MEDICAL EDUCATION SYSTEMS

Circadian Rhythm: An Overview

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Circadian Rhythm: An Overview

Circadian rhythm (diurnal rhythm) any 24-hour periodicity in the behavior or physiology of animals or plants. Examples are the sleep/activity cycle in many animals and the growth movements of plants. Circadian rhythms are generally controlled by biological clocks.

Learning Objectives

Upon successful completion of this course, you will be able to:

- Define what is meant by the term “circadian rhythm”
- Identify the role that circadian rhythms play in human life
- Identify potential disorders related to those rhythms and indicate their causes
- Identify the available treatments for disorders in circadian rhythms

Circadian Rhythm Sleep Disorder

Definition

Circadian rhythm sleep disorder is a persistent or recurring pattern of sleep disruption resulting either from an altered sleep-wake schedule or an inequality between a person's natural sleep-wake cycle and the sleep-related demands placed on him or her. The term circadian rhythm refers to a person's internal sleep and wake-related rhythms that occur throughout a 24-hour period. The sleep disruption leads to **insomnia** or excessive sleepiness during the day, resulting in impaired functioning.

The Fourth Edition Text Revision of the ***Diagnostic and Statistical Manual of Mental Disorders*** (*DSM-IVTR* , a handbook used by mental health professionals to diagnose mental disorders) defines circadian rhythm sleep disorder as one of several primary **sleep disorders** . Within the category of primary sleep disorders, it is classified as one of the dyssomnias, characterized by irregularities in an individual's quality, timing, and amount of sleep. In earlier versions of the *DSM* , the disorder is called sleep-wake schedule disorder.

Description

Circadian rhythm sleep disorder involves an alteration of an individual's circadian system or a mismatch between a person's natural, or endogenous, circadian system and the external, or exogenous, demands placed on it. It can lead to insomnia at certain times of the day or excessive sleepiness throughout the day. The insomnia or excessive sleepiness results in impaired functioning in social, occupational, or other environments.

The *DSM-IV-TR* lists four types of circadian rhythm sleep disorder: delayed sleep phase type, jet lag type, shift work type, and unspecified type.

Causes and symptoms

Causes

The delayed sleep phase type of circadian rhythm sleep disorder is marked by a delay of the sleep-wake cycle as it relates to the demands of society. It is often due to a psychosocial stressor (an event in a person's environment that causes **stress** or discomfort), especially for adolescents. The delayed sleep-wake cycle leads to chronic sleep deprivation and habitually late sleeping hours. Individuals with this type often have difficulty changing their sleeping patterns to an earlier and more socially acceptable time. Their actual sleep, once it begins, is normal. It is the timing of their sleeping and waking that is persistently delayed.

The jet lag type of circadian rhythm sleep disorder is characterized by disruptions arising from a mismatch between a person's circadian cycle and the cycle required by a different time zone. The more time zones that are traveled, the greater the disruption. Eastbound travel, in which sleep-wake hours are advanced, typically causes more problems than westbound travel, in which sleep-wake hours are delayed. People who travel often and cross many time zones when they travel are most susceptible to this type.

The shift work type of circadian rhythm sleep disorder is distinguished by disruptions due to a conflict between a person's endogenous circadian cycle and the cycle required by shift work. Individuals who work the night shift often experience this problem, especially those people who switch to a normal sleep schedule on days off.

Also, people who work rotating shifts experience this problem because of the changing sleep-wake schedules they experience. The disruptions caused by shift work result in inconsistent circadian schedules and an inability to adjust to the changes consistently. The jet lag type of circadian rhythm sleep disorder is characterized by disruptions arising from a mismatch between a person's circadian cycle and the cycle required by a different time zone. People who travel often and cross many time zones when they travel are most susceptible to this type of circadian rhythm sleep disorder.

The unspecified type of circadian rhythm sleep disorder is characterized by a pattern of sleep-wake disturbance and circadian mismatch that is not due to the causes of the other three types. Examples of other causes include irregular sleep-wake patterns and non-24-hour sleep-wake patterns. If an individual's sleep-wake pattern is based on a period of time of slightly more than 24 hours, their circadian rhythm can become progressively delayed.

Symptoms

Individuals with the delayed sleep phase type of the disorder exhibit habitually late sleep hours and an inability to change their sleeping schedule consistently. They often show sleepiness during the desired wake period of their days. Their actual phase of sleep is normal. Once they fall asleep, they stay asleep for a normal period of time, albeit a period of time that starts and stops at an abnormally late time.

Individuals with the jet lag type of circadian rhythm sleep disorder demonstrate sleepiness during the desired wake portion of the day due to the change in time zone. They have difficulty sleeping during the desired sleep portion of the day. They also have difficulty altering their sleep-wake schedule to one appropriate to the new time zone.

Individuals with the shift work type of the disorder feel sleepy or fall asleep during the desired wake period, which includes the time spent at work. People with rotating shift schedules, especially schedules that gradually change, exhibit sleep disturbance and wake period sleepiness. Insufficient sleep time, family and social expectations, and alcohol use worsen this problem.

Individuals with the unspecified type of circadian rhythm sleep disorder also exhibit daytime and evening sleepiness or insomnia, especially those people who have a non-24-hour sleep pattern. People with irregular sleep patterns have difficulty knowing when they will fall asleep and wake up.

Demographics

The delayed sleep phase type of the disorder usually begins during adolescence and can continue without treatment through adulthood. People with this type may have a family history of delayed sleep phase. The delayed sleep phase type of the disorder is thought to impact up to 4% of adults and up to 7% of adolescents.

The shift work and jet lag types of the disorder often result in more severe symptoms for late-middle-aged and elderly people. It is estimated that up to 60% of night shift workers have the shift work type of circadian rhythm sleep disorder.

Diagnosis

In order to diagnose circadian rhythm sleep disorder, patients are often asked for records of their sleep and wake times in order to determine if a **diagnosis** is warranted. Interviews and direct observation in a sleep lab may also be utilized. A diagnosis requires a pattern of sleep disruption caused by a mismatch between a person's circadian sleep-wake pattern and the pattern required by that person's environment. The disruption can be persistent or recurrent and leads to impaired functioning, often in a social or occupational context.

To differentiate circadian rhythm sleep disorder from other diagnoses, the sleep disruption must not occur exclusively during the cause of another sleep disorder or other disorder. The disturbance in sleep must not be due to the direct physiological effects of a substance, whether used for medication or abuse, or to a general medical condition.

The delayed sleep phase type of the disorder requires a persistent pattern of delayed sleeping and awakening and an inability to change the pattern. The jet lag type requires sleepiness and wakefulness at inappropriate times relative to the local time zone; there must be repeated travel more than one time zone away. The shift work type requires excessive sleepiness during the

desired wake period and an inability to sleep during the desired sleep period, both due to changing shift work or night shift work.

Diagnosis of any type of circadian rhythm sleep disorder must be distinguished from normal adjustments a person makes in reaction to a schedule change. The sleep disruptions must be persistent and recurring and lead to social or occupational problems. People who prefer unusually late or early sleep schedules or people adjusting to a new sleep schedule should not receive this diagnosis unless they meet the other criteria.

Treatments

Treatment of the delayed sleep phase type depends on the severity of the case. Mild cases may be addressed by an individual simply adhering to strict sleep and wake times. Severe cases may require incremental changes in sleep time, where a person sleeps 15 to 30 minutes earlier each day until an appropriate pattern is reached. Other methods of altering delayed sleep patterns include prescribing a night of sleep deprivation or the use of chronotherapy, a method in which sleep is delayed for three hours each night until the sleep pattern is rotated around the clock.

Often, treatment is ignored for persons with the jet lag type because people eventually return to their regular time zone and normal sleep-wake cycle and no longer exhibit symptoms. For people who travel often, it is preferable to adjust to the new time zone by sleeping at times appropriate to that zone if they intend to be there for one week or longer. **Diets** that target jet lag are also effective for some people, and **light therapy** , which involves exposure to a lighted device to simulate daytime, may be helpful to some people to adjust to new time zones.

People with the shift work type of the disorder benefit most from a non-changing work schedule. If rotating or changing shifts are unavoidable, rotations that occur in a clockwise direction, where shifts get progressively later and later, are preferable to those in a counter-clockwise direction. Also, when attempting to sleep, it is a good idea to create a comfortable sleeping environment by eliminating daytime noise and light.

