some multivariate data even suggest age to be the single most predictive factor of sleep disturbance among shift workers (448). Reinberg et al. (449) reported that the amplitude of entrained temperature rhythm (as assessed with cosinor analysis) in older refinery workers was inversely related to shift work tolerance, i.e. greater tolerance with higher amplitude rhythm. In a later study, however, stability of temperature acrophase vis a vis the sleep/wake cycle appeared to be a more important factor (450). Gander et al. (441) have also noted that older flight crews (age 50–60) with lower amplitude temperature rhythms experienced greater sleep loss than younger flight crews, whose temperature rhythms appeared more robust. Again, relationships between time of temperature nadir and sleep quality were less straightforward. However, among nurses 22–49 on shifting schedules, increasing age and sleep disturbance were not related to temperature rhythm amplitude (451), perhaps owing to the younger ages of the subjects. Preliminary experimental results of a 6-hour phase advance suggest that temperature rhythms (both acrophase and amplitude) adjust more quickly in older subjects relative to middle-aged subjects (356), although REM sleep occurrence, presumably dependent on the temperature cycle, was essentially unchanged (452,453). Both this (452) and another study (454,455) suggest that sleep quality is differentially impaired with advancing age even under a 6-hour phase advance, thereby confirming the vulnerability of sleep disruption in old age cited above.

Among animal studies, Rosenberg (456) reported that the sleep of older rats took longer to re-entrain to a 180-degree light–dark phase shift than younger rats. More recently, he reported that sleep of older hamsters entrained to an 8-hour phase advance in less time than younger animals (457), and a preliminary phase response curve has been noted (458). Attempted 8-hour phase delays were uninterpretable due to masking. Studies of phase-shifting primarily measuring locomotor activity generally show similar results (459). In another study of rhythms of activity, food intake and water intake, entrainment did not occur at all in some aged animals (381). More recently, age differences in similar phase shifts in enzymatic activity of the pineal have been noted (460). Mistlberger et al. (461) have reported possible age-related deficits in food-entrained rest-activity rhythms in the rat.

Despite this fairly consistent body of evidence in both humans and animals suggesting age differences in entrainment mechanisms, the precise nature of the deficiency is not well understood. For example, it is unclear whether under nonphase shifted conditions deficient entrainment is a consequence of reduced exposure to relevant zeitgebers or an actual dysfunction of input to the core oscillator. Monk (428) has raised the possibility of impoverished time cues in the often home-bound, socially isolated elderly subjects, but studying such subtle cues may prove to be tedious. In one recent study, age was positively correlated with napping regardless of whether the older subject lived alone or with a partner. However, advancing age was correlated (negatively) with bedtime only if the subject lived alone (462). On the other hand, adequate signal transduction, at least through visual pathways, would appear to be intact in older non-demented humans without visual impairment given preliminary data suggesting positive effects of bright light in improving sleep quality (137). Taken as a whole, these results appear to indicate that the entire psychosocial milieu may assume far greater importance as zeitgebers in old age, particularly in view of at least partial deterioration of the core time-keeping mechanisms themselves.

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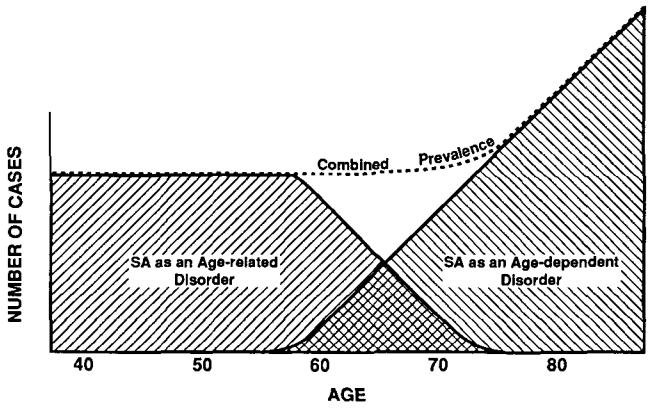

FIG. 5. Heuristic model suggesting sleep apnea as both an age-related and age-dependent condition with potential overlap of distributions in the 60–70-year-old age range. Cross-sectionally note that the number of cases observed may remain high and increase with age, despite a presumed decrease in age-related sleep apnea. See text for a more complete description of evidence in support of such a dual-condition model. (From reference 786.)

Sleep pathology: Sleep-related respiratory disturbance (SRRD) and periodic leg movements (PLM)

SRRD

A huge body of knowledge has accumulated over the last decade concerning impaired respiration during sleep. Excellent summaries of this literature can be found elsewhere. The purpose of this section is to discuss SRRD in relation to chronological age, particularly as to whether various symptoms, risk factors, mechanisms, morbidity and mortality may be differentially associated with SRRD in the aged. If the constellation of any or all of these factors appears substantially different in older, relative to younger, populations, this would lend credence for the heuristic model for SRRD and aging shown in Fig. 5 (463). To the extent that such associations are unaffected by chronological age, a unitary model, simply showing the parabolic increase in prevalence by age, may be more appropriate.

There can be no question that, on the basis of clinical case series, the occurrence of breathing abnormalities in sleep increases with age, at least up to age 60 (74,76,167). Snoring has also been investigated in a number of populations across the life span and shows clear age-related prevalence (464–467), at least up to age 80 (468), although some studies place a window of vulnerability at a somewhat younger age (469–473). Some have interpreted the latter data as evidence for sleep apnea as two different conditions, one manifesting itself in middle-age (i.e. as a specific, age-dependent condition) and one occurring in old age (i.e. as in many other age-related conditions). The age effect may be clearer in self- rather than spouse-reported snoring (474), and absolute figures for snoring prevalence probably vary as a function of survey questions (475). Beginning with the early report of Webb (205), a number of cross-sectional studies of elderly subjects have shown relatively high age-related prevalence of SRRD (116,117,192,193,195–197,200,202,203,476–483). Additionally, several longitudinal reports note increases in SRRD in elderly subjects studied over time (484,485), although not all data concur (486,487). [This could be explained by the variability inherent in single-night studies (184,185,187–190).] In the most comprehensive series of the cross-sectional studies, Ancoli-Israel, Kripke and colleagues have demonstrated that 24% of the independently living elderly (over age 65) population, 33% of a similarly aged acute care in-patient population and 42% of an elderly nursing home population exceeded a minimal criterion level (i.e. apnea index of 5 events per hour) of SRRD (195,488). Given the aging of most industrialized societies, these figures indicate that enormous numbers, clearly in the tens of millions, of the over age 65 population incur some form of disturbed respiration in sleep.

Data related to type of respiratory events and gender do not strongly support a two-condition model. Although at one time SRRD in the aged was thought to consist predominantly of central apneas (76,167,489), most (192,200,202,476,490,491) but not all (196) newer data suggest that, even with surface transducers, the observed patterns are obstructive. Similarly, the male predominance in clinically significant sleep apnea, well recognized in younger populations, appears to persist in the elderly as well (117,192,195–197,200,476, 478,481). Several reports on nonclinical middle-aged populations show this as well (480,481,491–494), although some contradictory evidence (i.e. equivalent levels of SRRD in middle-aged men and women) has been noted (200). Postmenopausal women without clinically significant sleep apnea have been shown to have some benefit from progesterone and estrogen (495,496), although the effects of progesterone in younger male sleep apnea patients are largely negative.

Relationships between obesity, age and SRRD are complex. Most symptomatic clinic patients with sleep apnea are at least mildly obese, and normative data suggest increases in average expected body weight up through age 69 (497). If increased body weight represents a distinguishing feature of age-dependent SRRD (Fig. 5), then body weight might be expected to be a stronger predictor of measured of sleep apnea in middle age than in the elderly, when chronological age should be more salient. Among nonclinical middle-aged populations including middle-aged male snorers (498), hypertensive males unselected for snoring (499) and nonobese middle-aged men and women (480,481,491,493,500), the effect of body weight would

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appear at least as important as age. However, age effects on SRRD relatively independent of body weight have been shown in asymptomatic middle-aged individuals (484,501). Moreover, in nonclinical elderly populations, most studies with larger samples continue to show effects of obesity at least as powerful as chronological age (117,195,197), even above age 70 (197). However, smaller studies with less than 100 subjects may have difficulty seeing the effect (202,203,476,477). Several other brief reports of ongoing studies also bear upon this issue. One recent report suggested that age and weight effects can be clearly separated at various levels of obesity up through age 69 and that even among snoring men at least 140% above ideal body weight, aging represents an additive effect on both sleep disordered breathing and hypoxemia (502). Preliminary reports by Young and colleagues (492,494) suggest that age/obesity effects in individuals ages 30–59 may be mediated by gender such that body weight effects may be clearer in women, whereas age effects may be more pronounced in men. In men ages 30–59, a peak prevalence of SRRD was noted in the 50–54 age range (463). Finally, a preliminary report of a prevalence study of a predominantly Hispanic population presented a somewhat different picture in that across an extremely wide age range (18–89), only age (and not obesity) related to sleep disordered breathing (503). Although this literature may hint at a differential impact of obesity at different ages, the evidence is too equivocal at this point to firmly support a two-condition model. It may also be that commonly used measures of adiposity (body mass index, % ideal body weight) are too general to provide valid results insofar as this issue is concerned.

