Workshop Report

Sleep, Health, and Aging

An Interdisciplinary Workshop of the
INTERNATIONAL LONGEVITY CENTER–USA

Sponsored by
International Longevity Center-USA
MetLife Foundation
Institute for the Study of Aging
National Institute on Aging
Canyon Ranch Health Resort

INTERNATIONAL
LONGEVITY CENTER–USA

60 East 86th Street
New York, NY 10028

212 288 1468 Tel
212 288 3132 Fax
info@ilcusa.org
www.ilcusa.org

An Affiliate of
Mount Sinai School
of Medicine

The International Longevity Center–USA (ILC–USA) is a not-for-profit, nonpartisan research, education, and policy organization whose mission is to help individuals and societies address longevity and population aging in positive and productive ways, and to highlight older people's productivity and contributions to their families and society as a whole.

The organization is part of a multinational research and education consortium, which includes centers in the United States, Japan, Great Britain, France, and the Dominican Republic. These centers work both autonomously and collaboratively to study how greater life expectancy and increased proportions of older people impact nations around the world.

Sleep, Health, and Aging

An Interdisciplinary Workshop of the
INTERNATIONAL LONGEVITY CENTER–USA

Sponsored by
International Longevity Center-USA
MetLife Foundation
Institute for the Study of Aging
National Institute on Aging
Canyon Ranch Health Resort

Acknowledgements

The ILC-USA gratefully acknowledges the MetLife Foundation for its generous financial support of this workshop.

Special thanks go to Gary Frost, Carrie Thompson, and all the faculty and staff at Canyon Ranch Health Resort for helping to shape the framework and content of this conference and for providing the accommodations and facilities.

For their ongoing support of ILC-USA programs to advance healthy aging, we gratefully acknowledge The Werner and Elaine Dannheisser Endowment and the Mollye and Bernard Mills Endowment.

Thanks to the Institute for the Study of Aging for its ongoing support of the scientific consensus workshops.

Finally, thanks go to ILC-USA's Nora O'Brien, director of partnerships and special projects, and Judith Estrine, executive editor, for their contributions to the workshop and to this report.

Canyon Ranch-International Longevity Center brings together scientists on particular critical topics to decide what can be agreed upon, and when a consensus is reached, to develop a research agenda. The participants are then asked to determine what information should be provided to the public, and finally, what messages are pertinent to policymakers at the foundation and governmental levels. Previous workshops have included *Prescription for Longevity, Maintaining Healthy Lifestyles, Achieving and Maintaining Cognitive Vitality with Aging, Biomarkers of Aging: From Primitive Organisms to Man, Longevity Genes, Is There an "Anti-aging" Medicine?, and Masculine Vitality: Pros and Cons of Testosterone in Treating the Andropause.*

The positions or views expressed in this report do not necessarily represent the opinions of the NIA, NIH, DHHS, or the federal government.

Participants

Co-Chairs
Robert N. Butler, M.D.
International Longevity Center–USA

Fred W. Turek, Ph.D.
Northwestern University

Rapporteurs
Andrew Monjan, Ph.D.
National Institute on Aging

Huber Warner, Ph.D.
National Institute on Aging

Participants
Sonia Ancoli-Israel, Ph.D.
University of California, San Diego

Richard Bootzin, Ph.D.
University of Arizona

Daniel J. Buysse, M.D.
University of Pittsburgh School of Medicine

Phillip Eichling, M.D., M.P.H., M.T.H.
Canyon Ranch Health Resort

Michael V. Vitiello, Ph.D.
University of Washington

Alexander N. Vgontzas, M.D.
Milton S. Hershey Medical Center

Terry B. Young, Ph.D.
University of Wisconsin, Madison

Phyllis C. Zee, M.D., Ph.D.
Northwestern University

Preface

In 1975 when the National Institute on Aging (NIA) was founded, research on sleep was given low priority by its parent organization at the National Institutes of Health. But because sleep problems are so common among older persons and the topic so neglected, the NIA conducted a workshop to stimulate research on this important topic. Over the years the field has gained momentum, attracting the attention of the scientific community and the public, and gaining financial support.

Quality of sleep is tied to quality of life and, indeed, to the genesis of disease. Sleep may play a salient role in increasing vulnerability to illness and disability. For example, sleep deprivation produces a prediabetic state, and evidence suggests that sleep is important in the maintenance of immune function.

Older persons have complex issues that influence their quality of sleep, and there are many intriguing issues associated with their sleep patterns. Aging is associated with sleep fragmentation, slow waves and fewer eye movements during REM sleep. Typically, the aged have multiple, complex, interacting physical and psychosocial pathology, all of which may impact directly on their quality of sleep. The day/night reversal of sleep and wakefulness, the incidences of confusion that can occur at twilight ("sundowning"), and the nocturnal delirium in persons suffering with dementia can be catastrophic.

While we do not fully understand its myriad functions, we know that sleep is both restorative and protective. We need more investments in research on sleep and its disturbances.

Robert N. Butler, M.D.
President and CEO
International Longevity Center-USA

Executive Summary

Insomnia is a common complaint in older adults, and, although occasional sleep complaints may not be associated with age, chronic sleep difficulties are experienced more often by older adults than by younger adults. The development of new sleep difficulties is associated with poor health or psychological factors, and untreated insomnia is liked to poor health and may be associated with increased morbidity and mortality risk. Chronic insomnia can have a serious impact on daily functioning and can result in reduced quality of life in older adults.

Some of the main factors contributing to insomnia in older persons are medical and psychiatric illness, medication use, circadian rhythm disorders, and primary sleep disorders. Resolving sleep difficulties, no matter what the cause, is related to better health quality. The most consistent changes in sleep associated with aging are earlier sleep onsets, earlier morning awakening, decreased amounts of deep or slow-wave sleep, and an increase in the number of awakenings.

Several factors have been implicated to produce sleep fragmentation in older persons, including fundamental age-related alterations in the neurobiology of circadian rhythms and sleep; environmental, behavioral, and social factors, low levels of physical activity, and lack of exposure to bright light; sleep disorders such as sleep apnea, restless legs syndrome, and periodic limb movement disorders; and chronic medical and psychiatric disorders.

There are prominent age-related changes in sleep homeostatic regulation. While older adults spend more total time in bed, nocturnal sleep is both shallow and decreased in total amount. Decreases in slow-wave sleep begins in midlife, whereas decreases in REM sleep and increased sleep fragmentation grow more common during late life. These changes in sleep quality and specific sleep stages are accompanied by an alteration in hormonal and metabolic profiles that may negatively affect health outcomes in aging.

Future research needs include the following:

- Longitudinal studies to confirm a causal role of mild-moderate sleep disordered breathing in cardiovascular and behavioral morbidity.
- Understanding the natural history of sleep disordered breathing with aging.
- Community trials in weight loss and exercise to decrease sleep disordered breathing.
- Recognition of sleep disordered breathing as a significant public health problem in federal and other prominent health initiatives.
- Continuation of existing educational programs and new conduits for public education initiated to inform the public of the role of overweight in sleep disordered breathing.
- Goals for the reduction of sleep disordered breathing via weight loss and exercise.
- Research on the relationship between sleep, cognition, aging, and neurophysiological mechanisms.
- Education programs at all levels of society that address the importance of adequate sleep in terms of brain functioning and physical health.

The Purpose of This Report

Sleep problems are among the most common health-related complaints of older persons (defined here as individuals aged 50 and above), but frequently physicians are not trained to recognize sleep disorders in this population or they assume that sleep disorders are an inevitable part of aging. Yet even physicians who correctly diagnose sleep disorders may not be able to offer treatments because of a paucity of effective therapies. More precisely, not enough research has been done on the causes of sleep disorders and effective therapies.

To address these problems, a small consensus workshop of leading researchers on sleep and aging convened to review and evaluate current data on:

- Good sleep as part of a healthy lifestyle throughout life
- Sleep problems in midlife and in older adults
- Treatments and interventions for improving sleep throughout life

These discussions led to the identification of research opportunities and the need for public and professional education.

Sleep, Health, and Aging

INTRODUCTION

More than half of all people aged 65 and older experience sleep problems. Insomnia affects approximately one-third of older Americans[1] and can result in excessive daytime sleepiness, attention and memory problems, depressed mood, falls, and a lower quality of life.[2-8] Other factors associated with aging may also contribute to sleep problems. These include disease, changes in environment, or concurrent age-related processes. However, the old dogma that poor sleep is a natural part of aging has been disproved. Data indicate that age itself does not predict insomnia, even in the presence of a decrease in sleep efficiency and decreased proportion of slow-wave sleep. Rather, the prevalence of insomnia and other sleep disorders is high in the population due to a variety of factors common in late life.[9-12]

SLEEP DISORDERED BREATHING

Defining sleep disordered breathing

Sleep disordered breathing encompasses the following:

- Obstructive sleep apnea (recurrent interruptions of breathing during sleep)
- Hypopnea (shallow breaths during sleep)
- Upper airway resistance syndrome

People with obstructive sleep apnea have frequent and repetitive episodes of oxygen deficiency, experiencing momentary awakenings that result in sleep deprivation. The clinical symptoms include loud snoring and excessive daytime sleepiness. The intermittent abnormal deficiency of oxygen in the arterial blood (a condition known as hypoxemia), and episodes of brain activation (known as arousal states) are associated with abrupt increases in systemic blood pressure. Some studies suggest that patients with sleep disordered breathing do not demonstrate the expected nocturnal dip in blood pressure.[13-15]

Using a definition of sleep disordered breathing as the occurrence of five or more breathing pauses per hour of sleep, estimates from the Wisconsin Sleep Cohort Study (WSC) suggest that 9 percent of women and 24 percent of men have some degree of undiagnosed sleep disordered breathing, and that 2 percent of women and 4 percent of men meet clinical guidelines for treatment.[16] These data are essentially the same as those found in a study in Pennsylvania, which showed a prevalence of clinically defined sleep apnea of 1.2 percent in women and 3.9 percent in men over the age range of 20 to 100 with mean age 48.8.[17]

Diagnosis is confirmed by polysomnography, which identifies apnea and hypopnea events. Severity can be expressed by the number of respiratory events per hour (also referred to as the apnea-hypopnea index). Clinically defined sleep apnea is generally determined by greater than 15 events per hour, depending on other symptoms, including daytime sleepiness.