Prognosis

Individuals with delayed sleep phase type often have great difficulty changing their sleep patterns and when they are able to change their circadian cycle, they have difficulty maintaining the changes.

People with jet lag type or shift work type can reduce symptoms often by simply decreasing the amount of travel or returning to a normal work schedule. When these changes are not possible, these individuals have trouble making the constant adjustments required to sleep and wake. People with the shift work type often report a reversal of symptoms two weeks after returning to a normal work and sleep schedule.

Prevention

Because circadian rhythm sleep disorder is usually related to environmental stressors, avoidance of these stressors (such as long-distance travel, shift work, and sleep-disrupting lifestyles) can prevent the disorder from beginning or continuing. People who are able to adhere strictly to a normal sleep-wake schedule can also offset circadian rhythm-related problems.

Circadian rhythm-metabolism link discovered

July 24th, 2008

UC Irvine researchers have found a molecular link between circadian rhythms – our own body clock – and metabolism. The discovery reveals new possibilities for the treatment of diabetes, obesity and other related diseases.

Paolo Sassone-Corsi, Distinguished Professor and Chair of Pharmacology, and his colleagues have identified that an essential protein called CLOCK that regulates the body's circadian rhythms, works in balance with another protein called SIRT1 that modulates how much energy a cell uses.

"This interplay has far-reaching implications for human illness and aging, and it is likely vital for proper metabolism," said Sassone-Corsi, one of the world's leading researchers on circadian rhythms. The study appears in the July 25 issue of *Cell*.

Circadian rhythms of 24 hours govern fundamental physiological functions in almost all organisms. The circadian clocks are intrinsic time-tracking systems in our bodies that anticipate environmental changes and adapt themselves to the appropriate time of day.

Disruption of these rhythms can profoundly influence human health and has been linked to metabolic disorders, insomnia, depression, coronary heart diseases and cancer.

It is estimated that up to 15 percent of our genes are regulated by these circadian clocks. Sassone-Corsi identified in 2006 that the protein CLOCK is an essential molecular gear of the circadian machinery.

Now, he and his colleagues have shown that the protein SIRT1 counterbalances the function of CLOCK. Even though SIRT1's function differs from CLOCK's, the two proteins interact, creating a bond that is finely regulated in the cell.

SIRT1 senses energy levels in the cell; its activity is modulated by how many nutrients a cell is consuming. It also helps cells resist oxidative and radiation-induced stress, and for this reason SIRT1 is known to help control the process of aging.

CLOCK and SIRT1 are both part of the epigenome, which consists of proteins existing in connection with a cell's DNA that take external environmental factors and make the cell's genes behave differently, even though those genes do not structurally change.

"When this balance between these two vital proteins is upset, normal cellular function can be disrupted," Sassone-Corsi said. "Because of the role these two enzymes play, changes in our sleep patterns or our diets can directly be translated into how our cells act."

The findings also suggest that proper sleep and diet could help maintain or rebuild the CLOCK-SIRT1 equilibrium and may help explain why lack of proper rest or disruption in our normal sleep patterns is known to increase hunger, which can lead to obesity and related illnesses and can accelerate the aging process.

The specific interaction between CLOCK and SIRT1 also could lead to the development of drugs aimed at facilitating healthy metabolism, thereby helping to solve major social and medical problems such as diabetes and obesity.

Source: University of California - Irvine

Sleeplessness and Circadian Rhythm Disorder

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Introduction

Background

Circadian rhythm describes the approximately 24-hour cycles that are generated by an organism. Most physiological systems demonstrate circadian variations. The systems with the most prominent variations are the sleep-wake cycle, thermoregulation, and the endocrine system. Circadian rhythm disturbances can be categorized into 2 main groups: transient disorders (e.g., jet lag; changed sleep schedule due to work, social responsibilities, illness) and chronic disorders. The most common chronic disorders are delayed sleep-phase syndrome (DSPS), advanced sleep-phase syndrome (ASPS), and irregular sleep-wake cycle. Katzenberg et al suggested genetic correlation (i.e., clock polymorphisms) to circadian rhythm patterns.[1]

Important terms are defined as follows:

- Circadian rhythm (from *circa,* meaning "about" and *dies*, meaning day) - Approximately 24-hour cycles endogenously generated by an organism (e.g., sleep-wake cycle)
- Ultradian rhythm - Biological rhythms shorter than a 24-hour cycle (e.g., sleep stages)
- Entrainment - Synchronization of the circadian rhythms with environmental cues
- Free-running clock - Persistence of circadian rhythms in the absence of environmental cues (e.g. in patients with impaired ability to entrain or in those without time cues)
- Zetterberg (time giver) - Specific environmental variables that provide time cues (e.g., light, food-availability cycles)
- Sleeplessness (insomnia) - Difficulty initiating or maintaining sleep
- Circadian rhythm disorders - Malfunction of the circadian timing system or the biological clock

DSPS is characterized by a persistent inability (>6 mo) to fall asleep and awaken at socially accepted times. Once asleep, these patients are able to maintain their sleep and have normal total sleep times. In contrast, patients with insomnia have a lower than normal total sleep time due to difficulties in initiating or maintaining sleep.

ASPS is characterized by persistent, early evening sleep onset (between 6:00 pm and 9:00 pm), with an early morning wake-up time, generally between 3:00 am and 5:00 am. ASPS is less common than DSPS and most frequently occurs in elderly patients and in individuals who are depressed.

An irregular sleep-wake schedule features multiple sleep episodes without evidence of recognizable ultradian or circadian features of sleep and wakefulness. As with ASPS and DSPS, total sleep time is normal. Daily sleep logs demonstrate irregularity not only of sleep but also of daytime activities, including eating.

Pathophysiology

The neural basis of the circadian rhythm, the suprachiasmatic nuclei (SCN), is located in the anterior ventral hypothalamus and has been identified as the substrate that generates circadian activity. SCN lesions produce loss of circadian rhythmicity of the sleep-wake cycle, the activity-rest cycle, skin temperature, and corticosteroid secretion. Other pacemakers that are not located in the SCN are observed. For instance, core body temperature rhythm persists despite bilateral ablation of SCN. Furthermore, free-running studies have provided evidence for multiple circadian oscillators. Under free-running conditions, circadian rhythm may split into independent components.

Frequency

United States

DSPS is common. Approximately 7-10% of patients who complain of insomnia are diagnosed with a circadian rhythm disorder, most often DSPS. The prevalence of DSPS is probably higher than that because the total sleep time is typically normal in patients with DSPS and because patients with DSPS adjust their lifestyle to accommodate their sleep schedule and do not seek medical treatment. In adolescence, the prevalence is approximately 7%.

True ASPS is probably quite rare. However, an age-related phase advance is common in elderly patients because they tend to go to sleep early and get up early.

The prevalence of irregular sleep-wake schedules has not been established but is said to be quite high. Irregular sleep-wake schedule is common in patients with Alzheimer disease.

Approximately 20% of US workers perform shift work; not all of these works develop shift work syndrome, and individual phase tolerance is observed.

International

Dagan et al reported the characteristics of 322 Israeli patients with circadian rhythm disorder.[2] Most patients (85%) with circadian rhythm disorder who seek medical help have DSPS. About 90% of patients with DSPS in the study by Dagan et al reported onset of DSPS in early childhood or adolescence. A cross-sectional nationwide epidemiologic study in Norway established an overall prevalence of DSPS to be 0.17% when strict International Classification of Sleep Disorders (ICSD) criteria were used.[3]

Mortality/Morbidity

The mortality rates associated with circadian rhythms are difficult to assess. Many deaths related to circadian rhythm disorders are the result of impaired performance secondary to sleep deprivation; therefore, many times, the deaths are categorized into different headings (e.g., motor

vehicle accidents, heavy machinery accidents, other accidents). Sometimes, deaths are sequelae of the use of hypnotics, alcohol, or both to treat insomnia.

- Shift workers have been found to have a 40% greater cardiovascular disease risk than nonshift workers. Frequency of GI symptoms, other psychosomatic symptoms, and psychiatric symptoms is also increased in shift workers.
- Daytime sleepiness in students with DSPS has been correlated with negative mood and increased smoking and alcohol consumption.
- Some of the features of depressive disorders, such as early morning awakening and decreased rapid eye movement (REM) latency, are suggestive of ASPS. Whether these changes are secondary to depression or actually cause it has not been established.

