The changes in behavior that occur on a 24-hour basis to match the 24-hour changes in the physical environment due to the rotation of the earth on its axis are a hallmark of life on the planet Earth. The nervous system of both lower and higher organisms has evolved over millions of years to meet the demands of the dramatic changes in the physical environment that occur in relation to the changes in the light-dark cycle, optimizing the survival and reproductive success of the organism. During the past 50 years, it has been clearly established that the 24-hour nature of life was not simply a response to the 24-hour changes in the physical environment imposed by celestial mechanics, but instead was due to an internal time-keeping system in the brain. Many neurological disorders are associated with abnormal 24-hour rhythms, including the sleep-wake cycle. The recent discovery of the molecular basis of the neural clock in animals offers neurologists new avenues for studying the pathophysiology of neurological disorders.
WHERE IS THE CIRCADIAN CLOCK, AND HOW DOES IT TICK?

Neuronal Perspective

The finding in the early 1970s that lesions on a small region of the hypothalamus in rodents led to a disruption of endocrine and behavioral circadian rhythms was the first step in the ultimate demonstration that the bilaterally paired SCN was the location of a master central circadian pacemaker, or clock, which regulated most if not all circadian rhythms in mammals. During the following 3 decades, many elegant studies were performed in mammals (mainly rodents), which in aggregate demonstrated that:

- Total destruction of the SCN abolishes many behavioral, endocrine, and metabolic circadian rhythms.
- Isolated SCN tissue in vivo and in vitro could maintain 24-hour neural firing and/or neurosecretory rhythms.
- Transplantation of fetal SCN tissue into the brains of arrhythmic SCN-lesioned animals could restore circadian rhythmicity, and the restored rhythm in some studies was shown to have genetically defined characteristics specific to the donor and not the SCN-recipient animals.
- Cultures of individual dissociated SCN neurons continue to express circadian oscillations in firing rates that differ from cell to cell.

This latter finding is particularly noteworthy because it demonstrates that the expression of circadian rhythms by a complex neural structure is not a property of a network of neurons that depend on their interaction with one another. Instead, individual SCN neurons have intrinsic 24-hour oscillatory properties; thus the ultimate underlying clock mechanism is within the neuron. Nevertheless, clearly the thousands of neurons in the SCN are not each keeping their own time independent of one another. Instead, they must somehow be coupled to one another such that, ultimately, a single coordinated circadian signal(s) is generated and conveyed to the rest of the brain and the peripheral organs of the body.

Although the SCN-driven circadian rhythms can be expressed in the absence of any 24-hour changes in the physical environment, under normal conditions the SCN circadian clock must be entrained to the 24-hour day. For most organisms, the light-dark cycle is the major environmental synchronizing agent, and in mammals, a special retinal hypothalamic tract connects the photoreceptors in the eye to the SCN. In addition to the retinal hypothalamic tract input to the SCN, the circadian clock receives neural inputs from a variety of neural areas in the brain. Of particular note are the serotonergic (5-HT) projections from the brainstem raphe nuclei that project both directly and indirectly to the SCN. In view of the central role of the 5-HT system in the causes of many neurological and psychiatric disorders, the 5-HT system may be involved in the disregulation of circadian rhythms that are often associated with these disorders.