Risk factors for sleep disordered breathing

1. Weight: The most important risk factor for sleep-disordered breathing is the presence of overweight or obesity. A recent prospective study from the WSC documented the role of weight gain in increasing incidence and progression of sleep disordered breathing, and weight loss in slowing its progression.[15] This study is important because it demonstrates that even modest weight loss can have a positive effect.

2. Alzheimer's disease: APOE-4, a genetic risk factor for Alzheimer's disease, was reported to be significantly associated with sleep apnea in a sample of adults ages 30 to 60 years in the Wisconsin longitudinal cohort sleep study.[18] Such an association between sleep disordered breathing and APOE-4 was not found in a much older (ages 79 to 97) Japanese-American cohort,[4] most likely reflecting differences in age, ethnic, and body mass index (BMI) factors. (BMI is a method of determining caloric nutritional status. It is measured as weight in kilograms divided by height in meters squared.) However, these findings support further studies on common genetic factors between sleep disturbances and cognitive decline.

Effects of sleep disordered breathing

The breathing pauses of sleep disordered breathing cause acute cardiovascular abnormalities. Apnea and episodes of hypopnea during sleep cause acute temporary changes in blood pressure, inducing elevations in mean arterial pressure (of 30 mmHg or more); fluctuations in heart rate and rhythm; increased sympathetic nerve activity; arousal and sleep fragmentation; and swings in pressure within the cavity of the chest.

Prospective data from the WSC[15] and cross-sectional data from several other studies support a role of sleep disordered breathing in hypertension. Several clinic-based studies and a cross-sectional analysis of self-reported cardiovascular disease in the Sleep Heart Health Study support a significant association between sleep disordered breathing and cardiovascular disease.[19] (Cross-sectional analysis involves a one-time study of a disease by its state and distribution in a population.) Additional analyses examining this association along the entire spectrum of sleep disordered breathing severity suggested that most of the elevation in risk of cerebrovascular disease occurs as the apnea-hypopnea index rises from 0 to 10 events per hour.

Sleep disordered breathing has been linked to considerable behavioral abnormalities, including excessive daytime sleepiness, decreased cognitive function, depression, as well as motor vehicle accidents and decreased quality of life.[16] Excessive daytime sleepiness is a cardinal feature of clinically recognized sleep disordered breathing.[20]

Several studies of sleep apnea patients have linked sleep apnea to high motor vehicle crash rates and poor performance on driving simulators.[20] Similar findings were reported in a population study of the WSC of undiagnosed sleep disordered breathing and state accident records.

New data from the WSC show a significant association of sleep disordered breathing with depression, a major cause of health care utilization.[21] Using the Zung depression inventory to measure depression, people with an apnea-hypopnea index greater than five, compared to those with no sleep-disordered breathing, had three times the odds of prevalent depression.

What can be done to reduce the incidence and associated morbidity of sleep disordered breathing?

a) Increased identification and treatment of undiagnosed sleep disordered breathing using case-finding based on primary care or population screening, and

b) Population-based interventions to prevent the development or halt the progression of sleep

disordered breathing. The high prevalence of sleep disordered breathing, particularly at the milder end of the spectrum however, raises several issues in that the effectiveness of case findings is hampered by the lack of adequate clinical resources to meet even current demands. Problems with patient acceptance of the available treatment modalities and uncertainty regarding the benefits from treatment of mild or asymptomatic sleep disordered breathing further hamper treatment.

Snoring is a strong marker for sleep apnea and upper airway resistance. Snoring without frank apnea and hypopnea events (simple snoring) is often considered to be at the mildest end of the sleep disordered breathing spectrum and is likely to progress. Snoring is not benign. The Nurses Health Study found that snoring was positively associated with the development of new hypertension, cardiovascular disease, and diabetes. Potentially modifiable risk factors for sleep-disordered breathing are overweight and obesity, alcohol, smoking, nasal congestion, and estrogen depletion in menopause.

Recent data suggest that sleep disordered breathing is associated with all of these factors, but at present weight loss is the only intervention strategy supported with adequate evidence. Interventions, such as exercise programs in conjunction with dietary control, to reduce overweight and obesity through both population and clinic-based programs hold the greatest promise for reducing the burden of mild sleep disordered breathing.

SLEEP DEPRIVATION

The metabolic syndrome

The metabolic syndrome is defined as a clustering of three or more of the following risk factors in an individual: abdominal obesity, elevated triglycerides, low level of high-density lipoprotein cholesterol, high blood pressure, and high serum glucose.

People with the metabolic syndrome are at increased risk for developing diabetes mellitus (type 2 diabetes) and cardiovascular diseases.

Insulin-resistance is the diminished effectiveness of insulin in lowering plasma glucose levels. Emerging data implicate sleep apnea as a risk factor for indicators of diabetes such as insulin-resistance and impaired glucose tolerance. In addition, sleep deprivation and sleep apnea may activate the sympathetic nervous system (which reduces digestive secretions, speeds up the heart, and contracts blood vessels) and activate proinflammatory cytokines, with impact on the cardiovascular system.[22,16] Moreover, sleep disordered breathing may be linked to abnormal lipid metabolism. Thus, sleep disordered breathing and sleep deprivation may play a significant role in the metabolic syndrome.

Using the 2002 census data, the third National Health and Nutrition Examination Survey (NHANES), it was estimated that 24 percent of U.S. residents (47 million) have the metabolic syndrome.[23] It also is associated with obesity, which is defined as a BMI greater than 30. Reports on increasing trends for obesity in the United States show that the greatest prevalence (35.8 percent and 39.6 percent for men and women, respectively) and increase (12.0 percent and 11.0 percent for men and women, respectively) in the NHANES of 1999 to 2000 is in the 60 to 74 age groups.[24]

However, sleep disordered breathing independent of obesity also is associated with the metabolic syndrome, with studies showing that middle-aged men with sleep apnea, when compared to age- and BMI-matched nonapnea controls, were found to have higher levels of plasma leptin, TNF*a*, and IL-6 (indicators of a fundamental pathologic process, they are referred to as "inflammatory markers"), and increased insulin-resistance indices (fasting plasma glucose and insulin).[25-26]

A study of data from healthy men, aged 16 to 83 years, looked at 24-hour profiles of plasma growth hormone and the stress hormone cortisol, and sleep using polysomnography sleep recordings. (Polysomnographs measure brain activity, movements, and breathing during sleep.[10]) It was found that the decrease in slow-wave sleep, i.e., the deepest, most recuperative stage of sleep, from early adulthood to later life was paralleled by a decrease in growth hormone secretion.

Association of sleep with cortisol concentrations, on the other hand, were independent of age and became significant only after age 50 when sleep became more fragmented and rapid eye movement (REM) sleep, i.e., the sleep that is associated with dreaming and memory storage, declined. The strong and robust relationships between non-REM slow-wave sleep and growth hormone secretion have led to the proposal that they both are under the control of similar types of neurons that may be located in different areas of the brain. Researchers have shown that drugs that increase one of the functions also increase the other. These data suggest that lifestyle behaviors and schedules resulting in chronic sleep restriction may increase susceptibility to metabolic syndrome independent of sleep-disordered breathing or other sleep disorders.

Total sleep loss in animals results in death, possibly as a result of exhaustion of the immune system. In humans, acute total sleep loss or severe partial sleep deprivation, i.e., 50 percent reduction of sleep, is associated with cumulative sleepiness and fatigue. More recently, it was shown that one night of sleep deprivation in young men results in a daytime increase of inflammatory markers such as IL-6. In this study, it was reported that those individuals with higher amounts of slow-wave sleep were more resistant to the effects of sleep loss on the plasma levels of IL-6.

Sleep deprivation can also lead to changes in other physiological systems, especially the production of appropriate levels of hormones and proper metabolic functioning. Studies of sleep deprivation in healthy adults provide additional data indicating potentially important effects on risk for insulin-resistance and its association with obesity and hypertension.

Partial sleep deprivation of otherwise healthy control subjects produces a level of insulin-resistance similar to that of diabetics. Carbohydrate metabolism, endocrine function, and gastrointestinal balance in young, healthy adults were studied after restricting sleep to four hours per night for six nights, as compared to a fully rested condition obtained by extending the bedtime period to 12 hours per night for six nights. The state of sleep debt was associated with decreased glucose tolerance and insulin sensitivity, elevated evening cortisol levels, and increased sympathetic activity. The alterations in glucose tolerance and hypothalamo-pituitary-adrenal function were qualitatively and quantitatively similar to those observed in normal aging.[27,9,10]

While there is agreement that total sleep loss is harmful to the health of humans, the field of sleep research is not unanimous as to whether small decreases in sleep have an affect on the human brain and body. Some researchers divide sleep into "core sleep," which is the slow-wave sleep, and "optional" or "buffer" sleep, which consists of stage 2 sleep and some REM sleep. Furthermore, recently published epidemiological studies have suggested that insomnia, paradoxically, is associated with prolonged life.

In a recent study that employed only modest sleep restriction (two hours per day for seven nights), it was shown that both young men and women experienced increased sleepiness as measured with multiple sleep latency test (MSLT) and impaired psychomotor skills as measured with a computerized test, the Psychomotor Vigilance Test (PVT). Furthermore, there was an increase of the plasma levels of inflammation markers IL-6 in both men and women, and of TNF*a*

only in men. These results, combined with the metabolic abnormalities reported in "habitual" short sleepers, suggest that even modest sleep loss is associated with a low-grade inflammation and insulin-resistance. Given the association between inflammation, insulin-resistance, obesity, diabetes, and cardiovascular morbidity, i.e., hypertension and ischemic attacks, one can speculate that even modest sleep loss, on a chronic basis, jeopardizes the health and longevity of older individuals.

Sleep homeostasis

The sleep-wake cycle appears to be controlled by two processes:

1) A circadian drive for wakefulness located in the suprachiasmatic nuclei (SCN) of the hypothalamus (the SCN is the biological clock that controls the circadian patterning of many neural, endocrine, and behavioral functions), and

2) A wake-dependent increase in sleep propensity probably situated within the classical pontine and thalamic sleep system, and more recently found within the hypothalamic preoptic area.