Race

Race has been associated with variations in incidence of obstructive sleep apnea (OSA); however, many variables may be associated with these differences, and further research is necessary to evaluate this.

Sex

The sex difference in circadian rhythm disorders seems to be age related.

- In children and adolescents, no significant prevalence based on sex is observed.
- In patients aged 20-40 years, little to no difference in prevalence based on sex is observed.
- In those older than 40 years, women are 1.3 times more likely to report insomnia than men.

Age

- Circadian rhythm cycles undergo changes during puberty, as do other physiologic systems. At this time, increased daytime sleepiness is seen along with the development of sleep-phase delay. Early school start times at this critically important developmental phase can be associated with symptoms of daytime sleepiness, poor concentration, and impaired performance.
- DSPS is the most common circadian rhythm disorder in children and adolescents. ASPS is more likely to appear in elderly individuals.
- Health risks associated with shift work, such as GI and psychosomatic symptoms, increase with age.
- Irregular sleep-wake rhythms can be seen in patients with neurological impairment, including those with dementia.

Clinical

History

The diagnosis of circadian rhythm disorders is primarily based on a thorough history. Differentiation of transient disorders from chronic disorders and primary disorders from

secondary disorders influences the direction of evaluation and treatment plans. As with all medical and psychiatric histories, the nature of the complaint is the first order of business. In cases of sleeplessness, distinguishing individuals with difficulty initiating sleep from those with difficulty maintaining sleep, those with significant daytime impairment, and those with nonrestorative sleep is important.

- Duration of symptoms: Transient changes can be seen with air flights of long duration, jet lag, transient stresses (e.g., illnesses), and short-term sleep schedule disruptions (e.g., shift work). Chronic circadian changes can be seen with advanced sleep-phase syndrome (ASPS), delayed sleep-phase syndrome (DSPS), and irregular sleep-wake cycles.
- Pattern of sleep-wake cycle: This is an important part of the history in patients with circadian rhythm disturbances. The pattern of the sleep-wake cycle allows diagnosis within the chronic subtypes. DSPS is characterized by a persistent inability (i.e., >6 mo) to fall asleep and awaken at socially accepted times. Once asleep, these patients are able to maintain their sleep and have normal total sleep times. This disorder is most frequently identified in adolescents, college students, and night workers. Differential diagnosis includes lifestyle preference, inadequate sleep hygiene, primary insomnia, jet lag, and psychophysiologic insomnia. Teenagers with DSPS are at increased risk for behavioral problems and depression.
- ASPS: This syndrome is characterized by persistent, early evening sleep onset (between 6:00 pm and 9:00 pm) with an early morning wake-up time, generally between 3:00 and 5:00 am. ASPS occurs much less frequently than DSPS and is seen most commonly in the elderly and in persons who are depressed. It needs to be differentiated from exogenous depression and excessive daytime sleepiness (EDS), which is associated with other sleep disorders (e.g., obstructive sleep apnea [OSA]). An irregular sleep-wake schedule features multiple sleep episodes without evidence of recognizable ultradian or circadian features of sleep and wakefulness. As with APSD and DPSD, total sleep time is normal. Daily sleep logs demonstrate irregularity not only of sleep but also of daytime activities including eating. Body temperature also randomly fluctuates.
- Shift workers: For shift workers, the need to adjust the biological clock is coupled with the social pressure of more noise and disturbance during the day, leading to difficulties in sleeping. This is most difficult for workers who must switch their schedule and rotate between morning, evening, and night shifts. For those who consistently work the same shift, only environmental issues affect sleep quality once the biological clock adjusts to the new time.
- Total sleep time: In both ASPS and DSPS delays, total sleep time is normal. Shift workers, even those who work a consistent night shift, tend to have shorter sleep times.
- Peak alertness: Patients with DSPS have their peak alertness in late evening and night, whereas patients with ASPS have their peak alertness in the early morning. Patients with irregular sleep-wake cycles demonstrate no consistent pattern of alertness.
- Concern about sleep pattern: Implicit in the diagnosis of circadian rhythm disorder is a desire to conform to traditionally accepted sleep-wake patterns.
- Recent travel: Jet lag is a form of transient circadian rhythm disturbance. It results from an inability to synchronize one's normal rhythm to rapidly changing time shifts of environmental cues. Although many of the symptoms have been associated with high-altitude flying in general, the distinguishing factor seems to be the length of symptoms.

Symptoms related to flight generally last less than 24 hours, whereas those of jet lag may persist for days. The duration of the flight is the primary determinant of the intensity and duration of the jet lag. In general, jet lag is most likely to be experienced if 3 or more time zones are crossed.

- Daytime sleepiness: Daytime sleepiness is seen in all circadian rhythm disorders, although the severity may vary from individual to individual and from day to day.
- Assess for the presence of consequences of daytime sleepiness, which include poor concentration, impaired performance (including a decrease in cognitive skills), and poor psychomotor coordination. Headaches may also be present. The presence of early morning headaches should suggest further investigation of OSA. For children and adolescents, early school hours are associated with shorter total sleep time and increased daytime sleepiness. This is more prominent in teenagers.
- Psychological assessment: Psychophysiological insomnia, depressive disorders, and other psychiatric disorders may present with symptom profiles similar to those of circadian rhythm disorders. Assess patients for these disorders.
- Patient attempts at treatment: Perform a careful inquiry concerning the use of commonly used sleep aids, including alcohol, herbal preparations, and over-the-counter (OTC) sleep aids. Residual sleepiness can be seen with some of these preparations as well as with prescription hypnotics and some of the allergy preparations. Johnson et al reported that 13% of the general population had used alcohol as a short-term sleep aid during the previous year.[4]
- Medication history: Obtain a careful medication history regarding the timing of administration of drugs. For example, beta-adrenergic drugs, typically used in the treatment of asthma, can delay sleep because of their stimulant effect. Amphetamines, caffeine, selective serotonin reuptake inhibitor (SSRI) antidepressants, steroids, nicotine, theophylline, and clonidine can also affect sleep.
- Snoring: Chronic loud snoring with or without witnessed apnea should direct the physician to evaluate the patient for risk factors for upper airway resistance syndrome and OSA.
- Other medical or psychiatric problems: The 2 most commonly seen medical diseases and disorders that affect sleep and daytime function are congestive heart failure and chronic obstructive pulmonary disease. Chronic pain syndromes and thyroid disease also affect sleep and daytime function. Hyperthyroidism is associated with sleep disruption, whereas hypothyroidism is associated with daytime sleepiness and fatigue.
- Environmental cues and sleep hygiene: This is particularly important to assess in shift workers. The intensity of light, level of noise, and environmental temperature can influence sleep. Exercise and stimulant intake prior to bedtime are frequent lapses in good sleep hygiene and can be easily addressed.

Physical

The physical examination complements the history in patients with insomnia. Focus the physical examination on identifying risk factors for other conditions that may precipitate, exacerbate, or mimic insomnia. These may include depression, OSA, and neurodegenerative disease.

- Affect: Assess general affect and sense of well-being in patients presenting with insomnia as a primary sleep complaint.

- Body mass index: Patients with obesity who have increased body mass indices are at increased risk for OSA.
- Craniofacial morphology: The head and neck examination is important in assessing risk for OSA. Patients with large tonsils, narrow oropharyngeal spaces, and large necks are at risk for OSA.
- Chest: Barrel chest (i.e., increased anteroposterior diameter) is associated with chronic lung disease. Crackles, murmurs, and cardiac enlargement evinced by displaced point of maximum impulse (PMI) suggest congestive heart failure.
- Digital clubbing: Clubbing may be associated with chronic lung disease or congenital heart disease, or it may be familial. This finding should suggest a need for further medical evaluation.
- Neurologic examination: Alzheimer disease and other neurodegenerative diseases frequently are associated with irregular sleep-wake cycles.