Regarding the two cardinal symptoms of sleep apnea (snoring and daytime sleepiness), there is little conclusive evidence that a substantially different pattern of relationship exists in older versus younger populations. The literature on sleepiness is somewhat less straightforward, however, perhaps owing to the complexity of assessing this symptom. Self-reports of snoring are widely acknowledged to lack sufficient positive predictive value, sensitivity and specificity relative to polysomnography (475,504–506). It is more relevant for the current discussion, however, to determine whether the pattern of association systematically differs by age. In a clinical population, patterns of association between reported snoring and sleep-disordered breathing were not affected by age or living alone (475). In nonclinical predominantly middle-aged (472, 499,507) and elderly populations (116,193,195), self-reported snoring did relate to measures of SRRD.

Different assessments of daytime sleepiness often show discrepant results relative to age effects and SRRD. The most customary objective measure of daytime sleepiness, the MSLT, was shown to relate to SRRD in a few studies of elderly volunteers (111,476,508), but a larger, more recent study could not document this effect (117). A number of studies have reported MSLT or Maintenance of Wakefulness Test (MWT) findings in clinical populations with sleep apnea (509–512). Although the focus of these studies was typically on the relative contributions of disturbed sleep and nocturnal hypoxemia to the daytime sleepiness, some age-relevant effects have been reported. In two of these studies, older patients with sleep apnea were shown to be less sleepy relative to younger patients with sleep apnea (510,512). In one study, age had no effect (511), and one study confirmed greater levels of confirmed MSLT-defined sleepiness in symptomatic elderly clinic patients relative to asymptomatic, age and sex-matched, elderly controls (509). In the largest of these studies (n = 466), Roehrs et al. (510) noted that the most alert sleep apnea patients (who were older) also had fewer breathing disruptions and desaturations during sleep. Both middle-aged (513,514) and elderly (515) drivers with SRRD are more likely to have a history of auto accidents.

Because there is less consensus on how to inquire about subjective sleepiness, it is not surprising that even in clinical populations, many investigators fail to find strong links between measures of disturbed respiration in sleep and questionnaire assessments of somnolence (504,506,516), although some do (517), even in geriatric patients (518). This situation holds largely true in nonclinical populations, where subjective sleepiness in middle-aged subjects have been shown both to relate (498,519,520) and not relate (499,507) to measures of SRRD. Conflicting evidence also exists in the elderly subjects (116,117,193, 195,199,521). Because individual researchers typically ask about this symptom in a variety of different ways using a variety of time frames, it is difficult to evaluate differential effects by age. As a final note, however, it may be that more detailed questions provide less ambiguous data. In the San Diego studies of several geriatric populations (195,488,522), responses involving falling asleep at inappropriate times (e.g. when conversing, taking an unintended nap) were related to various measures of SRRD, whereas more global responses regarding daytime sleepiness did not (195).

Age-related changes in upper airway function have been described by White et al. (523), who measured epiglottic pressure and noted strong relationships between increased pharyngeal resistance and age in asymptomatic males aged 25–77 during wakefulness. Similar correlations between increased age and reduced pharyngeal area were noted in slightly younger normal males, using acoustic reflection techniques (524). Neither of these studies found such age rela-

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tionships in women. For pharyngeal resistance and, possibly, area as well, these normative age-related findings reflect those seen in clinical sleep apnea cases (525–528). In a small group of elderly volunteers (all male), McGinty et al. (477) noted that 25% of subjects with SRRD showed elevated pharyngeal resistance, whereas only 10% without SRRD did so. Consistent with these studies suggesting vulnerability of airway to collapse as a function of age are studies suggesting that respiration in sleep in elderly men without clinically significant sleep apnea were far more sensitive to effects of alcohol than comparison groups of older women, young men or young women (529–531). Because alcohol ingestion (primarily in males) results in an increased pharyngeal resistance, which is strongly associated with age (532), this provides further support for age-related susceptibility to upper airway collapse, as do data suggesting that alcohol decreases genioglossus electromyographic (EMG) activity (533). The alcohol effect on SRRD may even be seen in elderly chronic alcoholic men who are abstinent (534,535). A different perspective on upper airway muscle activity was provided by Suratt et al. (536), who showed that elevated, rather than decreased, EMG activity was characteristic of sleep apnea patients, suggesting that the EMG activity represented a compensatory mechanism. Similarly, nonobese male subjects without sleep apnea (ages 41–66) showed increased activity of the alae nasi and, possibly, genioglossus in sleep relative to younger (23–31-year-old) male subjects without sleep apnea. Regardless of the specific mechanism involved, these results again suggest parallels between the altered upper airway function in normal aging and that seen in a more extreme form in sleep apnea patients, at least in males. Curiously, in view of the alae nasi findings, age was uncorrelated to the extent of the increase in sleep-disordered breathing following nasal packing (537–539) in normal subjects, although the younger ages of male subjects in these studies (<45 years) could have been a factor in the negative results. Mouth ventilation during sleep has also been reported to increase with age (540) in men. Another interesting, potentially adaptive, alteration occurs in elderly subjects, who have been reported to typically spend less time supine than young or middle-aged adults or children (541).

Some of the most convincing evidence suggesting that SRRD represents a fundamentally different and less pathological condition in the elderly undoubtedly derives from the retrospective mortality study of He et al. (542) comparing treated (n = 139) and untreated (n = 246) clinic patients with sleep apnea. In this important study, untreated clinic patients (mean age about 53) with sleep apnea were compared with treated patients with mortality as an outcome. For patients under 50 years of age (but not those over 50), the presence of sleep apnea [defined as an apnea index (AI) of 20 events per hour or higher] was shown to predict subsequent mortality. Because the untreated patients in both the young and old groups did not differ in AI, the results of this study have been interpreted to suggest that impaired respiration in sleep may have less deleterious effects in older subjects. Similar age-dependent results have been reported in abstract form by Thorpy et al. (543,544) in 269 patients with a mean age of 50.

Although the He et al. study has been criticized on methodological grounds (545,546), it represents the largest series of treated/untreated patients followed over time. An alternative approach to such a retrospective clinical trial are cohort studies, in which a defined, nonclinical population varying in the extent of a particular risk factor (SRRD) are tracked over time. Reports on small numbers of middle-aged (501) and elderly (199,547,548) subjects followed over time show unclear results insofar as mortality is concerned, however two studies with over 100 subjects have reported associations between SRRD and mortality within the aged. Ancoli-Israel et al. noted that among elderly women (mean age 84) in a nursing home, the respiratory disturbance index (RDI) was highly predictive of survivorship (549). Bliwise et al. (550) reported similar results in independently living elderly persons (mean age 67), although confounds with chronological age (older cohort members dying more quickly) were unavoidable. Additionally, Berry et al. (199) have presented a 1-year follow-up on a small group of elderly subjects suggesting associations between SRRD and the development of hypertension. To summarize, results from clinical populations would appear to suggest that the impaired respiration seen during sleep in the elderly may have minimal association with mortality or morbidity, whereas cohort studies of older subjects imply otherwise. Until prospective clinical trials occur in any age group, however, the issue of differential outcomes as a function of age will be in doubt. As a final note, Fletcher et al. (551) have recently reported that elderly chronic obstructive pulmonary disease (COPD) patients who episodically desaturated during sleep to 85% or lower had reduced survival time relative to COPD patients without nocturnal oxygen desaturation.