Molecular Perspective

Since the circadian clock in mammals resides in the SCN, and individual SCN cells can maintain circadian rhythmicity, the molecular mechanisms by which 24-hour rhythms can be generated must reside within the SCN cells. This molecular machinery remained a complete mystery until just a few years ago when the first mammalian circadian clock gene, called Clock, was discovered. Prior to the discovery and cloning of the Clock gene in 1997, many genes and their protein products were known to be expressed in the SCN on a rhythmic basis, and protein synthesis was clearly important for the expression of circadian timing. The core elements of the molecular mammalian circadian clock, however, remained unknown despite the fact that molecular components of the Clock in the fruit fly, Drosophila, and the filamentous fungi, Neurospora, had been identified in the 1980s. Because no mammalian orthologs to per or tim had been identified in the early 1990s, and no other genes in mammals were even possible candidate circadian genes, a team of investigators at Northwestern University (Evanston, Ill) applied a directed “forward genetic” approach in mice to identify the first circadian clock genes in mammals. The approach involved using a chemical mutagen to induce a high random mutation rate in the germ line of mice. The offspring of these animals were then screened for an abnormal circadian phenotype that would be due to a dominant or semidominant random mutation of a gene involved in the generation of circadian rhythms. One such animal was identified early in the screen. This founder animal had a free-running period of the activity rhythm in constant darkness that was an hour longer (~24.7 hours) and 6 SD from the mean period observed in wild-type mice (Figure 1). Breeding of this putative mutant animal and its offspring established that the change in phenotype was due to a mutation that was inherited in a classical mendelian fashion. In mice carrying 2 copies of the mutated gene, the period of the activity rhythm was initially 27 to 28 hours under free-running conditions, and quite often the activity rhythm became arrhythmic after extended exposure to constant darkness (Figure 1). The gene responsible for the altered phenotype has been mapped and cloned.

Soon after the Clock gene was discovered, there were many rapid advances that integrated the mouse and fly molecular circadian clock gene stories. Until recently, no specific gene had been identified as a component of the molecular circadian clock in humans. However, the discovery of the genes in mice ensured that it was only a matter of time before the presently known (and unknown) clock genes would be implicated in human circadian function. Indeed, the recent report that a missense mutation in the human per2 gene underlies advanced sleep phase syndrome in at least some humans indicates that other abnormal clock gene alleles will be discovered to underlie unusual circadian phenotypes in humans.
RELEVANCY OF THE CIRCADIAN CLOCK TO THE PRACTICE OF NEUROLOGY

As noted earlier in this review, the circadian clock can influence the 24-hour overall temporal organization in a direct as well as indirect fashion by controlling the timing of the rhythm of sleep and wake that in turn has a strong influence on the timing of many rhythms. Furthermore, changes in the sleep-wake and activity-rest cycle itself can influence the circadian clock; thus, it is often difficult to separate the influence of the circadian and sleep-wake system in contributing to various disorders. Indeed, the highly integrated nature of these 2 systems suggests that they should be considered in combination when trying to relate temporal disorganization to various disease states, including neurological disorders.

Disorders of circadian temporal organization come in 2 general varieties: those imposed by the lifestyle of the individual (eg, in shift workers or in individuals moving rapidly across time zones [the jet-lag syndrome]), and those that arise from endogenous alterations in normal rhythmicity. Disturbed sleep and circadian rhythms are apparent in many neurological disorders. Briefly reviewed in this section are the sleep and circadian rhythm disturbances that have been associated with the most common neurological disorders, including epilepsy, dementia, cerebrovascular disease, movement disorders, neuromuscular disorders, demyelinating disease, and headache. A more extensive coverage of this subject can be found in a recent review by Zee and Grujc.

Epilepsy

It has been known for more than a century that seizures occur preferentially in most patients at particular times of the day or night, with some patients expressing seizures during the day and others during sleep. In general, primary generalized seizures occur during the day, while secondary generalized convulsions occur most often during sleep. The time of day dependency of seizures tends to disappear with aging, although it is not known if age-related changes in the sleep-wake and circadian clock systems influence age-related changes in the daily temporal control of seizures. Just as sleep and arousal states influence the occurrence and expression of seizures, seizures in turn affect sleep; poor sleep is associated with many neurological disorders, which may contribute to the pathological symptoms of the primary disorders. For example, the severity of neurological abnormalities in patients with epilepsy is positively correlated with the degree of sleep disturbance. In addition to sleep, other circadian rhythms (eg, endocrine and neuroendocrine) often show abnormal phasing and/or amplitude in epileptic patients.