Causes

Most of the time, the biological clock or the circadian rhythm is in synchronization with the 24-hour day-night environment. However, in some individuals, the biological circadian rhythm of sleep and wakefulness is out of phase with the conventional or desired sleep-wake schedule. Postulated reasons for that breakdown are as follows:

- Sensitivity to zeitgebers (i.e., environmental cues): This may be altered or disrupted, which can be demonstrated under free-running conditions. Altered or disrupted sensitivity to zeitgebers is probably the most common cause of circadian rhythm disorder.
- Disrupted pacemaker function: A dysfunction may be present in the internal coupling mechanisms of biological pacemakers (e.g., the coupling of the sleep-wake cycle with temperature cycle).
- Environment: Light, higher levels of noise, and elevated room temperature are not conducive to good sleep and are important variables to consider in shift and night workers
- Travel: The severity of jet lag is related to the direction of travel (i.e., more frequently seen when traveling in an eastward direction) and the number of time zones crossed. Most patients experience jet lag if they cross 3 or more time zones. The rate of adjustment is 1.5 h/d after an eastward flight and 1 h/d when the flight is in a westward direction. Other factors that may affect severity of jet lag are age, ability to sleep while traveling, the time of the day at destination, and exposure to light. More recent studies even look at cabin pressure and the slight oxygen deprivation experienced during flights as contributing factors to symptoms of jet lag.
- Neurologic disease: Alzheimer disease is one of the more common examples of neurological disease associated with circadian rhythm disturbance; however, irregular sleep-wake cycles also can be seen in other neurodegenerative diseases. The phenomenon of sundowning is best described in Alzheimer disease and is characterized by sleep disruptions with awakenings and confusion.
- Shift work: Rapid shift changes and shift changes in the counterclockwise direction are most likely to cause symptoms.
- Other factors: Lifestyle and social pressure (to stay up late) can exacerbate circadian rhythm disorder.

A circadian rhythm gene discovered

30. March 2005 14:57

A few rare people who consistently nod off early, then wake up wide-eyed much before dawn, can blame a newly-found mutant gene for their sleep troubles, Howard Hughes Medical Institute researchers announced today.

This odd “time-shift” trait — called familial advanced sleep phase syndrome (FASPS) — was studied in one affected family by neurologist Louis J. Ptacek, a Howard Hughes Medical Institute researcher, and Ying-Hui Fu, at the University of California, San Francisco. Their report appears in the March 31, 2005, issue of the journal Nature.

The sleep-shifting mutation they found is in “a gene that was not previously shown in mammals to be a circadian rhythm gene,” Ptacek explained. It's not yet clear how the mutant gene works to shift people's sleep time, their circadian rhythm, he added. But follow-on experiments in fruit flies and mice yielded results that are intriguing.

When the mutant gene was inserted into the flies, for example, it did the opposite of what was seen in the human family: it lengthened circadian rhythm. Yet in genetically engineered mice, the same gene change made the mice early risers — mimicking what was seen in humans with FASPS.

So, studies of all three organisms — flies, mice and humans — “will help us understand the similarities and differences” in how the gene works in different settings, in different genetic backgrounds, he said. Experiments can be done in mice and flies, with results applying to humans, while the studies of humans can inform what's being seen in the flies and mice.

In addition, “these results show that the gene is a central component of the mammalian circadian clock, and suggest that mammalian and fly clocks may have different regulatory mechanisms, despite the highly conserved nature of their individual components," the research team wrote in Nature. Such studies may help unravel some of the fundamental mysteries of how circadian rhythms are established and maintained in creatures that have evolved along very different paths.

As for the affected individuals, Ptacek said most are able to live normal lives, and some are proud of being able to arise before dawn and get a lot done while everything is quiet. A few, however, are constantly bothered by living out of sync with everyone else's daily schedule.

“Some of them would never come to a doctor” to find out what's going on with their sleep pattern, Ptacek said, “because they aren't troubled by it. Often, they have adjusted and accommodated their jobs to match their ability. But others are bothered by being out of phase with the rest of the world.”

He said the FASPS subjects don't seem to sleep any more or less than other people; they just sleep at different times. And there is apparently no connection to the better-known problem called narcolepsy.

Ptacek said it was also found — in the family's six affected individuals — that "they all have asthma, and they all have migraine headaches, with aura. Now, that could be purely coincidental, but a more important possibility is that these are part of the same syndrome." So far, however, "we haven't even looked at that yet."

He estimated that a very small number (about .3 percent) of the human population seems to have this "circadian clock" shift. And in earlier research, Ptacek and his colleagues had discovered an entirely different gene that causes a similar clock-shift. Both arise because of so-called point mutations in the genes. This means that altering a single base-pair in the gene's long DNA chain is enough to change a person's sleep behavior. Evidence from tissue culture experiments with the second gene suggests the change causes a protein — an enzyme called a kinase that is made by the gene - to be less active than normal.

The lead author of the paper in Nature is Ying Xu, a member of the team in San Francisco. Other team members are at the University of Vermont and the University of Utah.

Circadian Rhythm: How Cells Tell Time

ScienceDaily (June 10, 2009) — The fuzzy pale mold that lines the glass tubes in Dr. Yi Liu's lab doesn't look much like a clock.

But this fungus has an internal, cell-based timekeeper nearly as sophisticated as a human's, allowing UT Southwestern Medical Center physiologists to study easily the biochemistry and genetics of body clocks, or circadian rhythms.

In a new study appearing online this week in the *Proceedings of the National Academy of Sciences*, Dr. Liu and his co-workers have found that this mold, which uses a protein called FRQ as the main gear of its clock, marks time by a sequence of changes in the protein's chemical structure.

Dr. Liu said the new finding might someday help researchers develop treatments for human sleep disorders and other problems associated with a faulty biological clock.

"This timekeeping protein is really the core component of the circadian clock," said Dr. Liu, professor of physiology at UT Southwestern and senior author of the study.
Despite the evolutionary distance from mold to man, mechanisms controlling their circadian clocks are very similar. In both, circadian rhythms control many biological processes, including cell division, hormonal release, sleep/wake cycles, body temperature and brain activity.

The researchers employed a fungus called Neurospora, an organism frequently used in studies on genetics and cell processes, especially circadian rhythms. It reproduces in the dark and rests in the light.

A decade ago, Dr. Liu discovered that FRQ controlled the cellular clock in Neurospora by chemical changes of its protein structure. As the day goes on, the cell adds chemical bits called phosphates to the protein. Each new phosphate acts like a clock's ticking, letting the cell know that more time has passed.

When the number of phosphates added to FRQ reaches a certain threshold, the cell breaks it down, ready to start the cycle again.

The researchers, however, did not know where the phosphates attached to FRQ, how many got added throughout a day, or how they affected the protein's ability to "tell" time.
In the current study, the researchers used purified FRQ to analyze the specific sites where phosphate groups attach. In all, the researchers found 76 phosphate docking sites.
"This is an extremely high number," Dr. Liu said. "Most proteins are controlled by only a handful of phosphate sites."

They also studied how these phosphates are added to FRQ daily and found that two enzymes are responsible for adding most of the phosphate groups in Neurospora. They also found that the total number of phosphates oscillates robustly day by day.

In addition, the researchers created a series of mutations in many of the phosphate docking sites, creating strains of mold that had abnormally short or long daily clocks.
In upcoming studies, the researchers plan to identify which enzymes add phosphates to specific sites and exactly how changes in a particular site affect a cell's clock.

Other UT Southwestern physiology researchers contributing to the work were co-lead authors Dr. Chi-Tai Tang, postdoctoral researcher, and Dr. Shaojie Li, former postdoctoral researcher; Dr. Joonseok Cha, postdoctoral fellow; Dr. Guocun Huang, assistant instructor; and Dr. Lily Li, former postdoctoral researcher. Researchers from the National Institute of Biological Sciences in China and the Chinese Academy of Sciences also participated.
The study was supported by the National Institutes of Health and the Welch Foundation.

Circadian Rhythm Disorder Overview

A person's circadian rhythm is an internal biological clock that regulates a variety of biological processes according to an approximate 24-hour period. Most of a person's body systems demonstrate circadian variations. The body systems with the most prominent circadian variations are the sleep-wake cycle, the temperature regulation system, and the endocrine system.

The malfunctioning of a person's circadian system, or biological clock, causes circadian rhythm disorders. The circadian rhythm disorder related to the sleep-wake cycle can be categorized into the following 2 main groups:

Transient disorders

Jet lag

Altered sleep schedule due to work hours or social responsibilities

Illness

Chronic disorders

Delayed sleep-phase syndrome (DSPS)

DSPS is characterized by a persistent (that is, lasting longer than 6 months) inability to fall asleep and awaken at socially acceptable times. Individuals with DSPS fall asleep late (for example, in the early morning hours) and wake up late (for example, in the late morning hours or in the early afternoon hours).