In addition to these studies of vital status in individuals undergoing prior polysomnography or ambulatory sleep monitoring, several other types of studies are relevant to age influences in links between SRRD and mortality. The well-known relationship between sleep times and mortality (37,552) (excess mortality for both high and low sleep amounts) is often used to infer associations between sleep apnea and mortality (553). An examination of these data, however, suggests

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little evidence that relationships between sleep length and mortality are age specific. In one study, however, older women (ages 60–69) may have shown such a trend (552). Age, however, was a significant confounder in the relationship between exhaustion upon awakening and incident myocardial infarct in a cohort study to the extent that elderly persons were *less* likely to show such relationships than younger persons (554, 555). These results appeared to be relatively independent of depression (556). More provocative are Mitler et al.'s data (557) on time of death, which suggest that both men and women over age 65 show a disproportionate number of deaths in the 6:00–10:00 a.m. time block. Deaths related to ischemic heart disease showed a similar distribution. By contrast, deaths in the under age 65 population (and deaths from nonischemic causes) showed a more random distribution across the 24-hour day. These data offer inferential evidence for stronger (rather than weaker) SRRD/mortality associations in the elderly population. However, several caveats are necessary. First, others examining time of sudden cardiac deaths found no associations between age and time of death (558). Second, the largest compilation of time-of-death data places a mean time of death at 7:12 a.m. (559), a time that is clearly ambiguous insofar as sleep in concerned. Finally, data from Muller et al. suggest that peak time for myocardial infarction (560) and sudden cardiac death (561,562) occurs later, anywhere in the entire 7:00 a.m.–12 noon time block. The temporal distribution of these patterns show no age dependence whatsoever and have been suggested to be more fundamentally related to platelet aggregability responsive to shifts from supine to standing position (563). Assuming that inferences from the time of death data are tenable, these data argue against the high SRRD prevalence in the aged having pathological significance insofar as cardiovascular mortality is concerned. However, there still exists the possibility that cerebrovascular events could be related to SRRD in the aged. In the Mitler et al. data (557) and elsewhere (564), peak incidence of stroke has been shown to occur at 6:00 a.m. or earlier. Because episodes of hypotension have been shown during episodes of sleep apnea in asymptomatic elderly men (565) and several studies have suggested that the stroke is related to snoring (566–569) and sleep apnea (570,571), the possibility exists that SRRD in the aged may be specifically related to cerebrovascular morbidity/mortality (see section below on Dementia for a more thorough explanation of this possibility).

PLMS

Compared to SRRD, about which at least some evidence has accumulated, vastly less is known about associations between PLMS and morbidity in the elderly. Age-related increases in PLMS occurrence have been noted cross-sectionally in clinical case series (74,76,167,572) and in research volunteers (573), although at least some evidence suggests PLMS are not at all uncommon in younger persons as well (574). Unlike SRRD and snoring, there appears to be no drop in prevalence in the oldest (e.g. over age 80) groups (167,194). Best evidence to date suggests that about 45% of the independently living over-65 population meet an arbitrary criterion for the presence of such movements (194), making PLMS a more common "pathology" than SRRD.

A number of factors have been considered to be the mechanisms underlying PLMS in old age. Supraspinal factors represent one possibility. Some alteration in the glabellar reflex has been noted in PLMS (575) but somatosensory-evoked potentials were generally unaltered (575,576), and only a few of the subjects in these studies were elderly. Age-related declines in dopamine receptors (577) may relate to PLMS in the elderly, since L-dopa administration may decrease the number of movements (578). However such imaging studies have yet to be performed in subjects with measured PLMS. At the spinal level, lumbo-sacral narrowing has been noted in some persons with PLMS (579), which fits with other data suggesting that proprioceptive feedback of limb position may be important in initiation and termination of episodes (580). Osteoarthritic changes or disc abnormalities, common in the geriatric population, might thus account for some of the high PLMS prevalence in the aged. Systemic factors may also be relevant. Venous insufficiency in the lower limbs has been speculated to relate to PLMS (581,582), perhaps indicating elevated sympathetic nervous system activity, which would be consistent with studies mentioned earlier in this review. This could represent a common occurrence in elderly persons, although recent data have suggested blood flow is typically increased, not decreased, in the lower limbs during sleep (583) in younger persons who presumably had little PLMS. In a retrospective study, high normal levels of blood urea nitrogen were related to PLMS in elderly women (584). However, a prospective study examining 24-hour creatinine clearance in elderly subjects was unable to document any association between renal function and PLMS (585). Iron deficiency anemia, another condition highly common in the geriatric population, was shown to relate to restless legs symptoms, particularly in women, in one early study (586), but has yet to be documented or discounted as a factor in the widespread PLMS of old age. In all likelihood, PLMS in the elderly probably represent a common endpoint of a variety of widely divergent central and/or systemic conditions that lead to a distinctive, pe-

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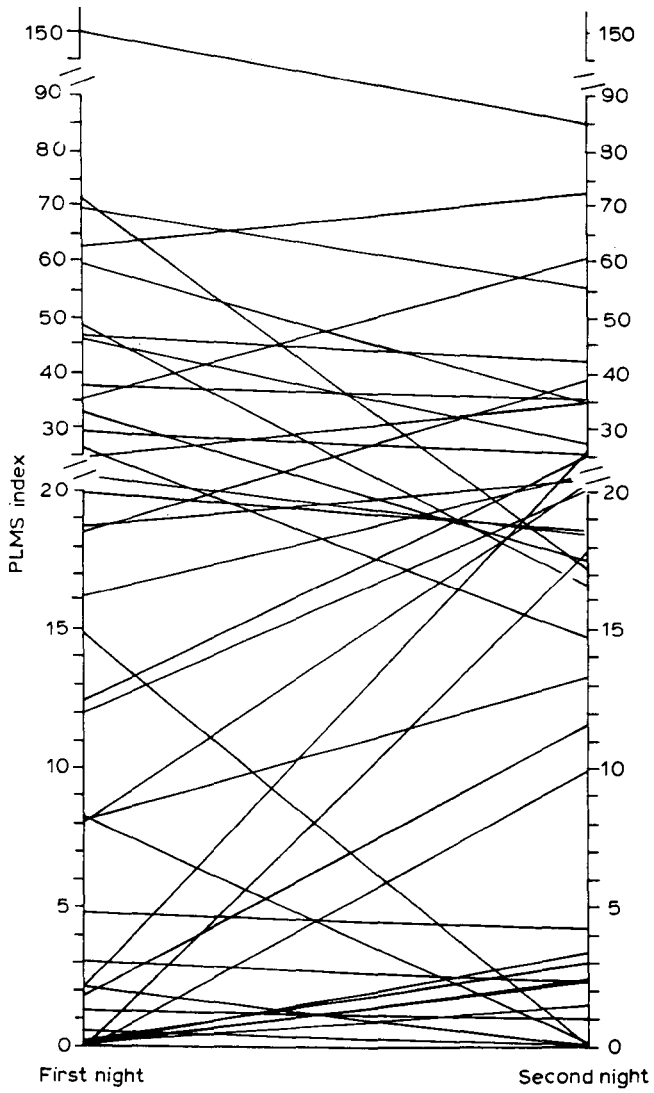

FIG. 6. Nightly variability in periodic leg movement index over 2 lab nights. (From reference 186.)

riodic motor output, perhaps related to cyclic (20–40-second) cycles in arterial blood pressure (587).

A mixed picture exists regarding characteristic sleep/wake symptoms and PLMS in old age. Although clinical case series suggest PLMS are a major cause of insomnia in old age (74,76,167), much of the apparently high prevalence of PLMS in elderly insomniacs could represent coincidental comorbidity. In one study of 63 elderly insomniacs (584), 23 demonstrated over 40 periodic leg movements during sleep yet only five and eight individuals experienced symptoms of restless legs and leg twitching, respectively. The latter symptom was weakly associated with the presence of PLMS. There appear to be no gross differences in PLMS characteristics between elderly research volunteers and elderly clinic patients (191). Other larger studies using elderly persons unselected for sleep/wake complaints have had considerable difficulty showing relationships between PLMS and general nocturnal sleep disturbance or daytime sleepiness (192–194), although more specific histories of leg kicking, restless legs symptoms and difficulty falling back to sleep did relate to PLMS (193,194). Given the number of variables examined and the relative strength of the relationships, however, the findings must be considered far from robust.