The SCN is the biological clock that controls the circadian patterning of many neural, endocrine, and behavioral functions. Although there is a growing body of research on the aging circadian system, relatively little exists on the aging sleep homeostatic mechanisms.

In older people, there is a reduced ability to fully and rapidly recover from prolonged wakefulness. During recovery from the stress of prolonged wakefulness, the sleep has less slow-wave sleep and is of shorter duration than in younger adults, as was found in several studies comparing sleep in young and old rats.[28-29]

Midlife is associated with an increased prevalence of common sleep disorders, e.g., obstructive sleep apnea and insomnia. The increased prevalence of insomnia in midlife appears to some extent to be secondary to loss of slow-wave sleep associated with the aging process. Furthermore, insomnia appears to be associated with hypercortisolemia and a daytime shift of IL-6 and TNF*a* secretory pattern, conditions that may lead to multiple health problems including visceral obesity, insulin-resistance, hypertension, and osteoporosis, which in turn, may affect longevity.

INSOMNIA

Insomnia is a subjective complaint of insufficient or nonrestorative sleep, which can generally be divided into two categories, depending upon the duration of the sleep difficulty. Insomnia may be either short-term (transient/acute) or chronic. In older persons, transient insomnia may be caused by bereavement, adjustment to medical difficulties and physical limitations. By definition, transient insomnia is short in duration and will generally improve without intervention or with short-term hypnotic medication therapy. Chronic insomnia, however, can result in impaired functioning and reduced quality of life in older adults.[30-31]

Insomnia is considered to be either primary or secondary in nature, depending upon the cause. If an individual finds it difficult to sleep because of pain or discomfort arising from a medical condition, the insomnia is secondary to the primary complaint of the illness. If no other factors exist, the insomnia is primary. In one of the few studies done in older adults on the effect of insomnia on quality of life, it was found that older adults with secondary insomnia had worse quality of life than those with primary insomnia.[32-33]

In general, complaints about sleep increase with age, as do specific complaints of insomnia. Estimates of the prevalence of insomnia in older persons vary widely depending upon the way insomnia is defined and the method of assessment used. In one study conducted by the National Institute on Aging on more than 6,000 older

adults, 28 percent reported difficulty falling asleep, and 42 percent reported both difficulty falling asleep and difficulty staying asleep.[34] At a three-year follow-up, 15 percent of the individuals with sleep complaints at the initial interview did not report sleep difficulties, and 5 percent of those without sleep complaints at the initial interview complained of difficulties three years later. Further analyses of these data showed that only 5.8 percent of individuals without risk factors for insomnia (medical, psychosocial, or psychiatric) at the initial visit reported insomnia at follow-up. These data suggest that sleep complaints are generally quite common in older adults, that developing a new sleep problem is associated with poor health or psychological factors, and that resolving sleep difficulties is related to better health quality.

The result of telephone interviews of 1,000 randomly selected U.S. adults indicated that the prevalence of occasional insomnia did not change with age; however, the prevalence of chronic insomnia was highest (20 percent) in adults age 65 and over.[35] This suggests that, although occasional sleep complaints may not be associated with age, older adults experience chronic sleep difficulties more often than do younger adults.

Insomnia in older adults is not benign. A number of research studies have shown, both cross-sectionally and longitudinally, that insomnia has a negative impact on cognitive functioning and quality of life.[36-37,30,38,31] Insomnia patients were found to have slower reaction time, poorer balance, and were more likely to forget numbers in the digit span test than carefully matched controls. Furthermore, these deficits were seen even after the insomnia patients spontaneously experienced a subjectively "good night of sleep."[39]

Individuals with insomnia complaints were found to have overall poorer quality of life than individuals without insomnia,[31] and individuals with insomnia identified more symptoms of depression and anxiety. It is unclear whether depression and anxiety lead to both sleep disturbance and impaired life quality, or whether the sleep disruption leads to the impaired quality of life and psychiatric difficulties. However, few studies have been done on the effect of insomnia on quality of life specifically in older adults.[37] A large epidemiological study of older adults in the United States found that sleep difficulties were associated with poorer self-perceived health status. Clearly, insomnia complaints should be carefully evaluated and treated appropriately.[1,34]

Before insomnia can be treated, its cause must be determined. In addition to primary sleep disorders, contributory factors in older persons include medical and psychiatric illnesses, medication, and circadian rhythm disorders. Older adults often have a number of medical conditions that can affect and impair sleep. Commonly, older adults complain of difficulty sleeping in response to physical discomfort caused by a physical ailment, such as arthritis, chronic obstructive pulmonary disease, cerebrovascular disease, neurological disorders, asthma, or headaches. In fact, some studies have shown that, in the absence of medical disorders, the sleep of older adults is not substantially disturbed.[40]

Depression

Depression is the psychiatric diagnosis most commonly associated with insomnia. Since the prevalence of depression is higher in older than in younger adults, sleep disturbances often are accompanied by depression.[41] Older adults with depression have more disturbed sleep than younger adults with depression,[42] and symptoms of depression are associated with increased likelihood of difficulties with sleep.[1]

Medications

Older adults often take multiple medications for medical and/or psychiatric problems, each of which can have an impact on sleep. Some of the drugs commonly used by older adults and known to affect sleep include alcohol, central nervous

system stimulants, beta-blockers, bronchodilators, calcium channel blockers, decongestants, stimulating antidepressants, and thyroid hormones. Drugs known to have sedating effects include the longer acting hypnotics, antihypertensives, antihistamines, anxiolytics, tranquilizers, and antidepressants.

Circadian rhythm changes

With age, circadian rhythms are advanced or shifted earlier relative to clock time. This can result in the internally driven sleep period moving earlier than the desired sleep period. Older adults commonly report that they can hardly stay awake until bedtime but are awake before the sun rises in the morning. The fact that older adults are likely to complain of sleep difficulties in the latter half of the night suggests that the endogenous timing of the sleep-wake cycle may contribute to sleep difficulties.

Circadian melatonin rhythms

The relationship between sleep timing and the timing of the circadian rhythm of plasma melatonin secretion was investigated in a group of healthy young and older subjects without sleep complaints.[43] Timing of sleep and the phase of the circadian melatonin rhythm were earlier in the older subjects although the duration of sleep was similar. Consequently, the older subjects awoke at a time when they had higher relative melatonin levels, in contrast to younger subjects, whose melatonin levels were relatively lower by wake time. These findings indicate that aging is associated not only with an advance of sleep timing and the timing of circadian rhythms but also with a change in the internal phase relationship between the sleep-wake cycle and the output of the circadian pacemaker.

Primary sleep disorders

Primary sleep disorders such as Periodic Limb Movement Disorder and sleep disordered breathing cause fragmentation of nighttime sleep. Studies have shown that these disorders are very common in older adults.[44-45] Oftentimes, these individuals do not recognize the disorder itself but rather complain of frequent nocturnal awakenings, sleepiness during the day, and/or nonrestorative sleep.

Behavior-related insomnia

At times the cause of insomnia in older adults may be behavioral in nature, such as the use of alcohol, caffeine, nicotine, and over-the-counter or herbal medicines, a poor sleep environment, and excessive napping.

Therapeutic strategies

Several therapeutic strategies are likely to become effective treatments for some of the insomnias associated with aging. The use of bright light therapy for phase disorders of the circadian rhythms is now commonplace.[46] Behavior modifications, such as stimulus control and sleep restriction, appear to be effective techniques for shortening sleep latency and wake after sleep onset times.[47]

Melatonin treatment is being tested for its sleep-inducing effects; however, it appears to be most effective at physiological doses in dealing with circadian dysynchrony.

A double-blind placebo-controlled clinical trial of melatonin was conducted on a group of individuals age 50 and older complaining of insomnia and a group without insomnia.[48] Self-reports of insomnia were confirmed by measurements of body movements through the night period at home (actigraphy) as well as by measurements of brain activity, movements, and breathing during sleep (polysomnography) in the sleep laboratory.

In addition to a placebo, each participant received different doses of melatonin (0.1, 0.3, and 3.0 mg) orally one-half hour before usual bedtime for one week in a random order, each followed by a

one-week washout period. The highest dose (3.0 mg) is the dose commonly found in over-the-counter preparations and results in blood levels 10 to 20 times the normal physiological levels produced by the lower doses. The most effective dose for improving the quality of sleep, measured as sleep efficiency or the proportion of time in bed actually sleeping, was 0.3 mg. The highest dose, like the lowest, also improved sleep efficiency, although to a lesser extent. However, the 3 mg dose also significantly reduced nighttime body temperature and increased daytime melatonin levels.

There was no relation found between a subject's own endogenous melatonin levels and sleep efficiency. Individuals with normal sleep were unaffected by any dose of melatonin. Further replications with larger groups with objectively defined sleep problems and with a broader range of medical co-morbidities are needed.

CHANGES IN SLEEP AND CIRCADIAN RHYTHMS WITH AGE

Our current understanding of the regulation of the human sleep-wake cycle indicates that sleep and wake behaviors are generated by a complex interaction of sleep homeostatic and endogenous circadian processes, as well as environmental factors.

The sensation of sleepiness, propensity to fall asleep, and depth of sleep are hallmarks of the compensatory response to sleep loss.[49] This drive toward sleep and the tendency to sleep longer and more deeply after sleep deprivation is referred to as "sleep homeostatic process." It has been postulated that the sleep homeostatic process is regulated by sleep factors that increase during wakefulness and decline during sleep. Recent studies suggest that the acetylcholine of the basal forebrain and adenosine may play an important role in this physiological drive.[50] The sleep homeostatic process regulates the amount of slow-wave sleep and depth of sleep.