Once asleep, however, persons with DSPS are able to maintain their sleep and have normal total sleep times. In contrast, persons without DSPS who are unable to sleep because of difficulties initiating and maintaining sleep have a lower than normal total sleep time than persons with DSPS.

Advanced sleep-phase syndrome (ASPS)

ASPS is characterized by a persistent early evening sleep onset time (between 6:00 pm and 9:00 pm) and an early morning wake-up time (between 3:00 am and 5:00 am).

ASPS occurs less frequently than DSPS and is most commonly seen in elderly individuals and in individuals who are depressed.

Irregular sleep-wake cycle

An irregular sleep-wake schedule features multiple sleep episodes without evidence of recognizable ultradian (a series of shorter biological rhythms occurring within a 24-hour period) or circadian features of sleep and wakefulness.

As in persons with ASPS and DSPS, total sleep time is normal in persons with an irregular sleep-wake schedule.

Daily sleep logs demonstrate irregularity not only of sleep but also of daytime activities, including eating.

Circadian Rhythm Disorder Causes

Most of the time, a person's biological clock, or circadian rhythm, is in synchronization with the 24-hour day-night environment. In some individuals, however, the biological circadian rhythm of sleep and wakefulness is out of phase with the conventional or desired sleep-wake schedule. Some reasons for this breakdown may include the following:

Sensitivity to zeitgebers ("time givers," such as light and other environmental cues): This sensitivity may be altered or disrupted, which can be demonstrated under certain conditions. Altered or disrupted sensitivity to zeitgebers is probably the most common cause of the circadian rhythm disorder of the sleep-wake cycle.

Disrupted pacemaker function: A dysfunction may be present in the internal coupling mechanisms of biological pacemakers, for example, the coupling of the sleep-wake cycle with the temperature cycle.

Environment: Light, higher noise levels, and elevated room temperature are not conducive to good sleep and are important variables to consider in both shift workers and night workers.

Travel: The severity of jet lag is related to the direction of travel and is more frequently seen in individuals traveling in an eastward direction. The number of time zones crossed also has an effect on the severity of jet lag, with most individuals experiencing jet lag if they cross 3 or more time zones. The rate of adjustment is 1.5 hours per day after a westward flight and 1 hour per day after an eastward flight.

Neurological disease: Alzheimer disease is one of the more common examples of neurological disease associated with a circadian rhythm disturbance; however, irregular sleep-wake cycles can also be seen in other neurodegenerative diseases. Sundowning, which is a common phenomenon in persons with Alzheimer disease, is characterized by sleep disruptions with awakenings and confusion.

Shift work: Rapid shift changes and shift changes in the counterclockwise direction are most likely to cause symptoms of a circadian rhythm disorder.

Lifestyle and social pressure to stay up late can exacerbate a circadian rhythm disorder.

Circadian Rhythm Disorder Symptoms

Symptoms commonly found in persons with a circadian rhythm disorder related to the sleep-wake cycle can include the following:

Difficulty initiating sleep

Difficulty maintaining sleep

Nonrestorative sleep

Daytime sleepiness

Poor concentration

Impaired performance, including a decrease in cognitive skills

Poor psychomotor coordination

Headaches

Gastrointestinal distress

When to Seek Medical Care

Medical care may be necessary if any of the following occur:

When poor sleep for more than 1 month is accompanied by one or more of the following:

Poor concentration

Forgetfulness

Decreased motivation

Excessive daytime sleepiness

Difficulty falling asleep

Nonrefreshing sleep

Habitual snoring

Questions to Ask the Doctor

A doctor may be able to answer questions about sleep-related issues. The following questions may help in identifying ways to improve sleep:

How can I make my environment more conducive to sleep?

Do any of my medications or herbal preparations cause insomnia?

How does caffeine influence my ability to fall asleep?

How can I minimize the effect of changing shift work on my ability to sleep?

How can I minimize the effect of jet lag when I travel?

What techniques can I use on my own to improve my ability to fall asleep and stay asleep?

How can I minimize my reaction to daytime stresses so I can fall asleep?

How does my family history influence my likelihood of having a sleep disorder?

What can I do to help my teenager not only fall asleep but also wake up in time for school?

Exams and Tests

A sleep log identifies the sleep-wake cycles in a person's normal environment, and it allows subjective assessment of alertness over a 2-week period. In keeping a sleep log, a person is asked to maintain a sleep diary describing the previous night's sleep. Data from the sleep diary may help to minimize distortions in sleep information recalled some time later while in the health care provider's office. Sleep logs can also be used for self-monitoring and as an addition to behavioral treatment.

Imaging studies, such as CT scan and MRI, may be done to evaluate for neurodegenerative diseases.

A multiple sleep latency test allows for objective measurement of sleepiness. This test is indicated when the clinical history is suggestive of narcolepsy.

The Epworth Sleepiness Scale is based on a questionnaire that rates a person's responses to 8 situations on a scale of 0-3 based on whether the situation was likely to be associated with dozing behavior. Although controversy exists as to what score constitutes abnormal sleepiness, a total score above 10 generally warrants investigation.

Actigraphy is done with the help of an Actigraph. An Actigraph is a small, motion-sensing device worn on the nondominant wrist, generally for 1 week. Actigraphy is based on the premise that a person's wrist motion decreases during sleep. This allows an overall measure of sleep-wake cycles over time.

Self-Care at Home

As always, maintaining good sleep hygiene is important. Good sleep hygiene consists of measures to reinforce the body's natural tendency to sleep, including the following:

Adhering to consistent sleep and wake times

Avoiding napping

Using the bed only for sleeping and intimacy

Avoiding stress, fatigue, and sleep deprivation

Avoiding vigorous exercise at least 4 hours prior to bedtime (Regular exercise is recommended.)

Avoiding cigarettes, alcohol, and caffeine at least 4-6 hours prior to bedtime

Avoiding large meals and excessive fluids before bedtime

Controlling the environment, including light, noise, and room temperature (A controlled sleeping environment is especially important for shift workers and night workers.)

Medical Treatment

Common circadian rhythm disorder treatments can include the following behavioral and environmental therapies:

Chronotherapy: This behavioral treatment consists of gradually shifting the sleep time in accordance with the person's desired schedule. Thus, in DSPS, a progressive delay of 3 hours per day is prescribed, followed by strict maintenance of a regular bedtime hour once the desired schedule is achieved. In ASPS, chronotherapy focuses on advancing a regular bedtime hour by 2-3 hours per night for 1 week until a desired schedule is achieved.

Bright light therapy: Persons with a circadian rhythm disorder respond well to light therapy, especially bright light therapy (greater than 600 lux). To modify the phase of the circadian rhythm, bright room light over time may also be sufficient; however, a higher intensity of light (greater than 6000 lux over 30-60 minutes) is often necessary to accomplish significant changes in sleep cycles. The timing of light therapy is also important because it affects the degree and the direction of the rhythm shift. For example, for persons with ASPS, light therapy applied in the early evening and nighttime hours delays the cycle, whereas, for persons with DSPS, light therapy applied in the early morning hours stimulates morning alertness and an earlier bedtime.

Enhancing environmental cues: This part of the treatment of a circadian rhythm disorder is important. Persons are encouraged to keep a dark and quiet room during sleep and a well-lit room upon awakening. Avoiding bright light exposure in the evening and enforcing regular hours for eating and other activities also help.

Lifestyle: Persons may respond to shifts in their active phases by exhibiting signs of sleep deprivation. For example, teenagers may have difficulty keeping late hours and getting up for an early morning class. Shift workers may have difficulty adjusting to new sleep cycles if their shifts are changed too rapidly before their bodies have had a chance to adjust.

Medications

Therapy for a circadian rhythm disorder is largely behavioral. Light therapy has been shown to be an effective modifier of circadian rhythms. The short-term use of hypnotics (medications that promote sleep) is a useful option in treating a circadian rhythm disorder and has improved the therapeutic response, especially in persons with Alzheimer disease.