Dementia

A wide variety of diurnal rhythm disturbances have been associated with Alzheimer disease (AD), the most common dementia in most industrialized countries. Disruption of nocturnal sleep with nocturnal wan-
also with the expression or number of neuropeptide cells in the SCN. While there are reports that the SCNs of patients with AD at autopsy show a decrease in vasoressin cell number and peptide levels, the functional significance of these changes is unknown.

In addition to AD, other disorders that induce dementia, such as Huntington disease and the various prion diseases, are associated with disturbed sleep-wake cycles. Interestingly, mice with a deletion of the prion protein exhibit prominent sleep fragmentation and an alteration in circadian period, indicating that the prion protein is somehow involved in the regulation of sleep and circadian rhythms.27 In addition to the pronounced sleep abnormalities that are the hallmark of the prion disease, fatal familial insomnia, circadian rhythmicity in various endocrine rhythms are abnormal or absent in patients with this disease, suggesting that the central circadian pacemaker itself may be affected.

Dementia owing to hepatic encephalopathy is also associated with disturbance of the sleep-wake cycle and circadian rhythmicity. Indeed, animal studies involving a surgical induction of hepatic encephalopathy have demonstrated that such a procedure results in abnormal endocrine and behavior rhythms.18 These rhythm disturbances can be reversed or attenuated with a low-protein diet or neomycin, indicating that altered circadian rhythmicity is caused by the effects of liver dysfunction on the circadian clock system.4 In humans, hepatic failure results in a variety of circadian abnormalities,19 including both an increased amplitude and a phase delay in the onset and offset of the nocturnal melatonin rhythm (Figure 2). The question of whether sleep and circadian rhythm abnormalities in humans with liver dysfunction are due to a direct effect on the circadian clock and/or sleep regulatory mechanisms or are a consequence of alteration in hepatic metabolism of hormones such as melatonin remains unanswered.

**Cerebrovascular Disease**

Sleep disturbances are common in people who have had stroke. This may not only decrease the quality of life, but also lead to an increase in morbidity. Quite often, the type of sleep disturbance is related to the location and size of the stroke. Because the brainstem and the thalamus are important in the regulation of sleep, strokes in these areas commonly affect sleep.

The circadian variation in the time of the onset of ischemic stroke is a good example of how the overall temporal organization of many physiological systems can effect human health and disease. Ischemic strokes (as well as myocardial infarction) most often occur in the morning during the first few hours of wakefulness. In the morning, upon awakening and moving to an upright posture, there is an increase in blood pressure and heart rate. In addition, there is an increase in platelet aggregability, catecholamine levels, and plasma renin activity. All these rhythmic changes interact to promote changes in vascular tone, which can increase the risk of ischemia.

**Movement Disorders**

Abnormal motor activity during wake and sleep is often associated with a disruption of sleep. Several movement disorders are specific to sleep, including periodic leg movement syndrome, rapid eye movement (REM) sleep behavior disorder, and nocturnal dystonia. In periodic leg movement syndrome, movements are followed by changes in the electroencephalogram that are suggestive of arousal from sleep; the resultant sleep fragmentation can lead to severe insomnia and excessive daytime sleepiness. The distinguishing feature of REM behavior sleep disorders is the loss of motor inhibition during REM sleep, which can result in increased and often dangerous motor activity during REM sleep, as the patient appears to be enacting events associated with dreaming. In contrast, nocturnal paroxysmal dystonia involves stereotypic body movements during non-REM sleep, particularly during slow-wave sleep. The debate as to whether nocturnal paroxysmal dystonia is a sleep or seizure disorder only highlights the fact that the sleep and wake states can influence seizure in the

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way that they affect activity in the brain.

Sleep abnormalities are often associated with waking movement disorders, including Parkinson disease, progressive supranuclear palsy, and the Shy-Drager syndrome. The finding of sleep difficulties in the majority of patients with Parkinson disease is perhaps not surprising since the disease is caused by a loss of function in brainstem nuclei that are also involved in the control of sleep. Various hormonal and physiological circadian rhythm abnormalities have been reported in patients with Parkinson disease, and this may be due to an altered input of brainstem nuclei to the SCN.