The difficulty in demonstrating specific morbidity associated with PLMS in elderly nonclinical populations must be qualified by the relative scarcity of studies examining this feature of sleep (c.f. SRRD) in old age. In addition, the highly variable nature of PLMS across nights (184,186,191,486) (Fig. 6), possibly four times as large as that seen in SRRD (186), makes it likely that any single result will be difficult to replicate. As a case in point, Ancoli-Israel et al. (194) have noted that the number of estimated awakenings the morning following a sleep study was the best single symptom correlate of PLMS the previous night in a nonclinical elderly population. The occurrence of clinical presentations of PLMS, often with accompanying dyskinesias and restless legs symptoms in persons 60 years old and above (588), cannot be minimized, but their significance in more mild forms remains uncertain.

SLEEP IN DEMENTIA

Dementing illnesses encompass a wide variety of nonreversible conditions, including Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Creutzfeld-Jakob disease and multi infarct (vascularized) dementia (MID). The largest proportion (as high as 70%) of demented patients, however, suffer from primary degenerative dementia (Alzheimer's disease [AD]). Most of the studies examining sleep in dementia probably include a preponderance of AD cases, but the diagnostic imprecision involved in arriving at a specific dementia diagnosis often makes it difficult to know precisely which patients have been studied. AD is typically diagnosed by exclusion after other reversible dementias (e.g. dementia due to folate deficiency, hypothyroidism, metabolic or toxic conditions) have been ruled out. Very few studies involving sleep have gone beyond such an exclusionary diagnosis to acquire neuropathological verification of AD or have related sleep patterns to specific areas of brain pathology in dementia. National Institute of Neurological Disorders and Stroke guidelines (589) suggest using a three-level system to indicate diagnostic uncertainty in the diagnosis of AD, classifying patients as definite, probable or possible AD. With rare exception (590,591), nearly all sleep studies use patients falling into the later two categories. Unfortunately, in some cases where the patients were only crudely screened,

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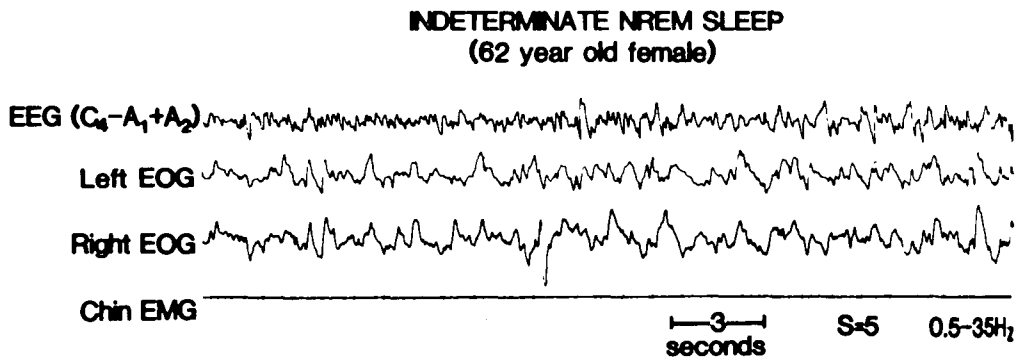

FIG. 7. Example of indeterminate NREM sleep in an AD patient. In last half of EEG tracing, note low amplitude delta activity not meeting the 75 μV amplitude criterion for slow wave sleep. Abundant slow EEG activity is apparent on two EOG channels, owing to frontal placements. (From reference 174.)

the weaker diagnosis of possible AD was more likely. The primary focus of this review will be on sleep in AD. The reader is directed elsewhere for reviews of sleep in other degenerative neurologic conditions (592–594).

EEG waveforms in dementia

Some appreciation of EEG waveforms in dementia is necessary for the sleep disorders specialist because these patterns are likely to represent major aberrations from what is typically encountered. The waking EEG of demented patients typically shows abundant diffuse slow activity encompassing both delta (0–3 Hz) and theta (3–7 Hz) frequencies (595,596). Focal slowing occurs less frequently unless a localized stroke has occurred or a lesion exists (597,598). Some studies have shown correlations between diffuse EEG slowing in AD and pathology-verified amyloid plaques and neurofibrillary tangles (599). In addition, both the incidence and frequency of dominant occipital (alpha) activity decrease in dementia (15,18). More recently, Prinz and Vitiello confirmed and extended the decrease in alpha frequency to very mild, early stage AD patients (600). Also of interest was the finding that depressed geriatric patients may also show slight decreases in dominant occipital frequency, even when medication effects were rigidly controlled (600).

The slowing of EEG activity in dementia may make discriminations between sleep and wakefulness exceedingly difficult. Systematic behavioral observations may be helpful in validation of electrophysiological state (229). In addition, differentiation of NREM stages may be challenging, and Reynolds et al. (174) have described so-called indeterminate NREM sleep (Fig. 7) in AD patients. The difficulties in thorough visual appreciation of the EEG of dementia has led many researchers to attempt computerized waveform analysis of these signals. Spectral approaches of the waking EEGs of demented patients generally show the greatest differences from elderly controls in delta or theta power relative to alpha measures (26,601–603). Topographically, both right (604) and left (26,605) temporal areas have been suggested to most likely be abnormal. Temporal asymmetry is equally likely in both waking and REM sleep (606). A major limitation in nearly all of these studies is their cross-sectional design. Longitudinal studies are required to adequately tease apart issues of severity, stage of disease and length of dementing illness. In one of the few such studies, Coben et al. (601) reported that increased theta power showed the earliest alterations in the progression of AD over time. This was followed by decreased alpha power and then, finally, increased delta power.

Apart from such descriptive information, perhaps a more relevant issue for computerized EEG analysis in dementia is whether such techniques provide any incremental information regarding diagnosis. Using waking EEG samples, several groups of investigators (607–609) have reported that theta activity (higher percentage and lower frequency) provided high specificity but only marginal sensitivity in identifying mild AD patients. More recently, however, Prinz and colleagues have, through use of sophisticated artifact-rejection methodology (610,611) reported that theta/delta (2–8 Hz) spectral power at occipital placements within artifact-free epochs of tonic REM sleep provided both specificity and sensitivity in excess of 90% for early-stage mild AD patients (612).

Sleep architecture

Before reviewing studies of sleep in dementia, it is important to emphasize that the sub-population of demented patients studied in the sleep laboratory is almost certainly biased by selection factors. Many demented patients are known to "sundown" (see below), and it may well be that the most profoundly demented cases simply cannot tolerate the laboratory procedures, although there are a few studies where grossly de-

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mented patients have been studied (613). It should also be mentioned that at least some of the results reported here, just as in studies of normal aging, could partially reflect sleep architecture alterations related to mild levels of SRRD or PLMS, which may vary appreciably from night to night.

More sleep disruption in demented patients relative to aged controls has been shown in a number of studies. Typically reported findings include lower sleep efficiency, higher percentage of stage 1 sleep and greater frequency of arousals and awakenings (157,174,181, 182,229,247,260,591,613–618). A recent meta-analysis has confirmed these reports (156). Vitiello, Prinz and colleagues have shown impressive evidence that measures such as sleep efficiency and number of awakenings closely parallel level of severity of dementia (247,590,613,617), although use of such information to classify patients versus controls was powerful only for moderate (as opposed to mild) levels of dementia (617). Decreases in stages 3 and 4 sleep have also been noted in dementia (157,163,247,591,613,615,617,619–621), although two research groups failed to find such differences (174,229,622), perhaps because of reduced levels of SWS seen in normal elderly controls. Benca et al.'s recent meta-analysis (156) also suggested no differences between demented patients and controls, although gross overrepresentation of the patient pools generating those findings may have played a role. One study even reported higher amounts of SWS in AD patients (616) using the modified scoring system for stages 3 and 4 mentioned previously (225) with a reduced amplitude criterion. This result emphasizes the bursting of low-amplitude slow wave activity occurring throughout the NREM sleep in many demented patients, as originally noted elsewhere (613,623), and has led to the visual scoring of indeterminate NREM sleep favored by some investigators (174) mentioned above (Fig. 7) in such patients. Decreases in spindling activity have also been noted in dementia (613,623).

Abnormalities in REM sleep are of particular interest in dementia (specifically, AD) because the integrity of cholinergic systems may be related to both REM and AD. Although REM sleep is probably dependent upon multiple neurotransmitter systems, the role of acetylcholine and its precursors in the induction of REM have been shown in both human and animal studies (624,625). In addition, AD is known to be characterized by reduced levels of choline acetyltransferase (626–628). These findings suggest that measurements of the intensity or quantity of REM should be attenuated in AD. REM as a function of total sleep time (REM%) has been suggested to be decreased in dementia in some (157,174,229,247,260,591,613,619), but not all (163,615–617,621,629), studies. Severity may play a role in the discrepancies. Vitiello et al. (630), for example, reported group differences in REM time only when comparing moderate and severe AD patients to controls.