Melatonin

Melatonin has been reported to be useful in the treatment of jet lag and sleep-onset insomnia in elderly persons with melatonin deficiency. Melatonin is used for enhancing the natural sleep process and for resetting the body's internal time clock when traveling through different time zones. Melatonin is believed to be effective when crossing 5 or more time zones but is less effective when traveling in a westward direction. Melatonin has also been used in the treatment of circadian rhythm sleep disorder in persons who are blind with no light perception.

Melatonin is available as an over-the-counter (OTC) preparation. Melatonin is still considered a diet supplement, and dosing guidelines have not been established. Because of the effect of melatonin on immune function, persons with immune disorders and those taking systemic corticosteroids or immunosuppressive drugs should be cautioned against taking melatonin. Melatonin may interact with other medications. Persons should consult their doctor before using melatonin.

Melatonin stimulants

Ramelteon (Rozerem) is a prescription drug that stimulates melatonin receptors. Melatonin is a hormone produced by the pineal gland during the dark hours of the day-night cycle (circadian rhythm). Melatonin levels in the body are low during daylight hours. The pineal gland (located in the brain) responds to darkness by increasing melatonin levels in the body. This process is thought to be integral to maintaining circadian rhythm. Ramelteon promotes the onset of sleep and helps normalize circadian rhythm disorders. Ramelteon is approved by the Food and Drug Administration (FDA) for insomnia characterized by difficulty falling asleep.

Hypnotics

Short-term use of hypnotics may be beneficial in selected patients. Patients interested in the use of hypnotics for a circadian rhythm disorder should discuss them with their doctor.

Benzodiazepines

Short-acting benzodiazepines are often chosen in the early treatment of a circadian rhythm disorder and are used in conjunction with behavioral therapy. Triazolam (Halcion) is a benzodiazepine frequently chosen for short-term use in addition to behavioral therapy. This short-acting agent is effective in helping persons fall asleep.

Triazolam is not effective in persons with sleep maintenance issues. For persons with sleep maintenance insomnia, a benzodiazepine with an intermediate half-life (for example, estazolam [ProSom]) or a long half-life (for example, quazepam [Doral]) may be considered.

Nonbenzodiazepine hypnotics

Nonbenzodiazepine hypnotics are gaining popularity because they do not have a significant effect on sleep architecture and are not associated with the rebound phenomenon seen with benzodiazepines. Zolpidem (Ambien) is a good short-term option for persons with DSPS who require pharmacologic support.

Treatment of sleep disorders associated with shift work

Modafinil (Provigil) is a stimulant indicated to treat workers with sleep disorders caused by their shift work. Modafinil has wake-promoting actions and is taken 1 hour before the start of the work shift.

Next Steps

Follow-up

Persons with DSPS who respond initially to chronotherapy may gradually shift back to their old sleep pattern. Often, chronotherapy must be repeated every few months to maintain long-lasting results.

Prevention

Control of the sleep environment with regulation of light-dark exposure has been helpful to shift workers in maintaining sleep.

For shift workers, shifting the schedule in a clockwise direction is better tolerated.

For persons who are traveling across multiple time zones, adjusting to the time zone of the new location prior to departure can modify the effects of jet lag.

Maintaining good sleep hygiene can prevent sleep disorders.

Outlook

The following provide an outlook into some sleep disorders:

Jet lag: This is a transient condition that has a good prognosis.

Shift work: Abrupt changes in schedule and counterclockwise shifts are associated with daytime sleepiness and impaired performance. Older persons may not adjust well to shift changes.

DSPS: This is typically seen in adolescents and young adults. This sleep pattern often resolves in adulthood.

ASPS: This is prominent in the elderly and often responds well to a combination of behavioral and pharmacologic intervention.

For More Information

National Sleep Foundation
1522 K Street, NW, Suite 500
Washington, DC 20005

American Academy of Sleep Medicine
One Westbrook Corporate Center, Suite 920
Westchester, IL 60154
(708) 492-0930

Web Links

Northwestern University, Center for Sleep & Circadian Biology, About Circadian Rhythms

National Sleep Foundation, Strategies for Shift Workers

National Sleep Foundation, Sleep and the Traveler

National Institute of Mental Health, How Biological Clocks Work

Sleepnet.com

Synonyms and Keywords

circadian rhythm disorder, biological clock, delayed sleep-phase syndrome, DSPS, advanced sleep-phase syndrome, ASPS, irregular sleep-wake cycle, ultradian rhythm, entrainment, zeitgeber, sleeplessness, insomnia, sleep-wake cycle, jet lag, sleep disorders, sleep deprivation, daytime sleepiness, shift worker, night worker

Sleeplessness and Circadian Rhythm Disorder Glossary of Medical Terms

Abnormal: Not normal. Deviating from the usual structure, position, condition, or behavior. In referring to a growth, abnormal may mean that it is cancerous or premalignant (likely to become cancer).
See the entire definition of Abnormal

Alcohol: An organic chemical in which one or more hydroxyl (OH) groups are attached to carbon (C) atoms in place of hydrogen (H) atoms. Common alcohols include ethyl alcohol or ethanol (found in alcoholic beverages), methyl alcohol or methanol (can cause blindness) and propyl alcohol or propanol (used as a solvent and antiseptic).

Rubbing alcohol is a mixture of acetone , methyl isobutyl ketone, and ethyl alcohol. In everyday talk, alcohol usually refers to ethanol as, for example, in wine, beer, and liquor. It can cause changes in behavior and be addictive.
See the entire definition of Alcohol

Alzheimer disease: See: Alzheimer's disease .
See the entire definition of Alzheimer disease

Ambien: Brand name for the sedative hypnotic drug zolpidem used for sleep. For more information, see: zolpidem .
See the entire definition of Ambien

Benzodiazepines: A class of drugs that act as tranquilizers and are commonly used in the treatment of anxiety. Benzodiazepines can cause drowsiness.
See the entire definition of Benzodiazepines

Blind: 1. Unable to see. Without part or all of the sense of sight.
2. In a clinical trial, not to know the treatment given or received. The participant is not told whether they are in the experimental or control arm of the study. Also called masked.
See the entire definition of Blind

Brain: That part of the central nervous system that is located within the cranium (skull). The brain functions as the primary receiver, organizer and distributor of information for the body. It has two (right and left) halves called "hemispheres."
See the entire definition of Brain

Caffeine: A stimulant found naturally in coffee beans, tea leaves, cocoa beans (chocolate) and kola nuts (cola) and added to soft drinks, foods, and medicines. A cup of coffee has 100-250 milligrams of caffeine. Black tea brewed for 4 minutes has 40-100 milligrams. Green tea has one-third as much caffeine as black tea.
See the entire definition of Caffeine

Chronic: This important term in medicine comes from the Greek chronos, time and means lasting a long time.
See the entire definition of Chronic

Circadian: Refers to events occurring within a 24-hour period, in the span of a full (24-hour) day, as in a circadian rhythm. Circadian rhythmicity is a fundamental property possessed by all organisms. These rhythms are driven by an internal time-keeping system: a clock. Changes in the external environment, particularly in the light-dark cycle, entrain this biologic clock. Under constant environmental conditions devoid of time cues, rhythms driven by the clock show a period near, but usually not exactly equal to, 24 hours.
See the entire definition of Circadian

Cognitive: Pertaining to cognition , the process of knowing and, more precisely, the process of being aware, knowing, thinking, learning and judging.

The study of cognition touches on the fields of psychology , linguistics, computer science, neuroscience , mathematics, ethology and philosophy.
See the entire definition of Cognitive

Condition: The term "condition" has a number of biomedical meanings including the following:

1. An unhealthy state, such as in "this is a progressive condition."
2. A state of fitness, such as "getting into condition."
3. Something that is essential to the occurrence of something else; essentially a "precondition."
4. As a verb: to cause a change in something so that a response that was previously associated with a certain stimulus becomes associated with another stimulus; to condition a person, as in behavioral conditioning.