Within the last several years, two important nuclei have been identified within the hypothalamus that are important for the control of sleep homeostasis. The first is a cluster of cells in the ventrolateral preoptic (VLPO) area of the hypothalamus. These VPLO cells exhibit activation, indicated by generation of cFos protein, (a marker protein for activated cells), only during sleep and independent of the circadian cycle, and are inhibited by noradrenaline, acetylcholine, and serotonin neurotransmitters associated with the waking state.[51-52]

Because the VLPO neurons are active only during sleep, it is proposed that they are central to the regulation of the sleep-wake cycle. Cell-specific damage of these neurons results in significant decreases in non-REM sleep (slow-wave sleep). These cells interact with the systems that activate the cortical areas that play an important role in regulating wake-sleep states.[53-55] More recently, a gene for narcolepsy in dogs and humans has been identified.[56-57] This gene codes for a family of brain chemical signaling agents (neuropeptides) known as hypocretins. These neuropeptides are made only in an area of the brain that also regulates basic body functions such as feeding and energy balance, blood pressures, and central regulation of the immune system. The brain cells that contain them make connections with many of the brain regions involved in regulating the sleep-wake cycle. The hypocretins may act as chemical signals involved in the mechanisms of homeostasis and alertness.

Gene regulation of sleep

Genes that regulate the sleep-wake cycle are being discovered. The first mammalian Clock Gene was identified and its structure was determined in 1994. Using data from the WSC, one change in the DNA code for this gene was found to be significantly associated with preference for later sleep times, equivalent to a 10- to 44-minute difference in preferred timing.

The circadian pacemaker (SCN)

Physiological sleepiness not only varies with the duration of prior waking, but also exhibits circadian variation. Circadian rhythms, which are observed in virtually every physiological and behavioral parameter, including sleep-wakefulness and endocrine rhythms, are generated by a circadian pacemaker located in the SCN of the hypothalamus.58-59

At the cellular and molecular level, it has been shown that there are age-associated changes in afferent and efferent pathways of the SCN. It is quite possible that disruption in the integrative neural systems could have serious deleterious effects in the function of other organ systems.

The circadian timing system

Sleep disturbances may also be caused in part by a fundamental change in the circadian timing system of older adults.[60] It has long been believed that the human circadian clock had a period of about 25.25 hours and that it speeds up when we grow older. This concept of the shortening of the period with age was used to explain the common observation that many older people went to sleep earlier in the evening and awoke earlier in the morning. Habitual wake time, the timing of the rise of hormone secretion, and endogenous temperature rhythms of older subjects occur at an earlier clock hour, suggesting that the earlier wake time may be due to an advance of the circadian clock.[61] These results also suggest that sleep disruption during the last half of the sleep period might be due to age-related increases in the phase angle between the core temperature minimum and the timing of sleep.[46,62-63]

Circadian rhythms

Age-related reductions in the amplitude of circadian rhythms have been observed for a wide variety of clock-regulated functions, ranging from temperature and endocrine rhythms to cycles of subjective alertness.[61,64-66] However, circadian rhythm amplitude can be well preserved in the "super healthy" older person.[67]

It now appears that the intrinsic period of the endogenous human circadian pacemaker is not significantly different between healthy old and young adults and is much closer to 24 hours than previously thought. The deterioration in the SCN may represent a pathologic rather than a normal change, indicating that age-related changes of rhythm *in vivo* may be due to defects either upstream or downstream from the SCN.

Age-related changes

With increasing age, prominent changes in sleep homeostatic regulation occur. While older people spend more total time in bed, nocturnal sleep is both shallow and decreased in total amount.[68] Polysomnographic assessment confirms the subjective decline in sleep quality with age in healthy older people.[10] Deep sleep decreased from 18.9 percent during young adulthood (ages 16–25) to 3.4 percent during midlife (ages 36–50). This decrease in slow-wave sleep was accompanied by decreases in growth hormone levels. Surprisingly, a further reduction in slow-wave sleep was not seen in late life.

The impact of age REM sleep and sleep fragmentation was not evident until late life (ages 71–83). During late life, REM sleep declined gradually by approximately 10 minutes per decade. Sleep fragmentation, as measured by wake time, also increased gradually, by 30 minutes per decade during late life. Interestingly, elevation of evening cortisol levels followed the same chronology as the decline in REM sleep.

Therefore, decreases in sleep quality may contribute to age-related changes in metabolism that may predispose older people to adverse health outcomes. In fact, the presence of disturbed sleep predicts overall health-related quality of life better than any other disease-activity measure in patients who suffer from chronic illnesses.[69]

MENOPAUSE AND SLEEP

Both sleep onset insomnia and sleep maintenance insomnia are characteristically increased during perimenopause and menopause. They are major features of the medical care of women going through menopause and should be appropriately addressed by the physician who treats menopausal women. In light of the Women's Health Initiative trials,[70] the general use of estrogen replacement has been eliminated.

Perhaps the most significant areas of research are as follows:

- Questions regarding the relation of estrogen to depression and insomnia remain unanswered, and, given the prevalence of depression, this is a very significant public health issue.
- The basic physiology of estrogen's effect on both circadian rhythm and thermoregulation needs to be elucidated, with further clarification for the sake of future treatments that may be specific to the sleep effects of estrogen. Research into selective receptor modifiers that might affect thermoregulation, as well as studies relating to phytoestrogens and other less potent estrogenic substances, are needed.

SLEEP AND COGNITION

Of the many losses and diminished capacities experienced with age, a decline in cognitive function is perhaps the most frightening. A number of research studies, both cross-sectional and longitudinal, have shown that disturbed sleep has a negative impact on cognitive functioning and quality of life.

A large epidemiological longitudinal study (Honolulu-Asia Aging Study, or HAAS) of older men (mean age of 76.6 years, range 71 to 93) investigated the association between sleep disturbances (insomnia and daytime sleepiness) and the incidence of dementia and cognitive decline.[4] It was found that there was a significant association between the self-report of excessive daytime sleepiness, found in 8 percent of the cohort, and a diagnosis of dementia three years later.

The risk was twofold (O.R. = 2.2) as compared to those not reporting daytime sleepiness, after adjusting for age and other factors. Cognitive decline also was significantly associated with excessive daytime sleepiness (O.R. = 1.4). In contrast, insomnia, found in 31 percent of the cohort, was not associated with either cognitive decline or dementia.

Memory

Recent research on the importance of sleep for the consolidation of memory suggests that different stages of sleep may facilitate the consolidation of different memory tasks. For example, post-training REM sleep may be important for procedural memory, and non-REM slow-wave sleep may be important for declarative memory.[71] However, there are contradictory findings in the literature. A possible role for the importance of REM sleep rather than slow-wave sleep in humans has been suggested.[72] Interestingly, the beneficial effect of REM sleep on memory consolidation appears to parallel the beneficial cognitive effects of cholinergic medications that increase REM sleep. It should be noted that human sleep and memory studies have demonstrated that memory consolidation can take place during sleep. This does not mean that sleep has a unique role not found in quiet wakefulness.

One possible exception is that in an experiment using a perceptual learning task, Stickgold et al. found that performance improved only after a night of sleep.[73] For a visual texture discrimination task, consolidation of learning required more than six hours of sleep on the night following training. Slow-wave sleep appeared necessary during the first two hours of sleep and REM sleep after the sixth hour of sleep. When subjects were totally sleep-deprived the night after training, no

improvement was seen even after two nights of recovery sleep. These data suggest an important role for human sleep in off-line (nonwaking) memory reprocessing. However, subjects tested after different periods of wakefulness were not kept in controlled conditions, such as quiet wakefulness or without visual stimulation. Thus, it is not clear whether sleep facilitated improved performance or waking experiences prevented improvement.

A study done on kittens demonstrated that sleep facilitates neural reorganization as a result of altered experience.[74] Kittens that had one eye sutured for 24 hours showed more neural accommodation to monocular visual experience following sleep than following waking experiences in either a lighted or darkened environment. Thus sleep, and not the lack of visual experience, facilitated neural plasticity for visual processing. There has not yet been a similar demonstration for memory.

Both hyperarousal and central nervous system depression are associated with deficits in cognitive functioning, whereas moderate levels of arousal are often associated with improved functioning. Variation in cognitive functioning related to circadian rhythms, sleep deprivation, and sleep disorders such as insomnia and sleep apnea can be understood within this broad framework.

For example, there is a strong circadian arousal effect on memory performance in which older human adults perform better in the morning than in late afternoon. This late afternoon deficit can be eliminated by caffeine,[75] suggesting that some of the deficit, at least, is mediated by physiological arousal. Parenthetically, insomniacs, who are often hyperaroused, show more evidence of continued cognitive processing in sleep than good sleepers.[76]

With regard to sleep deprivation and the resulting daytime sleepiness, many studies have shown that the speed of performance slows and that there are lapses in attention. There are relatively few deficits in accuracy in executive functioning tasks during even severe sleep deprivation. This is in contrast to marked sleep inertia effects on cognition when subjects are awakened out of slow-wave sleep after being sleep-deprived.[77]

Cognitive deficits and sleep apnea

There is a large and increasing research literature on the cognitive deficits associated with sleep apnea. A summary of the results from different research designs can serve as a good model for other areas. There are five broad types of research designs:

1) Cross-sectional studies comparing sleep apnea patients to nonpatients have found that sleep apnea impairs attention, short-term memory, perceptual learning, acquisition in long-term memory, and categorization;

2) Studies examining whether oxygen deficit or sleep disruption are most associated with deficits have found that most cognitive deficits are associated with hypoxemia, although attention deficits are also associated with disrupted sleep;

3) Studies examining whether nasal continuous positive air-pressure (nCPAP) reverses cognitive deficits found that many deficits are reversed, but only on nights on which nCPAP is used; some deficits reflecting executive functions do not reverse[32] (nCPAP is a device that provides a continuous flow of oxygen to the sleeper);

4) Cross-sectional studies of normal populations have typically found small or no relationship between sleep disordered breathing and cognitive functioning. In a Sleep Heart Health Study cognitive substudy in which participants were generally older adults and a substantial portion of the sample had disordered breathing, deficits in attention, manual dexterity, psychomotor efficiency, and executive functioning were found;[78] and

5) Longitudinal studies of normal populations have not found predictive effects of baseline

disordered breathing with cognitive functioning on subsequent measurement occasions; but similar to the cross-sectional studies of normal populations, the proportion of individuals with sleep disordered breathing is either small or the severity is low.

Memory at the molecular level

Research at the molecular level is examining the molecular processes underlying the role of sleep in the consolidation of long-term memory using specific phosphorylated cyclic AMP-responsive element binding protein (CREB)-mutant mice.[79] Results indicate that like sleep deprivation, inhibition of protein kinase A (PKA) or protein synthesis disrupts memory consolidation only at discrete times following training, and these times vary depending upon the strength of the training protocol.