Several pieces of evidence have suggested positive relationships between higher psychometric test performance and higher REM sleep amounts in dementia. Studies of both demented (247,613,630) and even nondemented (215) elderly persons as well as middle-aged alcoholics (631) have shown such relationships, although the findings are not unanimous (163,229). In Feinberg et al.'s early study (157), correlations between psychometrics and REM sleep were actually higher in nondemented aged controls than in demented patients, although the patterns of correlations were similar in both groups. An animal model for such decreased REM sleep in dementia has been proposed by Stone et al. (216,251), who noted positive correlations between selected REM measures and one-trial passive avoidance learning, as well as other more complicated memory tasks (632) in old, but not young, rats. Additionally, improved glucose regulation increased both test performance and REM sleep duration in old, but not young, rats (633).

Lengthened REM latency (REML) in dementia relative to controls is a particularly controversial finding, with some studies reporting such results (247,620), others finding no apparent differences (163,174,591, 616,621) and some studies even suggesting a trend for shorter REML in demented patients (157,260). If REML is lengthened in dementia, this may have diagnostic utility because REML is typically shortened in affective disorders (156), and the differential diagnosis between dementia and depression is a common problem in geriatrics (see below). REML was once considered to have considerable progress in this regard (629). Nonetheless, disagreement over definitions of REML (e.g. whether wake time after sleep onset is included and how sleep onset is defined) may play a role in determining how sensitive and specific an indicator for dementia and depression this measure may be (615,617,630).

Given the decreases in sleep efficiency and greater number of arousals and awakenings in demented patients relative to controls, it may be somewhat surprising that depressive disorders of the senium may actually be related to still greater levels of sleep disturbance. This was actually foreshadowed by observations made nearly 40 years ago (634), but more recently this has been demonstrated by several polysomnographic studies comparing AD patients with age-matched depressives. These studies have shown that the demented patients had significantly less disturbed sleep (174,260,629). Recent questionnaire data also reiterate that many AD patients do not have sleep disturbance (635). Often, depression may mimic de-

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mentia in the elderly patient (636–638), and a commonly encountered problem in clinical geriatrics is the simultaneous presentation of both depressive symptoms and mental impairment in a given patient. Because of the more severe sleep disturbance associated with depressive syndromes, the classical presentation of disturbed sleep, even on bedside exam, may provide relevant information in making this differential (639). Within the sleep laboratory, several reports of 2-year follow-ups of patients with initially mixed presentation of depressive and cognitive syndromes indicated the relative primacy of depression in disrupted sleep (260,640). Although the usual interpretation of these differences typically involves the neurobiological basis for late-life affective disorder, an equally interesting implication is that individual differences in extent and site of degeneration in AD may relate to relative sparing of deterioration in sleep. A final important caveat in all of these studies involving comparisons of demented and depressed patients is that inclusion of depressives from clinical referral sources (as opposed to community based populations) may serve to magnify to some extent the amount of sleep disturbance observed (81,201).

As mentioned previously, the Pittsburgh group recently has initiated a unique and innovative series of studies employing total or REM sleep deprivation as probes to differentiate depressive syndromes and dementia in old age (302,303,641,642). These studies, driven by the two-process model of sleep regulation, suggest that both elderly depressed and demented patients rebound from total sleep deprivation with increased sleep efficiency during recovery sleep, although the depressives continue to show somewhat lower sleep efficiencies postdeprivation (303). REM latencies increased in both groups following deprivation, whereas REM latency decreased in aged controls. In the elderly depressives, increases in slow wave sleep during recovery were related to clinical improvement, which was interpreted in terms of antidepressant effects of sleep loss and the two-process model (642). Perhaps more relevant for a discussion of dementia was the fact that REM sleep deprivation produced little evidence of REM rebound in depressives but a modest increase in REM activity in AD (302), suggesting at least some continued homeostatic regulation within the cholinergic system. Nonetheless, absolute levels of REM activity in AD in this study were lower than controls and depressives in both baseline and recovery, as has been reported in some other (157,591,629,630,643), but not all (174,260,303), baseline (i.e. nonexperimental) data. Of considerable diagnostic importance (given the common mixed clinical presentation of depression and dementia in late life) is whether recovery sleep following sleep deprivation can differentiate these syndromes. Using total sleep deprivation, Buysse et al. (641) reported that elderly depressive patients with cognitive symptoms showed more robust REM rebound effects than did demented patients with depressive symptoms. However, it is unclear why the former group should show greater REM rebound effects than a purely depressive group subjected specifically to REM deprivation (302).

Sleep-related respiratory disturbance (SRRD)

The possibility that SRRD could be associated with dementia stems from three basic facts: (1) SRRD is highly prevalent in the elderly, who are most likely to suffer from dementia; (2) SRRD reflects, in part, neurologic dysfunction within the CNS; and (3) intellectual deficits are known to accompany SRRD. The first point has been summarized earlier in this review. The second issue has been reviewed at length elsewhere (644,645). The final point requires further elaboration here.

The earliest reports of Pickwickian syndrome described patients' difficulties with concentration and lapses in memory (646). As many as 78% of apnea patients in one series were noted clinically to suffer from inability to concentrate and 48% were noted to suffer personality change (647). Later studies in primarily middle-aged (648–661) but also elderly (509,518,662,663) individuals confirmed psychometrically that poor intellectual performance, anxiety, depression, hostility and general mood disturbance were associated with SRRD. These types of intellectual and personality changes (AD patients, for example, are frequently dysphoric and combative) suggested some gross parallels to dementia. Despite these results, a few studies of nondemented, healthy elderly subjects have been unable to show such effects (116,199,201,476,664). In those studies showing associations between mental impairment and SRRD, considerable controversy exists as to whether the relationships are independent of decreases in daytime vigilance. Decreases in daytime alertness are characteristic of many organic mental syndromes (665), and it would appear that in SRRD both increased sleepiness and nocturnal desaturation may have an impact (666).

The psychometric studies described above generally imply that demented patients should show higher levels of SRRD than aged controls, but data on this point clearly conflict (667–679). The extent of the rates of sleep disordered breathing and the relatively mild nocturnal desaturation, even in those studies reporting significant differences between AD patients and elderly controls, would have to be considered minor relative to sleep apnea cases seen in sleep clinics. Some mild levels of sleep-disordered breathing in dementia would probably be expected anyway since this is character-

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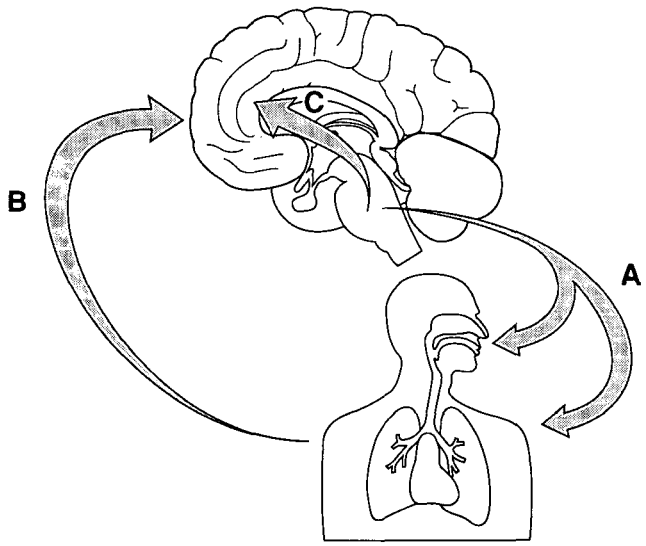

FIG. 8. Heuristic model suggesting possible interactions of higher order mental function with sleep-related respiratory disturbance. Possible defective ventilatory control mechanisms (A) may induce a syndrome affecting higher brain function (B) either through hypoxemic effects or repeated arousals and sleep deprivation. Some sleepiness may also be a function of primary neuronal degeneration (C) as in the case of many organic mental syndromes (See references 665, 695.)

istic of disturbed ventilatory control mechanisms in many neurologic conditions (see Fig. 8). This is an exceedingly complex area and the reader is directed elsewhere for further discussions of the issues involved (679–682).