Contrast: Short for "contrast media." Contrast media are X-ray dyes used to provide contrast, for example, between blood vessels and other tissue.
See the entire definition of Contrast

CT scan: Computerized tomography scan. Pictures of structures within the body created by a computer that takes the data from multiple X-ray images and turns them into pictures on a screen. CT stands for computerized tomography.
See the entire definition of CT scan

Dysfunction: Difficult function or abnormal function.
See the entire definition of Dysfunction

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Endocrine: Pertaining to hormones and the glands that make and secrete them into the bloodstream through which they travel to affect distant organs. The endocrine sites include the hypothalamus, pituitary gland, pineal gland, thyroid, parathyroids, heart (which makes atrial-natriuretic peptide), the stomach and intestines, islets of Langerhans in the pancreas, the adrenal glands, the kidney (which makes renin, erythropoietin , and calcitriol), fat cells (which make leptin). the testes, the ovarian follicle (estrogens) and the corpus luteum in the ovary). Endocrine is as opposed to exocrine. (The exocrine glands include the salivary glands, sweat glands and glands within the gastrointestinal tract.)
See the entire definition of Endocrine

Environment: The sum of the total of the elements, factors and conditions in the surroundings which may have an impact on the development , action or survival of an organism or group of organisms.
See the entire definition of Environment

Epilepsy (seizure disorder): When nerve cells in the brain fire electrical impulses at a rate of up to four times higher than normal, this causes a sort of electrical storm in the brain, known as a seizure. A pattern of repeated seizures is referred to as epilepsy . Known causes include head injuries, brain tumors, lead poisoning, maldevelopment of the brain, genetic and infectious illnesses. But in fully half of cases, no cause can be found. Medication controls seizures for the majority of patients.
See the entire definition of Epilepsy

Exacerbate: To make worse. For example, smoking may exacerbate systemic lupus erythematosus .
See the entire definition of Exacerbate

Excessive daytime sleepiness: A neurological disorder in which there is a sudden recurrent uncontrollable compulsion to sleep. Excessive daytime sleepiness is also known as narcolepsy.
See the entire definition of Excessive daytime sleepiness

Family history: The family structure and relationships within the family, including information about diseases in family members.
See the entire definition of Family history

Fatigue: A condition characterized by a lessened capacity for work and reduced efficiency of accomplishment, usually accompanied by a feeling of weariness and tiredness. Fatigue can be acute and come on suddenly or chronic and persist.
See the entire definition of Fatigue

FDA: The Food and Drug Administration, an agency within the U.S. Public Health Service, which is a part of the Department of Health and Human Services.
See the entire definition of FDA

Food and Drug Administration: The FDA, an agency within the U.S. Public Health Service, which is a part of the Department of Health and Human Services.
See the entire definition of Food and Drug Administration

Gastrointestinal: Adjective referring collectively to the stomach and small and large intestines.
See the entire definition of Gastrointestinal

Gland: 1. A group of cells that secrete a substance for use in the body. For example, the thyroid gland. **2.** A group of cells that removes materials from the circulation. For example, a lymph gland.
See the entire definition of Gland

Herbal: 1. An adjective, referring to herbs, as in an herbal tea.
2. A noun, usually reflecting the botanical or medicinal aspects of herbs; also a book which catalogs and illustrates herbs.

The word "herbal" was pronounced with a silent "h" on both sides of the Atlantic until the 19th century but this usage persists only on the American side.
See the entire definition of Herbal

Hormone: A chemical substance produced in the body that controls and regulates the activity of certain cells or organs.
See the entire definition of Hormone

Hospital: It may seem unnecessary to define a "hospital" since everyone knows the nature of a hospital. A hospital began as a charitable institution for the needy, aged, infirm, or young.
See the entire definition of Hospital

Hygiene: The science of preventive medicine and the preservation of health. From the name of Hygeia, the daughter of Asklepios, the Greek god of medicine (whose staff with entwined snake is the symbol of medicine). Asklepios (known to the Romans as Aesculapius) had a number of children including not only Hygeia but also Panaceia, the patroness of clinical medicine. Hygeia also followed her father into medicine. As the patroness of health, Hygeia was charged with providing a healthy environment to prevent illness. In Greek, "hygieia" means health.
See the entire definition of Hygiene

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Immune: Protected against infection. The Latin immunis means free, exempt.
See the entire definition of Immune

Immunosuppressive: 1. Pertaining to immunosuppression , the suppression of the immune system .
2. An agent capable of suppressing the immune response .
See the entire definition of Immunosuppressive

Insomnia: The perception or complaint of inadequate or poor-quality sleep because of one or more of the following: difficulty falling asleep; waking up frequently during the night with difficulty returning to sleep; waking up too early in the morning; or unrefreshing sleep. Insomnia is not defined by the number of hours of sleep a person gets or how long it takes to fall asleep. Individuals vary normally in their need for, and their satisfaction with, sleep. Insomnia may cause problems during the day, such as tiredness, a lack of energy, difficulty concentrating, and irritability.
See the entire definition of Insomnia

Internal medicine: A medical specialty dedicated to the diagnosis and medical treatment of adults. A physician who specializes in internal medicine is referred to as an internist. A minimum of seven years of medical school and postgraduate training are focused on learning the prevention, diagnosis, and treatment of diseases of adults.

Subspecialties of internal medicine include allergy and immunology, cardiology (heart), endocrinology (hormone disorders), hematology (blood disorders), infectious diseases, gastroenterology (diseases of the gut), nephrology (kidney diseases), oncology (cancer), pulmonology (lung disorders), and rheumatology (arthritis and musculoskeletal disorders).
See the entire definition of Internal medicine

Intervention: The act of intervening, interfering or interceding with the intent of modifying the outcome. In medicine, an intervention is usually undertaken to help treat or cure a condition. For example, early intervention may help children with autism to speak. "Acupuncture as a therapeutic intervention is widely practiced in the United States," according to the National Institutes of Health. From the Latin intervenire, to come between.
See the entire definition of Intervention

Jet lag : A temporary disorder that causes fatigue, insomnia, and other symptoms as a result of rapid air travel across time zones.
See the entire definition of Jet lag

Medical school: A school with a curriculum leading to a medical degree. The mission of every medical school includes medical teaching, research, and patient care. All medical schools share the goal of preparing students in the art and science of medicine, and providing them with the background necessary to enter the period of graduate medical education. The years of medical school preceding graduate medical education are typically divided into a preclinical phase and a clinical phase.
See the entire definition of Medical school

Melatonin: A hormone produced by the pineal gland, melatonin is intimately involved in regulating the sleeping and waking cycles, among other processes. Melatonin supplements are sometimes used by people who have chronic insomnia. Always see your doctor before taking melatonin, as it is not recommended for all patients with sleep problems.
See the entire definition of Melatonin

Modafinil: An oral drug first approved by the FDA in 1998 for the treatment of narcolepsy , a condition in which there is an uncontrollable desire to sleep . Modafinil promotes wakefulness. In 2004 the FDA also approved modafinil for the treatment of obstructive sleep apnea and sleeping problems caused by shift work.
See the entire definition of Modafinil

MRI: Abbreviation and nickname for magnetic resonance imaging . For more information, see: Magnetic Resonance Imaging ; Paul C. Lauterbur ; Peter Mansfield .
See the entire definition of MRI

Narcolepsy: A neurological disorder marked by a sudden recurrent uncontrollable compulsion to sleep . Narcolepsy is often associated with cataplexy (a sudden loss of muscle tone and paralysis of voluntary muscles associated with a strong emotion), sleep paralysis (immobility of the body that occurs in the transition from sleep to wakefulness), what are called hypnagogic hallucinations (pre-sleep dreams) and automatic behaviors (such as doing something

"automatically" and not remembering afterwards how one did it).
See the entire definition of Narcolepsy

Neurological: Having to do with the nerves or the nervous system.
See the entire definition of Neurological

Neurology: The medical specialty concerned with the diagnosis and treatment of disorders of the nervous system -- the brain, the spinal cord, and the nerves.
See the entire definition of Neurology

Objective: In a microscope, the objective (also called the objective lens) is the lens nearest to the object being examined whereas the lens closest to the eye is termed the ocular (the eyepiece).
See the entire definition of Objective

Onset: In medicine, the first appearance of the signs or symptoms of an illness as, for example, the onset of rheumatoid arthritis . There is always an onset to a disease but never to the return to good health. The default setting is good health.
See the entire definition of Onset

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Pacemaker: A system that sends electrical impulses to the heart in order to set the heart rhythm. The pacemaker can be the normal "natural" pacemaker of the heart or it can be an electronic device.
See the entire definition of Pacemaker