This is an exciting window of opportunity as research on the relationships between sleep, cognition, aging, and neurophysiological mechanisms is just beginning to coalesce.

HOW OLDER PERSONS ARE TREATED FOR SLEEP DISORDERS

The interrelationships between sleep and health are crucial, particularly for older individuals. The degree to which declining physical and mental health impacts sleep quality in the aged population was for many years an under-appreciated phenomenon. The earliest epidemiological studies of sleep complaints typically reported that they were more common in women and increased with age, with some studies finding prevalences as high as 40 percent to 50 percent in the older population. Further studies confirmed these basic findings. However, a wave of epidemiological studies published in the late 1980s began to demonstrate that when other potential causes of disturbed sleep are accounted for, such as medical or psychological burden, chronological age often explained little of the observed prevalence of age-associated poor sleep quality.[80]

Two observations come readily from these epidemiological data. The first is that fully half of the population of older persons do not report disturbed sleep or at least are content with the sleep that they achieve. The second is that much, if not all, of the sleep complaints that are seen with advancing age are apparently not part of the aging process per se, but are associated with other factors such as medical burden, which itself tends to increase with advancing age.

Regarding this first observation, while approximately half do not complain of poor sleep, numerous studies have shown that even optimally aging, noncomplaining older adults have sleep patterns that are considerably "degraded" from those seen in healthy young adults.[80-82] This finding is consistent with the more recent epidemiological literature indicating that while aging, per se, results in significant changes in sleep, it does not of necessity result in complaints of disturbed sleep or insomnia. It has been suggested[83] that, despite their objectively disturbed sleep, healthy older individuals appear to adapt their perception of what is "acceptable" sleep and therefore do not necessarily complain.

The second observation that all of the sleep complaints that are seen with advancing age are not part of the aging process per se, but rather are associated with other factors such as medical burden, has been followed up by opportunistic studies[80] that demonstrated that screening large samples of older adults for health before screening for sleep disturbance and sleep disorders left very few subjects who had a significant sleep complaint or disorder. In other words, poor health and sleep disorders co-segregate.

Recently the NIA-funded Established Populations for Epidemiologic Studies of the Elderly (EPESE) examined this apparent relationship between sleep complaints and physical and mental health across a three-year window in some 6000+ subjects. Data from the

EPESE study have demonstrated that development of a complaint of insomnia is commonly associated with an emergent medical or psychological co-morbidity.[1] Further, EPESE data also indicated that resolution of a complaint of insomnia is commonly associated with contemporaneous resolution of a medical illness.[84]

The major implication of the secondary nature of many sleep disturbances reported by older persons has led to the current clinical wisdom of "treat the primary problem effectively and the secondary, or symptomatic, sleep disturbance will likely resolve." This is not an unreasonable and functional approach, but it may be far from the best clinical practice. A multimodal cognitive-behavioral approach to primary insomnia has recently been demonstrated to be so effective in treating primary insomnia[85-87] that it has been provisionally extended to include secondary or co-morbid insomnia.

Rybarczyk and colleagues at Rush-Presbyterian in Chicago are currently comparing the efficacy of cognitive-behavioral and relaxation treatments versus an attention control (wellness/stress class) for treatment of insomnia among patients with three common age-related chronic illnesses: osteoarthritis, chronic obstructive pulmonary disease, and coronary artery disease with exceptionally high rates of co-morbid insomnia. Clearly, other well-designed and controlled studies such as Rybarczyk's[88] will be needed to address this extremely important question.

Much has been made of the observation that there may be two kinds of apnea that manifest themselves in the late middle-aged to older segments of the population. One is age-related and is associated with significant daytime sequelae that seems to impact individuals as they age from their 40s to 70s and then gradually drops as these individuals die (typically of apnea-related disorders, such as coronary artery disease, stroke, etc.). The other is an age-dependent disorder that begins to impact individuals in their 60s, increases in prevalence across the rest of the life-span, and is not necessarily associated with significant daytime sequelae.[89-92] A crucial question facing both researchers and practitioners of sleep medicine is whether to treat age-dependent sleep apnea, particularly in the absence of any significant daytime sequelae. This question is of great concern, as it is closely interwoven with the related question of whether sleep apnea contributes to cognitive impairment and ultimately Alzheimer's disease in older persons.[93-94]

Periodic limb movement disorder

There is considerable controversy concerning whether periodic limb movement disorder (PLMD) is a true disorder, that is, whether or not it is a clinical symptom resulting in sleep disturbance or significant insomnia. A body of literature exists[95-100] indicating that there is little reason to support the notion that PLMD is a true disorder as there is little relationship noted between the presence of PLMs and either sleep fragmentation or daytime sequelae. This is of concern as PLMs are quite frequent in older persons.

Treating institutionalized and/or demented aged

All of the issues confronting the practitioner in effectively treating sleep disturbances in cognitively intact, community-dwelling older patients are magnified in the treatment of sleep disturbances in older patients who are demented, institutionalized, or both. The current state-of-the-art in effectively treating sleep disturbances in the demented and the complexities of treating sleep disturbances in the institutionalized aged have been comprehensively reviewed.[101-104] Following is a proposed research agenda[105] to further study the field:

- Longitudinal changes in sleep during the course of dementia.
- Randomized controlled trials of treatments for behavioral disturbances using measures of sleep, daytime function, and impact on caregivers in addition to behavioral and psychiatric outcome measures.

- Randomized controlled trials to assess comparative efficacy of specific pharmacological and nonpharmacological approaches to sleep management.
- Long-term efficacy and safety of newer hypnotic agents in demented patients with sustained sleep disorders.
- Studies targeted at a better understanding of the impact of improved sleep quality on the cognitive function of demented patients.
- Empirical validation of algorithms for assessing and managing sleep in dementia.
- Controlled health services trials of effect of changes in institutional policies on residents' sleep.

Hypnotics

Approximately one-half of all patients who complain to their physicians of insomnia are treated with hypnotics. Although these drugs may be useful in the management of transient insomnia, they generally fail to provide long-term relief from chronic sleep disturbances. Prolonged use can result in habituation, loss of efficacy, and drug-induced insomnia. Paradoxically, hypnotics can worsen existing sleep disturbances by inducing drug-dependency insomnia, and, when the drug is discontinued after intermediate to long-term use, rebound insomnia and nightmares may occur. Hypnotics may also exacerbate undiagnosed sleep apnea.

Adverse daytime effects of hypnotics include impaired cognition, slowed psychomotor functioning, and injuries induced by falls. Chronic hypnotic use also has been associated with increased mortality risk. Two NIH consensus conferences have endorsed the cautious use of hypnotics for temporary, situational, or intermittent conditions (such as stress-related sleep disturbance), but otherwise strongly recommended against their use for other conditions, such as chronic insomnia.

Nevertheless there is considerable disagreement in the sleep research and sleep medicine communities with regard to chronic use.[106-111] The single point of agreement between these often contentious points of view is the need for appropriately designed and executed long-term randomized trials. The vast majority of past hypnotic trials have been of relatively short duration, typically under two to three months.

Adding to the complexity of the pharmacotherapeutic picture are the issues of alternative therapeutic agents such as melatonin and valerian, both of which have extremely limited data to support their effectiveness as sleep aids, and the emerging research efforts exploring the efficacy of agents that may have their actions via the somatotrophic hormonal axis[112-113,103] or the related gabaergic system[114] to improve the sleep quality of older persons. (Somatotropin is a protein hormone that promotes body growth, fat mobilization and inhibition of glucose utilization. The gabaergic system, of which GABA is the key component, is involved in the inhibitory mechanisms of the central nervous system.)

Exercise and sleep

There is considerable evidence to substantiate claims of the beneficial effect of regular exercise—both endurance (aerobic) and resistance (weight) training—on health and quality of life in older individuals.[115-117] Regular exercise is linked to a number of positive outcomes, such as increased aerobic capacity, increased strength, improved body composition (increased lean and decreased fat mass), improved balance and decreased risk of falls, decreased depressive symptoms, increased functional capacity and improved sense of energy and general well-being. Regular exercise may also be associated with improved immune function, although there are only limited data in support of this relationship. Regular exercise has been demonstrated to lower risk for a number of diseases, including hypertension, stroke, coronary

artery disease, hyperinsulinemia, insulin-resistance and non-insulin-dependent diabetes mellitus, and disease-related mortality.

Epidemiological studies consistently support the view that acute and chronic exercise promotes sleep.[118] A large (n = 1190) Finnish study found that, in response to open-ended questions, both men and women reported exercise as the most important sleep-promoting factor, and respondents who reported getting regular exercise had less daytime sleepiness compared to those who were more sedentary. It is noteworthy that 43 percent of those who reported increased amounts of exercise during the previous three months (n = 81) reported improved subjective sleep, compared with only 1 percent, whose self-reported sleep deteriorated. Conversely, 30 percent of those subjects who reported decreased exercise in the previous three months (n = 73) reported deterioration in their sleep, compared to the 4 percent who reported improved sleep quality.

Epidemiological data clearly support the hypothesis that regular exercise is associated with improved sleep quality.[119-121,33] However, at this time there are no published randomized controlled trials examining the influence of exercise on the objectively measured sleep of older individuals either complaining of sleep disturbance or of older insomniacs, and no randomized controlled trials of impact of exercise on the subjective sleep of insomniacs. Such studies will be required before we can clearly delineate the beneficial effect of regular exercise on sleep quality in older individuals and the long-term impact of such improved sleep on health, longevity, and quality of life.

Naps in older persons

Daytime sleepiness among older persons occurs less frequently than does insomnia. However, sleepiness and napping both increase with age; daytime sleepiness has a prevalence of approximately 15 percent to 40 percent in older persons[122-125] compared with a lower prevalence of approximately 7 percent to 15 percent in the general adult population.[126-128] Daytime sleepiness has been related to a number of psychological and physical variables; sleepiness is related to snoring, sleep apnea, medications, poor general health, and depression. Daytime sleepiness is more frequent in older men than women.