Nonetheless, one possibility deserving of mention here is that SRRD could be a cause of dementia, more specifically with dementia of vascular origin. Some preliminary longitudinal data (682) are consistent with this possibility. Because SRRD may be associated with hypertension, cardiac arrhythmias, decreased stroke volume and cardiac output, circulatory insufficiency in the brain could lead to greater likelihood of ischemic regions and/or localized infarcts. Hypotension has been shown in some studies to accompany breathing events (565), and stroke is probably more likely to occur within sleep (537,564). Moreover, a cardinal symptom of SRRD—snoring—has been associated with stroke (566–569,683) and stroke patients have been reported to have appreciable amounts of sleep apnea (570,571). MID is accompanied more frequently by cardiovascular disease relative to AD (684), and MID has a shorter survival time and more insidious course than nonvascular dementias (685). Although multi-infarct vascularized dementia is notoriously difficult to define (686,687), several studies have implied a higher prevalence of SRRD (676,688,689), although not always snoring (677), in MID relative to AD. SRRD might therefore be related to dementia to the extent that some cases of the latter are caused by cardiovascular/cerebrovascular disease. Preliminary studies with single photon emission computed tomography (SPECT) have shown possible white matter hypoperfusion in the brains of younger sleep apnea patients (690), but in all likelihood, future studies with magnetic resonance imaging (MRI) or adequate neuropathological verification will be needed to confirm the role of disturbed breathing in sleep in vascular dementia.

Regardless of the inconclusive state of the research literature, an obvious clinical question which arises is whether the demented patient with presumed AD and SRRD should be treated for the breathing disorder in sleep. The decision to treat is probably best determined by the exigencies of any individual case, but the clinician must be cognizant of several facts. First, it is entirely possible that an AD patient may be treated successfully for sleep apnea, and yet the downward progression of dementia will continue unabated, although a few case reports suggest dementia may possibly reverse (553,691–694). To date, there are no known treatments of any type that can actually reverse the dementing process in AD. If the AD patient with SRRD is also somnolent, some of the sleepiness may be mitigated by reducing the arousals and desaturations occurring in sleep. Somnolence, however, may also reflect primary neuronal degeneration (695) or circadian rhythm dysfunction (see below) and may not resolve, even with successful sleep apnea treatment. Second, the range of treatment modalities in demented patients with sleep apnea may be limited. Specifically, nasal CPAP or BiPAP, which may otherwise be a viable treatment for sleep apnea in geriatric patients, may be poorly tolerated by demented patients, who are likely to become agitated and confused at night. Third, ethical considerations involving both the inevitable decline of the patient and the duress on the family must be considered. The prolongation of the slow "death of the mind" experienced by the patients and their caregivers may only serve to prolong the anguish and instill a false hope for a miracle cure. On the other hand, perhaps at the earliest stages of dementia when patients are living at home and are relatively independent in activities of daily living, any treatment ameliorating the excess disability experienced by the patients would be worthwhile.

Sundowning and circadian rhythms

The most dramatic and familiar aspect of sleep disturbance in dementia is sundowning. This type of sleep disturbance may be the single most common cause of institutionalization of demented geriatric patients (696–698). Pollak and Perlick (699) have recently confirmed these findings using an open-ended questionnaire not specifically focusing on caregiver sleep dis-

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ruption. Families may be able to tolerate mental confusion, the memory loss and, to some extent, the incontinence of a demented family member. When the caregivers' sleep is disrupted night after night by an agitated demented patient, who wanders through the house or awakens with loud and confused vocalizations, this may well be the straw that breaks the camel's back. Sundowning is often considered to represent nocturnal delirium. However, delirium, defined as a "psychiatric syndrome characterized by a transient disorganization of a wide range of cognitive functions due to widespread derangement of cerebral metabolism" (700), is a psychiatric diagnosis, not a description of behavior. Nocturnal exacerbation of delirium has been recognized since the time of Hippocrates (700), and DSM-IIIR employs aberrations in sleep/wake cycle to make the diagnosis (701). As Lipowski has noted, delirium can occur at any age and is seen in a wide variety of toxic, metabolic, infectious, nutritional and substance-induced states (702) and may frequently, but not invariably, accompany dementia.

Sundowning can be defined as the differential nocturnal exacerbation of disruptive behaviors and agitation. However, researchers have reached little or no agreement on what constitutes the syndrome. The term is employed frequently in clinical geriatrics (703–706), and one study even attempted systematic treatment for "sundown syndrome" without even bothering to define it (707). The first apparent attempt to investigate sundowning was made by Cameron (708), who brought demented patients into a dark room for about an hour during the day. Cameron noted that patients became delirious shortly after this. This study was poorly controlled and has never been replicated.

The prevalence of delirium may be very high in geriatric patients. As many as 50% of geriatric patients may be delirious upon admission to a general medical unit or develop delirium during an acute care hospital stay (709–711), although other studies place these figures somewhat lower, at about 20% (712,713). One assumes that most of these individuals experienced sleep disturbance as part of their delirium. These high prevalence figures may reflect the broad time referent used in some of these studies. By contrast, O'Dell et al. (714) noted that on a single day, the prevalence of DSM-IIIR definable delirium in a 400-bed skilled nursing facility was only 0.24%. Liston (715) has also suggested such a lower prevalence.

Because few studies have operationalized definitions for sundowning, figures are scarce regarding the prevalence of this condition. However, some data are available. Agitation may be a relevant description for much of what falls under the rubric of sundowning. Cohen-Mansfield et al. (716) noted a characteristically nocturnal pattern of agitation in two of eight highly agitated nursing home patients who were observed behaviorally for 3 minutes every hour of the 24-hour day. Evans (717) used less frequent behavioral observations (two 10-minute observation windows occurring at any point between 1000 and 1200 hours and between 1600 and 1800 hours on two separate days) and found sundowning in 11 of 89 (12.4%) nursing home patients. Both of these reports employed nursing home staff ratings to determine the presence of sundowning. In another study using less specific nursing staff ratings (judgments made for an entire 8-hour shift based on a 2-week time frame), Cohen-Mansfield et al. (718) noted that about 14% of 408 nursing home patients showed higher likelihood of specific agitated behaviors (such as pacing and verbal aggression) during the evening than during the day shift. In a related, but somewhat different, approach, Bliwise et al. (719) reported that research assistants observing 24 highly demented nursing home patients four times an hour, 24 hours a day over a period of 10 days noted that sleep was least likely in the 3:00 p.m. to 7:00 p.m. time period, which encompassed sunset during the periods of observation. Although this study did not assess agitation, the results raised the possibility that the late afternoon or early evening may be vulnerable to disruptive behaviors. Similar results have been reported by Jacobs et al. (720) with the wrist actigraph. Using a time lapse video tape monitoring system, Martino-Saltzman et al. (721) reported that "inefficient" travel behavior (i.e. wandering) was most likely to occur from 7:00 to 10:00 p.m.

Caregiver reports regarding nocturnal behavioral disruption in demented patients represent another source of evidence regarding the occurrence of sundowning. Data based on caregivers' retrospective reports suggested a 1-month prevalence of nocturnal behavioral disruption of about 28% in a group of 60 AD patients (722). A pattern of morning exacerbation was less common (20%), however, as expected, nearly all of these patients (85%) showed evidence of nontemporally specific disturbed behavior (e.g. wandering, combativeness, hallucinations). Three other descriptive studies of well-characterized AD patients uniformly have noted significant sleep disturbance in about 40% of the patients studied (723–725), although it was unclear if this sleep disturbance was accompanied by sufficient agitation and confusion to warrant the label of sundowning. One recent study placed the figure at closer to 15% (635). In these studies, time sampling frame was also unspecified, thus leaving open the possibility that sundowning may have occurred at some point in the course of the dementia, rather than concurrently with evaluation.

Factors associated with the behavioral syndrome of sundowning are unclear. Evans (717) noted that nursing home patients who sundowned were more likely

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to be demented, have recent room transfers, be incontinent and have fewer medical diagnoses than those who did not sundown. However, other variables that might be expected to relate to sundowning (e.g. visual/auditory impairment, use of psychotropic, cardiovascular or analgesic medication, morning–afternoon differences in blood pressure and temperature) did not differentiate the groups. One study (722) reported that caregiver-reported cases of sundowning in noninstitutionalized AD patients were related to a faster rate of decline in selected mental abilities but not to general level of function (e.g. faster rates of decline in ideokinetic praxis were related to sundowning). This was consistent with the inability of sundowning patients to respond nonlinguistically to environmental zeitgebers, such as day/night and light/dark.