Pediatric: Pertaining to children.
See the entire definition of Pediatric

Pediatrics: "Pediatrics is concerned with the health of infants, children and adolescents, their growth and development, and their opportunity to achieve full potential as adults." (Richard E.Behrman in Nelson's Textbook of Pediatrics)
See the entire definition of Pediatrics

Pharmacy: A location where prescription drugs are sold. A pharmacy is, by law, constantly supervised by a licensed pharmacist.
See the entire definition of Pharmacy

Pineal gland: A small gland located deep within in the brain. It is believed to secrete melatonin, and may therefore be part of the body's sleep-regulation apparatus.
See the entire definition of Pineal gland

Prescription: A physician's order for the preparation and administration of a drug or device for a patient. A prescription has several parts. They include the superscription or heading with the symbol "R" or "Rx", which stands for the word recipe (meaning, in Latin, to take);

the inscription, which contains the names and quantities of the ingredients; the subscription or directions for compounding the drug; and the signature which is often preceded by the sign "s" standing for signa (Latin for mark), giving the directions to be marked on the container.
See the entire definition of Prescription

Prescription drug: A drug requiring a prescription, as opposed to an over-the-counter drug, which can be purchased without one. The word "prescription" comes from the Latin "praescriptus" compounded from "prae", before + scribere, to write = to write before. Historically, a prescription was written before the drug was prepared and administered.
See the entire definition of Prescription drug

Prognosis: 1. The expected course of a disease .
2. The patient's chance of recovery.
The prognosis predicts the outcome of a disease and therefore the future for the patient . His prognosis is grim, for example, while hers is good.
See the entire definition of Prognosis

Progressive: Increasing in scope or severity. Advancing. Going forward. In medicine, a disease that is progressive is going from bad to worse.
See the entire definition of Progressive

Provigil: Brand name of the drug modafinil. See: Modafinil .
See the entire definition of Provigil

Psychiatry: The medical specialty concerned with the prevention, diagnosis , and treatment of mental illness.
See the entire definition of Psychiatry

Pulmonology: The study and science of the anatomy , physiology , and pathology of the lungs . See also: Pulmonary medicine .
See the entire definition of Pulmonology

Rebound: Return of the original symptoms when maneuvers or treatment is discontinued.
See the entire definition of Rebound

Scan: As a noun, the data or image obtained from the examination of organs or regions of the body by gathering information with a sensing device.
See the entire definition of Scan

Sensitivity: 1. In psychology, the quality of being sensitive. As, for example, sensitivity training, training in small groups to develop a sensitive awareness and understanding of oneself and of ones relationships with others. **2.** In disease epidemiology, the ability of a system to detect epidemics and other changes in disease occurrence. **3.** In screening for a disease, the proportion of persons with the disease who are correctly identified by a screening test.

4. In the definition of a disease, the proportion of persons with the disease who are correctly identified by defined criteria.
See the entire definition of Sensitivity

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Sleep : The body's rest cycle.
See the entire definition of Sleep

Sleep disorders: Any disorder that affects, disrupts, or involves sleep . The most common sleep disorder is probably snoring, although it is usually not medically significant. Insomnia, sleep apnea , restless leg syndrome , and sleepwalking are also sleep disorders. Most large medical centers have diagnostic and treatment facilities dedicated to sleep disorders.
See the entire definition of Sleep disorders

Sleeplessness: Insomnia . See also Fatal familial insomnia .
See the entire definition of Sleeplessness

Snoring: A rough rattling noise made on inspiration during sleep by vibration of the soft palate (the back of the roof of the mouth) and the uvula (the prominent structure dangling down at the back of the mouth).
See the entire definition of Snoring

Stress: Forces from the outside world impinging on the individual. Stress is a normal part of life that can help us learn and grow. Conversely, stress can cause us significant problems.
See the entire definition of Stress

Syndrome: A set of signs and symptoms that tend to occur together and which reflect the presence of a particular disease or an increased chance of developing a particular disease.
See the entire definition of Syndrome

Systemic: Affecting the entire body. A systemic disease such as diabetes can affect the whole body. Systemic chemotherapy employs drugs that travel through the bloodstream and reach and affect cells all over the body.
See the entire definition of Systemic

Therapeutic: Relating to therapeutics , that part of medicine concerned specifically with the treatment of disease . The therapeutic dose of a drug is the amount needed to treat a disease.
See the entire definition of Therapeutic

Therapy: The treatment of disease .
See the entire definition of Therapy

Wrist: The proximal segment (the near part) of the hand consisting of the carpal bones and the associated soft parts.
See the entire definition of Wrist

Zeitgeber: An environmental agent or event that provides the cue for setting or resetting a biological clock. To be synchronized with our environment , we need the input of Zeitgebers. The most important Zeitgeber in nature is light. Social factors, chemical factors and activity can also serve as Zeitgebers. Light is a so-called photic type Zeitgeber, whereas activity, for example, is called a non-photic Zeitgeber for the biological clock.
See the entire definition of Zeitgeber

Zolpidem: Brand name: Ambien. A sedative hypnotic drug in a class closely related the benzodiazepines, affecting the central nervous system, used as a sleep drug. For more information, see: zolpidem .
See the entire definition of Zolpidem

Circadian Rhythm Examination

Select the **best** answer to each of the following items.

1. Circadian rhythm (diurnal rhythm) is any 24-hour periodicity in the behavior or physiology of animals or plants. Examples are the sleep/activity cycle in many animals and the growth movements of plants. Circadian rhythms are generally controlled by _____.

a. the pituitary gland
b. a person's environment
c. biological clocks
d. None of the above

2. The delayed sleep phase type of circadian rhythm sleep disorder is marked by a delay of the sleep-wake cycle as it relates to the demands of society. It is often due to a psychosocial stressor (an event in a person's environment that causes stress or discomfort), especially for adolescents.

a. True
b. False

3. The _____type of circadian rhythm sleep disorder is characterized by disruptions arising from a mismatch between a person's circadian cycle and the cycle required by a different time zone. The more time zones that are traveled, the greater the disruption.

a. the unspecified type of circadian rhythm sleep disorder
b. jet lag
c. delayed sleep phase
d. None of the above

4. The shift work type of circadian rhythm sleep disorder is distinguished by disruptions due to a conflict between a person's endogenous circadian cycle and the cycle required by shift work. Individuals who work the night shift often experience this problem, especially _____.

a. older workers
b. new employees
c. those people who switch to a normal sleep schedule on days off
d. None of the above

5. Individuals with the unspecified type of circadian rhythm sleep disorder also exhibit daytime and evening sleepiness or insomnia, especially those people who have a non-24-hour sleep pattern. People with irregular sleep patterns have difficulty knowing _____.

a. what time it is
b. how to go to sleep
c. when they will fall asleep and wake up
d. None of the above

6. The delayed sleep phase type of the disorder usually begins during adolescence and can continue without treatment through adulthood. People with this type may have a family history of delayed sleep phase. The delayed sleep phase type of the disorder is thought to impact up to _____% of adults.

a. 4
b. 10
c. 15
d. 24

7. In order to diagnose circadian rhythm sleep disorder, patients are often asked for records of their sleep and wake times in order to determine if a diagnosis is warranted. Interviews and direct observation in a sleep lab may also be utilized. A diagnosis requires a pattern of sleep disruption caused by a mismatch between a person's circadian sleep-wake pattern and the pattern required by that person's environment. The disruption can be persistent or recurrent and leads to impaired functioning, often in a social or occupational context.

a. True
b. False

8. Treatment of the delayed sleep phase type depends on the severity of the case. Mild cases may be addressed by an individual simply adhering to strict sleep and wake times. Severe cases may require incremental changes in sleep time, where a person sleeps _____ each day until an appropriate pattern is reached.

a. 10 minutes
b. 15 to 30 minutes earlier
c. an hour earlier
d. None of the above

9. Because circadian rhythm sleep disorder is usually related to environmental stressors, avoidance of these stressors (such as long-distance travel, shift work, and sleep-disrupting lifestyles) can prevent the disorder from beginning or continuing. People who are able to adhere strictly to a normal sleep-wake schedule can also offset circadian rhythm-related problems.

a. True
b. False

10. UC Irvine researchers have found a molecular link between circadian rhythms – our own body clock – and metabolism. The discovery reveals new possibilities for the treatment of _____.

a. diabetes
b. obesity
c. other related diseases
d. All of the above

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