The distinction between daytime sleepiness and napping is not precise. However, several studies have examined the occurrence of napping, as opposed to the symptom of daytime sleepiness. Such studies indicate that the frequency of napping also increases with age.[129-133] However, these studies report widely variable prevalence figures for napping, which likely are related to factors such as cultural influences, differences in age, health, and employment status of subjects, and different methods for determining the presence of napping. Although sex differences in napping have not been consistently reported, studies that show differences find that men report more frequent napping than women.[1,123]

It is unclear whether daytime napping and even daytime sleepiness represent voluntary, optional behaviors or an involuntary expression of pathological sleepiness. In trying to address this issue, some studies have reported a positive association between daytime sleepiness and insomnia complaints[122-123] or a positive correlation between the frequency of naps and middle-of-night awakenings.[131-132] However, other studies show no relationship between naps and nocturnal sleep,[133-134] and still others note a positive correlation between naps and nocturnal sleep length for a 24-hour sleep duration.[123,105,131]

Two studies have experimentally investigated the relationships between daytime napping and performance and nighttime sleep. One showed an

increase in total 24-hour sleep time among those who napped, but polysomnographic studies showed a reduction in nocturnal sleep time during napping as well as a reduction in nighttime sleep efficiency. (Polysomnographic studies continuously monitor normal and abnormal physiologic activity during sleep.) Evening alertness was improved among nappers. No changes were noted in circadian rhythm measures or performance.[135] A similar study[136] showed that afternoon performance and subjective sleepiness and fatigue were both improved, suggesting that brief naps may have a positive but short-acting effect.

As noted above, cross-sectional epidemiologic studies have shown that daytime sleepiness is associated with worse health. Recent data from large cohort and epidemiologic longitudinal studies[137-139] suggest that daytime sleepiness can also be associated with adverse health consequences. It is unclear whether sleepiness and napping per se increase morbidity and mortality. A more likely explanation is that sleepiness is attributable to some other health factor, which also leads to adverse health outcomes. Thus, daytime sleepiness may be an early indicator of subclinical as well as clinically evident medical illness. It should also be noted that other studies have failed to find an association between daytime sleepiness/napping and mortality.[140]

FUTURE DIRECTIONS AND RECOMMENDATIONS

- Longitudinal studies are needed to confirm a causal role of mild-moderate sleep disordered breathing in cardiovascular and behavioral morbidity in order to fully determine the cost of morbidity attributable to sleep disordered breathing.
- Understanding the natural history of sleep disordered breathing with aging is crucial.
- Community trials in weight loss and exercise to decrease sleep disordered breathing severity and occurrence are desperately needed.
- Recognition of sleep disordered breathing as a significant public health problem in federal and other prominent health initiatives is needed; programs targeting obesity in children should identify sleep disordered breathing as one of the important negative health outcomes.
- Existing educational programs (National Institutes of Health and the National Sleep Foundation) should continue, and new conduits for public education should be initiated, to inform the public of sleep disordered breathing; in particular, of the role of overweight in sleep disordered breathing.
- Goals for the reduction of sleep disordered breathing via weight loss and exercise should be set; a surveillance system to document trends in sleep disordered breathing should be established.
- The findings that there appear to be distinct changes in sleep quality that occur through the adult age span that also mark specific alterations in hormonal systems that are essential for metabolic regulation need to be pursued.
- Research on the relationship between sleep, cognition, aging, and neurophysiological mechanisms is an exciting area that needs further development.

The importance of adequate and regular sleep, along with weight management, healthy eating habits, and regular exercise, should be part of public education and policy. These measures may include:

- Education of young and middle-aged individuals of the importance of adequate sleep in terms of brain functioning and physical health.
- Explanation of the association of sleep loss/disturbance to obesity and its sequelae.
- Education of middle-aged individuals about the association of stress and sleep disturbance and the need for better coping mechanisms to reduce stress.
- Education of employers and public policymakers on the association between sleep loss/irregular sleep, e.g., shift work, and the public safety and health of employees.
- Education of physicians and health professionals on the importance of early detection and intervention of common sleep disorders, e.g., sleep apnea, insomnia in middle-aged individuals.
- Future research needs include the delineation of the needs versus the ability to sleep in older adults, and establishing the effects of insomnia upon the quality of life.

Literature Cited

1. Foley D, Monjan A, Brown SL, Simonsick EM, Wallace RB, Blazer D. 1995. Sleep complaints among older persons: an epidemiologic study of three communities. *Sleep* 18: 425–32.

2. Bixler EO, Vgontzas AN, Lin HM, Vela-Bueno A, Kales A. 2002. Insomnia in central Pennsylvania. *J Psychosom Res* 53: 589–92.

3. Brassington GS, King AC, Bliwise DL. 2000. Sleep problems as a risk factor for falls in a sample of community-dwelling adults aged 64–99 years. *J Am Geriatr Soc* 48: 1234–40.

4. Foley D, Monjan A, Masaki K, Ross W, Havlik R, White L, Launer L. 2001. Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older Japanese-American men. *J Am Geriatr Soc* 49: 1628–32.

5. Cricco M, Simonsick EM, Foley DJ. 2001. The impact of insomnia on cognitive functioning in older adults. *J Am Geriatr Soc* 49: 1185–89.

6. Jean-Louis G, Kripke DF, Ancoli-Israel S. 2000. Sleep and quality of well-being. *Sleep* 23: 1115–21.

7. Moore P, Bardwell WA, Ancoli-Israel S, Dimsdale JE. 2001. Association between polysomnographic sleep measures and health-related quality of life in obstructive sleep apnea. *J Sleep Res* 10: 303–08.

8. Stepnowsky C, Johnson S, Dimsdale J, Ancoli-Israel S. 2000. Sleep apnea and health-related quality of life in African-American elderly. *Ann Behav Med* 22: 116–20.

9. Spiegel K, Leproult R, Van Cauter E. 1999. Impact of sleep debt on metabolic and endocrine function. *Lancet* 354: 1435–39.

10. Van Cauter E, Leproult R, Plat L. 2000. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *JAMA* 284: 861–68.

11. Van Cauter E, Plat L, Copinschi G. 1998. Interrelations between sleep and the somatotropic axis. *Sleep* 21: 553–66.

12. Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP. 2000b. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia [see comments]. *J Clin Endocrinol Metab* 85: 1151–58.

13. Loredo JS, Clausen JL, Nelesen RA, Ancoli-Israel S, Ziegler MG, Dimsdale JE: 2001. Obstructive sleep apnea and hypertension: are peripheral chemoreceptors involved? *Med Hypotheses* 56: 17–19.

14. Morrell MJ, Finn L, Kim H, Peppard PE, Safwan BM, Young T. 2000. Sleep fragmentation, awake blood pressure, and sleep-disordered breathing in a population-based study. *Am J Respir Crit Care Med* 162: 2091–96.

15. Peppard PE, Young T, Palta M, Skatrud J. 2000b. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 342: 1378–84.

16. Young T, Peppard PE, Gottlieb DJ. 2002. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 165: 1217–39.

17. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A. 2001. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med* 163: 608–13.

18. Kadotani H, Kadotani T, Young T, Peppard PE, Finn L, Colrain IM, Murphy GM Jr, Mignot E. 2001. Association between apolipoprotein E epsilon4 and sleep-disordered breathing in adults. *JAMA* 285: 2888–90.

19. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier NF, O'Connor GT, Boland LL, Schwartz JE, Samet JM. 2001. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 163: 19–25.

20. Young T, Blustein J, Finn L, Palta M. 1997. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. *Sleep* 20: 608–13.

21. Young T, Peppard P. Sleep disordered breathing in the general adult population: A risk dactor for depression. AJRCCM 2002, 165: A230.

22. Newman AB, Nieto FJ, Guidry U, Lind BK, Redline S, Pickering TG, Quan SF. 2001. Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. *Am J Epidemiol* 154: 50–59.

23. Ford ES, Giles WH, Dietz WH. 2002. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 287: 356–59.

24. Flegal KM, Carroll MD, Ogden CL, Johnson CL. 2002. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 288: 1723–27.

25. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. 2002. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* 165: 677–82.

26. Vgontzas AN, Bixler EO, Kales A, Criley C, Vela-Bueno A. 2000a. Differences in nocturnal and daytime sleep between primary and psychiatric hypersomnia: diagnostic and treatment implications. *Psychosom Med* 62: 220–26.

27. Spiegel K, Leproult R, Colecchia EF, L'Hermite-Baleriaux M, Nie Z, Copinschi G, Van Cauter E. 2000. Adaptation of the 24-h growth hormone profile to a state of sleep debt. *Am J Physiol Regul Integr Comp Physiol* 279: R874–R883.

28. Basheer R, Shiromani PJ. 2001. Effects of prolonged wakefulness on c-fos and AP1 activity in young and old rats. *Brain Res Mol Brain Res* 89: 153–57.

29. Shiromani PJ, Lu J, Wagner D, Thakkar J, Greco MA, Basheer R, Thakkar M. 2000. Compensatory sleep response to 12 h wakefulness in young and old rats. *Am J Physiol Regul Comp Physiol* 278: R125–R133

30. Roth T, Ancoli-Israel S. 1999. Daytime consequences and correlates of insomnia in the United States: results of the 1991 National Sleep Foundation Survey II. *Sleep* 22 Suppl 2: S354–S358.

31. Zammit GK, Weiner J, Damato N, Sillup GP, McMillan CA. 1999. Quality of life in people with insomnia. *Sleep* 22: S379–S385.

32. Kribbs NB, Pack AI, Kline LR, Getsy JE, Schuett JS, Henry JN, Maislin G, Dinges DF. 1993. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. *Am Rev Respir Dis* 147: 1162–68.

33. Vitiello MV, Prinz PN, Schwartz RS. 1994. Slow wave sleep but not overall sleep quality of healthy older men and women is improved by increased aerobic fitness. *Sleep Res* 23: 149.

34. Foley DJ, Monjan A, Simonsick EM, Wallace RB, Blazer DG. 1999a. Incidence and remission of insomnia among elderly adults: an epidemiologic study of 6,800 persons over three years. *Sleep* 22 Suppl 2: S366–S372.

35. Ancoli-Israel S, Roth T. 1999. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey I. *Sleep* 22 Suppl 2: S347–S353.