In Feinberg et al.'s (157) classic description of sleep in DSM-II defined chronic brain syndrome patients, the authors found that three of 15 patients awakened out of REM sleep in "states of delirium with fixed ideas . . . of an everyday nature rather than bizarre" (p. 133). Although this description shares certain characteristics with REM sleep behavior disorder (see below), the possibility exists that some episodes of sundowning simply could be caused by awakening from any stage of sleep. For example, Evans (717) reported that patients who sundowned were more likely to be subjected to staff awakenings every 2 hours (for change of sheets and bed clothes) than those who did not sundown. Cohen-Mansfield (726) also reported that such nocturnal bed checks by staff were related to many types of aggressive behavior during the daytime hours in nursing home patients over a 2-week period. Although Cameron (708) presented no evidence for it, the possibility remains that such a phenomenon could have resulted in the confusion originally noted in his patients. If the patients fell asleep in a dark room, their confusion could have been a consequence of awakening rather than a function of illumination (163) (see specific hypotheses below).

A thorough and comprehensive set of studies by Cohen-Mansfield et al. (727–730) are noteworthy insofar as factors associated with agitation are concerned. Although the emphasis of most of these studies has been on agitation per se regardless of time of occurrence (716,726) the description of relationships between types of agitation and patient factors are valuable. These studies suggest that agitated, aggressive behaviors were more related to physical pain and relatively recent surgery whereas non-aggressive agitated behaviors were related to cognitive impairment and impairment in activities of daily living (727,728). Of considerable interest was the fact that previous psychiatric history appeared unrelated to agitation, although past stressful events (e.g. financial problems, holocaust experiences, death of spouse) were related to nonaggressive physical behavior (730). Nursing home residents with higher levels of cognitive functioning were more verbally agitated (728). Finally, in a study examining nursing ratings from each shift, Cohen-Mansfield et al. (729) reported that all types of agitation was generally more common in the day shift, followed by evening and then night shift. However, because subjects also slept less during the day, it was unclear whether this was not simply a function of more time awake during the day.

A number of specific conditions may account for sundowning:

REM sleep behavior disorder (REMBD). This syndrome (731,732), occurring primarily in elderly males, shows some parallels with animal models of lesions within the pontine tegmentum. In REMBD, patients often carry out complex and bizarre motor activity without awareness of their physical surroundings. Although a few of the patients in the original series were demented, it now appears that most are not (733) and may be essentially normal neurologically. Because of these factors and the relatively low prevalence of this condition relative to sundowning, REMBD is probably a distinct disorder from the sundowning seen in dementia, although it has been described in a series of Parkinson's patients (734) and elderly patients with brainstem deterioration (735).

Complex partial seizures. Because recurrent seizure activity is occasionally seen in later stages of dementia, it is possible that some sundowning-like behavior, particularly if originating from sleep, could be associated with complex partial seizures, which are characterized by abnormal movements, vocalizations and other complex motor behavior. In one series, about 15% of patients with abnormal motor activity in sleep were shown to have such EEG activity (736). This could account for a few cases of sundowning.

Sleep apnea. Another possible mechanism in accounting for sundowning is that of sleep apnea, or more specifically, awakenings subsequent to episodes of apnea that may result in sundowning-like behavior. For example, Moldofsky et al. (737) found that overnight change in mental status (i.e. greater confusion after final morning awakening) related to nocturnal hypoxemia, and others have noted this as well (679). Kripke et al. (553) reported on two elderly men with nocturnal confusion, whose symptoms ameliorated upon successful sleep apnea treatment. In a study with thorough nocturnal observations, however, Hoch et al. (678) documented that spontaneous nocturnal behavioral symptoms (e.g. getting out of bed, loud vocalizations, attempts to remove electrodes) were unlikely to occur following awakenings subsequent to sleep apnea episodes. Thus, although, as mentioned above, awaken-

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ings from sleep are likely to be associated with confusion (157,717,726), this may be unrelated to sleep apnea.

Neuroleptic-induced akathisia. Many behavioral rating scales used to assess agitation employ, at least in part, ratings of motor restlessness. Such akathisia is a well-known side effect of neuroleptic use and can sometimes be mistaken as agitation (738,739). Because a large proportion of dementia patients have a history of such medication intake, it is conceivable that some apparent sundowning could reflect such restlessness. Most studies quantifying sundowning behaviors, however, rely on broader definitions than motor activity in the lower limbs (e.g. vocalizations).

Deterioration of the suprachiasmatic nucleus (SCN). One of the most intriguing hypotheses in accounting for sundowning in cases of dementia is that behavioral disruption represents dysregulation of the circadian sleep/wake system. Indirect evidence supporting this hypothesis comes from a long series of animal studies implicating the SCN as the putative biological clock (see above section on circadian rhythms in normal aging) as well as a small series of neuropathological studies of dementia cases suggesting selective deterioration of this group of cells (339,342,349,740). More recently, the deterioration of the hypothalamus in AD has been shown to be specific for the SCN and not include the supraoptic or paraventricular nuclei (741).

It must be stressed that the studies cited below examining rhythms in dementia are almost certainly biased in that most have taken place in entrained conditions and may reflect masking effects or changes in input to the putative core oscillator itself rather than alterations in the oscillator itself. Again, research involving polysomnographic and other physiological measurements of circadian rhythms in dementia is highly subject to patient selection bias. A sundowning patient will not tolerate wires near his/her face and head, an indwelling catheter or a rectal temperature probe.

Insofar as sleep/wake is concerned, there is some evidence that profoundly demented AD patients spent slightly more time asleep during the daytime hours relative to less severely impaired AD patients though evidence for a complete loss of rhythm amplitude is minimal. Prinz et al. (247,613) have shown that although demented patients spend more time asleep in the daytime than aged controls, the majority of their sleep continues to occur during the night. The relative proportion of daytime sleep (as a percentage of 24-hour sleep) was higher in severely demented, institutionalized patients (14%) than in noninstitutionalized moderately (5%) or mildly (2%) demented patients (618) but did not approach the 50% figure one might expect with a complete loss of rhythm amplitude. Allen et al. (229) reported that three of 30 demented patients slept more during the day than at night. Thus, the polysomnographic results to date, although subject to selection bias and performed under entrained conditions, suggest that sleep/wakefulness in dementia shows only mild "day–night" reversal.

Studies of rest/activity rhythms in AD patients have shown that such patients are characterized by higher intra- and inter-daily variability relative to controls (742,743) and several studies of heterogeneous nursing home patients (many of whom presumably meet the criteria for AD) using both wrist actigraphy and behavioral observations have confirmed considerable fragmentation in sleep/wake state across the 24-hour day (719,720,744–747). In all likelihood, institutionalization per se, with its attendant reduction in outdoor illumination exposure and social zeitgebers, serves to undermine the integrity of the sleep/wake rhythm (748). A recent study using actigraphy reported that patients with multi-infarct dementia had more disruption to the sleep/wake cycle than AD patients (749), although an earlier polysomnographic study reported similar levels of fragmentation in both types of dementia (229). Wrist actigraphy has also yielded data suggesting an apparent delayed acrophase in activity in AD patients relative to controls (750), which is inconsistent with sleep log data suggesting earlier bedtimes in AD patients (751) and data raising the possibility of advanced acrophase in the temperature cycle of AD patients (752,753) (see below).

Wagner's report (754) of an 86-year-old man with AD studied in time isolation is the only report of free-running rhythms in dementia. Sleep/wake appeared totally dispersed around the 24-hour day with uniformly short sleep bouts. There was also evidence of agitation and apparent "sundowning" between 1700 and 1900 hours on 3 of 5 days and between 0330 and 0600 hours on all 5 days in isolation. These very provocative preliminary findings link sundowning behaviors to a diminished sleep/wake rhythm amplitude. Although such studies are excruciatingly difficult to carry out, only future work performed under these conditions and employing appropriate neuropathological criteria will be able to confirm the neurophysiological basis for sundowning in dementia.

Studies of the circadian body temperature rhythm have typically failed to show differences in phase or amplitude between AD patients and age-matched controls (357,415), although in one of these studies, there was some suggestion of instability of temperature regulation in the AD patients (357). In general, brain-damaged patients without known SCN damage continue to show diurnal temperature variation with only mild perturbations in acrophase (755). Because tumors in the SCN are known to disrupt the temperature

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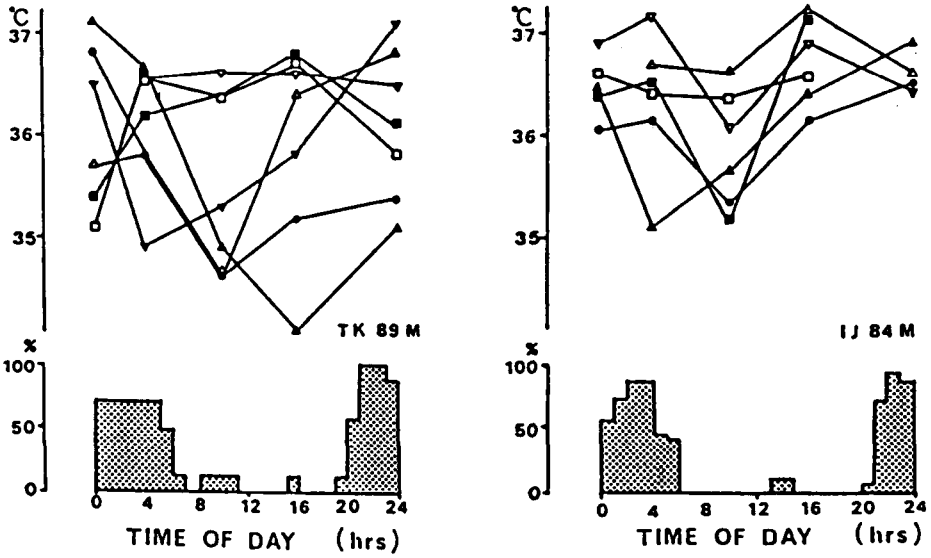

FIG. 9. Examples of "disorganized" body temperature curves in two grossly demented nursing home patients. Curves show 7 days of oral temperature data, based on intermittent sampling four times a day. Bottom part of figure shows percentage of observations in which sleep was observed. Note wide day-to-day variation in peaks and troughs of the temperature cycle suggesting dysfunction in the circadian timing system. (From reference 758.)

rhythm dramatically (756,757), it would appear that to the extent that the SCN is spared in certain AD patients, the temperature rhythm may persist. More recently, Campbell, Gillin and colleagues (752,753) have reported that male AD patients were phase advanced in body temperature relative to nondemented aged male controls, whereas female AD patients were phase-delayed relative to nondemented female controls. The phase advance in the males appeared larger than the phase delay in the females. Additionally, Okawa et al. (758) reported "disorganized" and apparently desynchronized temperature rhythms in demented nursing home patients relative to non-demented nursing home patients (Fig. 9). Some of the patients with "disorganized" temperature rhythms also demonstrated nocturnal behavior disruption.

As for other rhythms, recent data suggest that normotensive AD patients have a blunted diurnal rhythm in blood pressure relative to elderly controls, even when daytime activity was controlled (759). Diurnal variation in heart rate was similar in both groups (759). In a brief report, Renfrew et al. (760) reported that six AD patients had lower melatonin rhythm amplitude relative to elderly controls. A detailed series of studies by Touitou et al. in six demented patients have shown generally that hormones with nocturnal circadian or sleep-related release (melatonin, luteinizing hormone, prolactin) show similar secretory patterns in AD and elderly controls, although prolactin release may be slightly phase advanced in AD (366,367,761,762). Cortisol provides a more complicated picture in that, although several studies report no diminution of the cortisol rhythm in dementia (397,403,763,764), there is some evidence that in certain AD cases (DST non-suppressors), blunted amplitude may exist (765). A later study did not find this but did note strong relationships between basal cortisol levels and level of dementia (764). This raises the possibility that hyperarousal (specifically, overactivity of the hypothalamic-pituitary-adrenal axis) may occur differentially in dementia and might relate to sundowning.

Despite these mixed results regarding alterations in the circadian timing system in AD, some data continue to suggest a link between nocturnal agitation and dysfunction within the circadian system. An observational study of grossly demented nursing home patients (766,767) found that agitated behaviors near the time of sunset showed seasonal variation i.e., sundowning was more frequent in the winter relative to the fall. Because of known seasonal variation in the body temperature cycle and other electrolytes in both normal aging and dementia (415,768) these observations provide a link between disruptive behavior and the circadian timing system.

Treatments

Treatments for sundowning represent one of the most vexing problems for the sleep disorders specialist. First, it is well worth emphasizing that treatment for the nocturnal confusion of delirium must begin with an examination of possible underlying toxic, infectious, metabolic or pharmacological causes for the disorder (702). In the absence of such reversible conditions, pharmacological treatment for the nocturnal agitation accompanying dementia usually involves neuroleptics;

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benzodiazepine hypnotics have minimal effects on such cases. Typically, medications such as haloperidol (0.5 or 1.0 mg t.i.d.) or thioridazine (25 mg t.i.d.) are employed, but long-term sequelae of both are unfavorable. The former may exacerbate extrapyramidal symptoms or lead to tardive dyskinesia; the latter may lead to orthostatic hypotension and also has anticholinergic effects. Several recent reviews present summaries of the various advantages and disadvantages of other neuroleptic medications (769,770). Devanand et al. have critically examined the literature and concluded that there is little evidence to favor any single neuroleptic in terms of behavioral effects (771) and indicated that periodic withdrawal be used to reconfirm need for such medication. Although not in common use, some have suggested beta blockers such as propranolol or pindolol in the management of more aggressive behavioral syndromes in geriatrics (770,772,773). Regardless of which medication is used, it must be recalled that antipsychotic medication is probably overprescribed in many institutional settings (774). In fact, physicians' reliance on antipsychotic medication in nursing homes was directly related to case load in one survey (775). Morgan (61) has reported a median prevalence of hypnotic drug usage across studies of institutionalized patients of about 34%, although new efforts by the Health Care Financing Administration have resulted in a possible decrease in usage in the United States (776). Undoubtedly, because of time constraints and patient load, nonpharmacological manipulations are frequently overlooked and may deserve more attention.

Nonpharmacologic treatments should be carefully considered and instituted if suitable environmental arrangements can be made. In the institutional setting, one possibility is the use of a regularly scheduled nocturnal activities hour (e.g. 2:00–4:00 a.m.), with an occupational therapist brought in especially for this purpose. This serves to minimize disruption to other patients and regular staff. In the home environment, an approach modeled after the British "night watchers" system (777) may help provide some needed overnight respite for family members. In addition, the time-honored nursing adage regarding avoidance of daytime napping may be worthwhile to consider. For example, some evidence of the integrity of homeostatic sleep mechanisms in dementia has been noted in both experimental (303) and correlational (719) studies. This implies that if sleep during the daytime is limited, less-fragmented sleep may ensue the next night. It may also be worthwhile to consider a possible role of untoward thermal challenge in the genesis of sundowning behavior, as neurochemical and neuroanatomical parallels between thermoregulation centers in the basal forebrain and those centers undergoing marked cholinergic deterioration in Alzheimer's Disease have been noted (778). Inadequate daytime illumination is another feature to consider. Demented patients may receive low exposure to bright outdoor sunlight (136), and several brief reports have suggested that exposure to bright light (779,780) may improve sleep in demented patients. However, immediate effects of activation and restlessness are also possibilities following light exposure (781), perhaps because of noxious effects of glare due to macular degeneration. Okawa et al. (758) have reported success with an omnibus treatment package of mild activity, light exposure and presumed sleep restriction, although no alteration in temperature rhythm was seen subsequent to alteration in sleep. Clearly, there is no reason why such behavioral approaches cannot be used to complement pharmacological treatments. If patients are physically active, however, extreme care should be used because of the known relationship of psychoactive drug use and hip fracture in the aged (782). Obviously, sleep disturbance at the very end of life may be exceedingly difficult to treat and may require the sleep disorders specialist to focus on creative environmental manipulations in addition to pharmacological management.

CLOSING COMMENTS

The research findings regarding sleep and sleep disorders in the elderly often conflict, and this review has attempted to highlight areas of agreement and areas of controversy. Investigators can often examine the same set of behaviors (e.g. daytime napping or sleepiness) from widely varying perspectives. In addition, issues in measurement error, sampling characteristics, definition of constructs and statistical analyses undoubtedly play a role as well in producing different results across studies. Despite the enormous growth in the field, as evidenced by the recent National Institutes of Health Consensus Conference (783), much remains to be understood both at the clinical and basic science level. Lest it be thought, however, that the existing mass of literature represents a surfeit of information, it must be stressed that few, if any, of these findings have been incorporated into the routine practices of geriatricians (784). The translation of research data into clinically relevant information remains the greatest challenge for researchers in this field today.

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