36. Katz DA, McHorney CA. 2002. The relationship between insomnia and health-related quality of life in patients with chronic illness. *J Fam Pract* 51: 229–35.

37. Lichstein KL, Durrence HH, Bayen UJ, Riedel BW. 2001. Primary versus secondary insomnia in older adults: subjective sleep and daytime functioning. *Psychol Aging* 16: 264–71.

38. Rumble R, Morgan K. 1992. Hypnotics, sleep, and mortality in older people. *J Am Geriatr Soc* 40: 787–91.

39. Hauri PJ. 1996. 1997. Cognitive deficits in insomnia patients. *Acta Neurol Belg* 97: 113–17.

40. Monjan A, Foley D. 1996. Incidence of chronic insomnia associated with medical and psychosocial factors: an epidemiologic study among older persons. *Sleep Res* 25: 108.

41. Blazer D, Burchett B, Service C, George LK. 1991. The association of age and depression among older persons: an epidemiologic exploration. *J Gerontol* 46: M210–M215.

42. Gillin JC, Duncan WC, Murphy DL, Post RM, Wehr TA, Goodwin FK, Wyatt RJ, Bunney WE, Jr. 1981. Age-related changes in sleep in depressed and normal subjects. *Psychiatry Res* 4: 73–78.

43. Duffy JF, Zeitzer JM, Rimmer DW, Klerman EB, Dijk DJ, Czeisler CA. 2002. Peak of circadian melatonin rhythm occurs later within the sleep of older subjects. *Am J Physiol Endocrinol Metab* 282: E297–E303.

44. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. 1991a. Periodic limb movements in sleep in community-dwelling elderly. *Sleep* 14: 496–500.

45. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. 1991b. Sleep-disordered breathing in community-dwelling elderly. *Sleep* 14: 486–95.

46. Klerman EB, Duffy JF, Dijk DJ, Czeisler CA. 2001. Circadian phase resetting in older people by ocular bright light exposure. *J Investig Med* 49: 30–40.

47. Hoch CC, Reynolds CF, Buysse DJ, Monk TH, Nowell P, Begley AE, Hall F, Dew MA. 2001. Protecting sleep quality in later life: a pilot study of bed restriction and sleep hygiene. *J Gerontol B Psychol Sci Soc Sci* 56: 52–59.

48. Zhdanova IV, Wurtman RJ, Regan MM, Taylor JA, Shi JP, Leclair OU. 2001. Melatonin treatment for age-related insomnia. *J Clin Endocrinol Metab* 86: 4727–30.

49. Dijk D-J, Czeisler CA. 1994. Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. *Neurosci Lett* 166: 63–68.

50. Basheer R, Porkka-Heiskanen T, Strecker RE, Thakkar MM, McCarley RW. 2000. Adenosine as a biological signal mediating sleepiness following prolonged wakefulness. *Biol Signals Recept* 9: 319–27.

51. Saper CB, Chou TC, Scammell TE. 2001. The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci* 24: 726–31.

52. Sherin JE, Shiromani PJ, McCarley RW, Saper CB. 1996. Activation of ventrolateral preoptic neurons during sleep. *Science* 271: 216–19.

53. Katzenberg D, Young T, Finn L, Lin L, King DP, Takahashi JS, Mignot E. 1998. A CLOCK polymorphism associated with human diurnal preference. *Sleep* 21: 569–76.

54. Katzenberg D, Young T, Lin L, Finn L, Mignot E. 1999. A human period gene (HPER1) polymorphism is not associated with diurnal preference in normal adults. *Psychiatr Genet* 9: 107–09.

55. Pedrazzoli M, Ling L, Finn L, Kubin L, Young T, Katzenberg D, Mignot E. 2000. A polymorphism in the human timeless gene is not associated with diurnal preferences in normal adults. *Sleep Res Online* 3: 73–76.

56. Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, Qiu X, de Jong PJ, Nishino S, Mignot E. 1999. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell* 98: 365–76.

57. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. 2000. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet* 355: 39–40.

58. Czeisler CA, Moore-Ede MC, Coleman RM. 1983. Resetting circadian clocks: applications to sleep disorders medicine and occupational health. In: Guilleminault C, Lugarsi E. *Sleep/Wake Disorders: Natural History, Epidemiology, and Long-Term Evolution*. New York: Raven Press. 243–260.

59. Edgar DM. 1994. Sleep-wake circadian rhythms and aging: potential etiologies and relevance to age-related changes in integrated physiological systems. *Neurobiol Aging* 15: 499–501.

60. Miles LE, Dement WC. 1980. Sleep and aging. *Sleep* 3: 119–220.

61. van Coevorden A, Mockel J, Laurent E, Kerkhofs M, L'Hermite-Baleriaux M, Decoster C, Neve P, Van Cauter E. 1991. Neuroendocrine rhythms and sleep in aging men. *Am J Physiol* 260: E651–E661.

62. Campbell SS, Gillin JC, Kripke DF, Erikson P, Clopton P. 1989. Gender differences in the circadian temperature rhythms of healthy elderly subjects: relationships to sleep quality. *Sleep* 12: 529–36.

63. Vitaterna MH, Takahashi JS, Turek FW. 2001. Overview of circadian rhythms. *Alcohol Res Health* 25: 85–93.

64. Carrier J, Monk TH. 2000. Circadian rhythms of performance: new trends. *Chronobiol Int* 17: 719–32.

65. Johnson MP, Duffy JF, Dijk DJ, Ronda JM, Dyal CM, Czeisler CA. 1992. Short-term memory, alertness and performance: a reappraisal of their relationship to body temperature. *J Sleep Res* 1: 24–29.

66. Monk TH, Buysse DJ, Reynolds CF III, Kupfer DJ, Houck PR. 1996. Subjective alertness rhythms in older people. *J Biol Rhythms* 11: 268–76.

67. Monk TH, Kupfer DJ. 2000. Circadian rhythms in healthy aging—effects downstream from the pacemaker. *Chronobiol Int* 17: 355–68.

68. Prinz PN, Vitiello MV, Raskind MA, Thorpy MJ. 1990. Geriatrics: sleep disorders and aging. *N Engl J Med* 323: 520–26.

69. van Manen JG, Bindels PJ, Dekker EW, Ijzermans CJ, Bottema BJ, van der Zee JS, Schade E. 2001. Added value of co-morbidity in predicting health-related quality of life in COPD patients. *Respir Med* 95: 496–504.

70. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J. 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 288: 321–33.

71. Plihal W, Born J. 1999. Effects of early and late nocturnal sleep on priming and spatial memory. *Psychophysiology* 36: 571–82.

72. Maquet P. 2001. The role of sleep in learning and memory. *Science* 294: 1048–52.

73. Stickgold R, Hobson JA, Fosse R, Fosse M. 2001. Sleep, learning, and dreams: off-line memory reprocessing. *Science* 294: 1052–57.

74. Frank MG, Issa NP, Stryker MP. 2001. Sleep enhances plasticity in the developing visual cortex. *Neuron* 30: 275–87.

75. Ryan L, Hatfield C, Hofstetter M. 2002. Caffeine reduces time-of-day effects on memory performance in older adults. *Psychol Sci* 13: 68–71.

76. Loewy DH, Bootzin RR. 1998. Event-related potential measures of information processing in insomniacs at bedtime and during sleep. *Sleep* 21: 98.

77. Ferrara M, De Gennaro L. 2000. The sleep inertia phenomenon during the sleep-wake transition: theoretical and operational issues. *Aviat Space Environ Med* 71: 843–48.

78. Kuo TF, Bootzin RR, Quan SF, Kaszniak A, Boland L, O'Leary DH, Walsleben J. Sleep-disordered breathing and neuropsychological functioning: a community-based study of the Sleep Heart Health Study. Unpublished work, 2003.

79. Graves L, Pack A, Abel T. 2001. Sleep and memory: a molecular perspective. *Trends Neurosci* 24: 237–43.

80. Vitiello MV, Moe KE, Prinz PN. 2002. Sleep complaints cosegregate with illness in older adults. Clinical research informed by and informing epidemiological studies of sleep. *J Psychosom Res* 53: 555–59.

81. Vitiello MV, Larsen LH, Drolet G, Madar EL, Moe KE. 2002. Gender differences in subjective-objective sleep relationships in non-complaining healthy older men and women. *Sleep* 25 Suppl: A61–A62.

82. Vitiello MV, Moe KE, Larsen LH, Prinz PN. 1997. Age-related sleep change: relationships of objective and subjective measures of sleep in healthy older men and women. *Sleep Res* 26: 220.

83. Buysse DJ, Reynolds CF, III, Monk TH, Hoch CC, Yeager AL, Kupfer DJ. 1991. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep* 14: 331–38.

84. Foley DJ, Monjan AA, Izmirlian G, Hays JC, Blazer DG. 1999b. Incidence and remission of insomnia among elderly adults in a biracial cohort. *Sleep* 22 Suppl 2: S373–S378.

85. Edinger JD, Wohlgemuth WK, Radtke RA, Marsh GR, Quillian RE. 2001. Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. *JAMA* 285: 1856–64.

86. Espie CA, Inglis SJ, Tessier S, Harvey L. 2001. The clinical effectiveness of cognitive behaviour therapy for chronic insomnia: implementation and evaluation of a sleep clinic in general medical practice. *Behav Res Ther* 39: 45–60.

87. Morin CM, Hauri PJ, Espie CA, Spielman AJ, Buysse DJ, Bootzin RR. 1999. Nonpharmacologic treatment of chronic insomnia. *Sleep* 22: 1134–56.

88. Rybarczyk B, DeMarco G, DeLaCruz M, Lapidos S, Fortner B. 2001. A classroom mind/body wellness intervention for older adults with chronic illness: comparing immediate and 1-year benefits. *Behav Med* 27: 15–27.

89. Bliwise DL. 1993. Sleep in normal aging and dementia. *Sleep* 16: 40–81.

90. Bliwise DL. 2000. Normal aging. In: Kryger MH et al. *Principles and Practice of Sleep Medicine.* 3rd ed. Philadelphia: W.B. Saunders and Co. 26–52.

91. Enright PL, Newman AB, Wahl PW, Manolio TA, Haponik EF, Boyle PJ. 1996. Prevalence and correlates of snoring and observed apneas in 5,201 older adults. *Sleep* 19: 531–38.

92. Young T. 1996. Sleep-disordered breathing in older adults: Is it a condition distinct from that in middle-aged adults? *Sleep* 19: 529–30.

93. Bliwise DL. 1996. Is sleep apnea a cause of reversible dementia in old age? *J Am Geriatr Soc* 44: 1407–09.

94. Bliwise DL. 2002. Sleep apnea, APOE4 and Alzheimer's disease 20 years and counting? *J Psychosom Res* 53: 539–46.

95. Bixler EO, Kales A, Vela-Bueno A, Jacoby JA, Scarone S, Soldatos CR. 1982. Nocturnal myoclonus and nocturnal myoclonic activity in the normal population. *Res Commun Chem Pathol Pharmacol* 36: 129–40.

96. Kales A, Bixler EO, Soldatos CR, Vela-Bueno A, Caldwell AB, Cadieux RJ. 1982. Biopsychobehavioral correlates of insomnia, part 1: role of sleep apnea and nocturnal myoclonus. *Psychosomatics* 23: 589–600.

97. Karadeniz D, Ondze B, Besset A, Billiard M. 2000a. Are periodic leg movements during sleep (PLMS) responsible for sleep disruption in insomnia patients? *Eur J Neurol* 7: 331–36.

98. Karadeniz D, Ondze B, Besset A, Billiard M. 2000b. EEG arousals and awakenings in relation with periodic leg movements during sleep. *J Sleep Res* 9: 273–77.

99. Montplaisir J, Michaud M, Denesle R, Gosselin A. 2000. Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. *Sleep Med* 1: 163–67.

100. Nicolas A, Lesperance P, Montplaisir J. 1998. Is excessive daytime sleepiness with periodic leg movements during sleep a specific diagnostic category? *Eur Neurol* 40: 22–26.

101. Alessi CA. 1991. Managing the behavioral problems of dementia in the home. *Clin Geriatr Med* 7: 787–801.

102. Alessi CA, Schnelle JF. 2000. Approach to sleep disorders in the nursing home setting. *Sleep Med Rev* 4: 45–56.

103. Vitiello MV, Borson S. 2001. Sleep disturbances in patients with Alzheimer's disease: epidemiology, pathophysiology and treatment. *CNS Drugs* 15: 777–96.

104. McCurry SM, Reynolds CF, Ancoli-Israel S, Vitiello MV. 2000. Treatment of sleep disturbances in Alzheimer's disease. *Sleep Med Rev* 4: 603–628.

105. Taub JM. 1971. The sleep-wakefulness cycle in Mexican adults. *Journal of Cross-Cultural Psychology* 2: 353–62.

106. Buysse DJ. 2000. Rational pharmacology for insomnia: time for a new paradigm. *Sleep Med Rev* 4: 521–27.

107. Buysse DJ, Ganguli M. 2002. Can sleep be bad for you? Can insomnia be good? *Arch Gen Psychiatry* 59: 137–38.

108. Kramer M. 2000. Hypnotic medication in the treatment of chronic insomnia: non nocere! Doesn't anyone care? *Sleep Med Rev* 4: 529–41.

109. Kripke DF. 2000. Chronic hypnotic use: deadly risks, doubtful benefit. *Sleep Med Rev* 4: 5–20.

110. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. 2002. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry* 59: 131–36.

111. Richardson GS, Roth T, Kramer JA. 2002. Management of insomnia—the role of zaleplon. *Med Gen Med* 4: 9.

112. Merriam GR, Barsness S, Buchner DM, Klete M, Moe KE, Larsen LH, Schwartz RS, Vitiello MV. 2001. Growth hormone-releasing hormone treatment in normal aging. *J Anti-Aging Med* 4: 331–44.

113. Prinz PN, Moe KE, Dulberg EM, Larsen LH, Vitiello MV, Toivola B, Merriam GR. 1995. Higher plasma IGF-1 levels are associated with increased delta sleep in healthy older men. *J Gerontol A Biol Sci Med Sci* 50: M222–M226.

114. Lancel M. 1999. Role of GABA(A) receptors in the regulation of sleep: initial sleep responses to peripherally administered modulators and agonists. *Sleep* 22: 33–42.

115. Drewnowski A, Evans WJ. 2001. Nutrition, physical activity, and quality of life in older adults: summary. *J Gerontol A Biol Sci Med Sci* 56, Spec No. 2: 89–94.

116. Cassel CK. 2002. Use it or lose it: activity may be the best treatment for aging. *JAMA* 288: 2333–35.

117. Karani R, McLaughlin MA, Cassel CK. 2001. Exercise in the healthy older adult. *Am J Geriatr Cardiol* 10: 269–73.

118. Driver H, Taylor S. 2001. Exercise and sleep. *Sleep Med Rev* 4: 387–402.

119. King AC, Oman RF, Brassington GS, Bliwise DL, Haskell WL. 1997. Moderate-intensity exercise and self-rated quality of sleep in older adults. A randomized controlled trial. *JAMA* 277: 32–37.

120. Singh NA, Clements KM, Fiatarone MA. 1997. A randomized controlled trial of the effect of exercise on sleep. *Sleep* 20: 95–101.

121. Tworoger SS, Yasui Y, Urlich CM, Aiello EJ, Bowen D, Vitiello MV, McTiernan A. Effect of a year-long moderate intensity exercise or stretching intervention on self-reported sleep quality in post-menopausal women. Unpublished work, 2003.

122. Ganguli M, Reynolds CF, Gilby JE. 1996. Prevalence and persistence of sleep complaints in a rural older community sample: the MoVIES project. *J Am Geriatr Soc* 44: 778–84.

123. Gislason T, Reynisdottir H, Kristbjarnarson H, Benediktsdottir B. 1993. Sleep habits and sleep disturbances among older persons—an epidemiological survey. *J Intern Med* 234: 31–39.

124. Middelkoop HA, Smilde-van den Doel DA, Neven AK, Kamphuisen HA, Springer CP. 1996. Subjective sleep characteristics of 1,485 males and females aged 50–93: effects of sex and age, and factors related to self-evaluated quality of sleep. *J Gerontol A Biol Sci Med Sci* 51: M108–M115.

125. Schmitt FA, Phillips BA, Cook YR, Berry DT, Wekstein DR. 1996. Self report on sleep symptoms in older adults: correlates of daytime sleepiness and health. *Sleep* 19: 59–64.

126. Breslau N, Roth T, Rosenthal L, Andreski P. 1996. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry* 39: 411–18.

127. Ford DE, Kamerow DB. 1989. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention. *JAMA* 262: 1479–84.

128. Welstein L, Dement WC, Redington D, Guilleminault C, Mitler MM. 1983. Insomnia in the San Francisco Bay Area: a telephone survey. In: Guilleminault C, Lugaresi E. *Sleep/Wake Disorders: Natural History, Epidemiology, and Long-Term Evolution*. New York: Raven Press. 73–85.

129. Buysse DJ, Browman KE, Monk TH, Reynolds CF, III, Fasiczka AL, Kupfer DJ. 1992. Napping and 24-hour sleep/wake patterns in healthy elderly and young adults. *J Am Geriatr Soc* 40: 779–86.

130. Gerard P, Collins KJ, Dore C, Exton-Smith AN. 1978. Subjective characteristics of sleep in older persons. *Age Ageing Suppl* 7: 55–63.

131. Tune GS. 1968. Sleep and wakefulness in normal human adults. *BMJ* 2: 269–71.

132. Tune GS. 1969. Sleep and wakefulness in 509 normal human adults. *Br J Med Psychol* 42: 75–80.

133. Webb WB. 1981. Patterns of sleep in healthy 50–60 year old males and females. *Research Communications in Psychology and Psychiatry and Behavior* 6: 133–40.

134. Aber R, Webb WB. 1986. Effects of a limited nap on night sleep in older subjects. *Psychol Aging* 1: 300–02.

135. Monk TH, Buysse DJ, Carrier J, Billy BD, Rose LR. 2001. Effects of afternoon "siesta" naps on sleep, alertness, performance, and circadian rhythms in older persons. *Sleep* 24: 680–87.

136. Tamaki M, Shirota A, Tanaka H, Hayashi M, Hori T. 1999. Effects of a daytime nap in the aged. *Psychiatry Clin Neurosci* 53: 273–75.

137. Foley DJ, Monjan AA, Masaki KH, Enright PL, Quan SF, White LR. 1999c. Associations of symptoms of sleep apnea with cardiovascular disease, cognitive impairment, and mortality among older Japanese-American men. *J Am Geriatr Soc* 47: 524–28.

138. Hays JC, Blazer DG, Foley DJ. 1996. Risk of napping: excessive daytime sleepiness and mortality in an older community population. *J Am Geriatr Soc* 44: 693–98.

139. Newman AB, Spiekerman CF, Enright P, Lefkowitz D, Manolio T, Reynolds CF, Robbins J. 2000. Daytime sleepiness predicts mortality and cardiovascular disease in older adults. The Cardiovascular Health Study Research Group. *J Am Geriatr Soc* 48: 115–23.

140. Rockwood K, Wolfson C, McDowell I. 2001. The Canadian Study of Health and Aging: organizational lessons from a national, multicenter, epidemiologic study. *Int Psychogeriatr* 13 Suppl 1: 233–37.

International Longevity Center-Canyon Ranch Series

Prescription for Longevity: Fads and Reality
Maintaining Healthy Lifestyles: A Lifetime of Choices
Achieving and Maintaining Cognitive Vitality with Aging
Biomarkers of Aging: From Primitive Organisms to Man
Is There an "Anti-aging" Medicine?
Longevity Genes: From Primitive Organisms to Humans
Masculine Vitality: Pros and Cons of Testosterone in Treating the Andropause
Sleep, Health, and Aging

Single copies are free.
Multiple copies are $3 each.

Publications available online at our website: www.ilcusa.org.

Sleep, Health, and Aging

INTERNATIONAL LONGEVITY CENTER–USA

60 East 86th Street
New York, NY 10028
212 288 1468 Tel
212 288 3132 Fax
www.ilcusa.org

An Affiliate of Mount Sinai School of Medicine

CR08-2003