Neuromuscular Disorders

Frequent complaints among patients with neuromuscular disorders include daytime sleepiness and fatigue. Both motor and respiratory disturbances during sleep undoubtedly contribute to daytime fatigue in patients with the most common neuromuscular disorders, including muscular dystrophy, amyotrophic lateral sclerosis, postpolio syndrome, and myasthenia gravis. In myotonic dystrophy, the most common form of muscular dystrophy, excessive sleepiness is quite often observed. Such hypersomnia could be due to neuronal damage in areas of the thalamus that are known to be involved in the regulation of the sleep-wake cycle, again highlighting the interdependence of sleep and neurological disorders.

Multiple Sclerosis

Multiple sclerosis, a demyelinating disorder that affects multiple central nervous system white matter tracts, is associated with prolonged sleep latency, frequent nocturnal awakenings, nonrestorative sleep, and early-morning awakenings. It is not surprising that sleep is affected in such a diverse manner since patients with multiple sclerosis have a diverse set of abnormalities that can affect the quality and quantity of sleep, including immobility, spasticity, urinary problems, respiratory control, and periodic leg movements.

Headaches

The most common types of headaches that are associated with sleep and circadian rhythmicity are migraine, cluster, and chronic paroxysmal hemicrania. Headache and sleep disorder frequently occur in the same patient, which may be due to the fact that some neurotransmitters that regulate sleep, such as serotonin and histamine, have also been implicated in some types of headaches. Both cluster and migraine headaches have a strong circadian component to their occurrence. Interestingly, cluster headaches occur most often in the spring and fall, when day lengths are changing the most rapidly. In mammals, the circadian clock in the SCN plays a central role in measuring the seasonal change in day length, which can in turn influence a wide variety of physiological systems. The finding of a seasonal change in headache occurrence is a reminder that we have just begun to understand the many ways in which the circadian clock system may affect and modulate neurological disorders.

RELEVANCE OF THE CIRCADIAN CLOCK TO NEUROSCIENCE

A few years ago a “birthday party” was held at Harvard Medical School to celebrate the 25th anniversary of the discovery that lesioning of the SCN abolished circadian rhythmicity in rats. This was the first clear experimental result that eventually led to the demonstration that the SCN was the site of the master circadian pacemaker in mammals. One of the themes of the party/symposium was that discoveries about SCN function were often at the forefront in terms of the use of new neuroscience approaches and techniques. Perhaps the main reasons for this were the “simple” nature of the circadian clock and the “simple” method for monitoring clock functions in mammals. The first simplicity was the relatively basic anatomical location (the SCN) of a neural center regulating complex behavioral and physiological rhythms. Whereas other behaviors such as reproduction, feeding, sleep, and learning involve many and diffuse areas of the brain, the generation of circadian rhythms could be located to a few thousand neurons in close proximity to one another. The second simplicity was the use of an elementary and inexpensive method for monitoring a “reporter output rhythm” of the central circadian clock: the rhythm of wheel-running behavior to assay the state of the circadian clock on a continuous basis for essentially the lifetime of the organism. At Northwestern University, for example, for many years we have been able to monitor the rhythm of wheel-running behavior of more than 1500 rodents, 365 days per year, with minimal disturbance to animals housed under different lighting and other environmental conditions. The justification for using this simple rhythmic behavior as a surrogate marker of the state of the circadian clock was the demonstration throughout the years that the same circadian clock that regulates the rhythm of wheel-running and locomotor activity regulates most if not all behavioral, physiological, and cellular rhythms.

This anatomically defined structure with an easily measured behavioral output allowed circadian rhythm researchers to use powerful new neuroscience approaches over time to study brain function at many different levels. These approaches include:

- The use of specific lesions and knife cuts to discover functionally important components and pathways of the circadian clock system;
- The use of the newly developed 2-deoxyglucose technique to link brain energy usages with function (the neurons of the SCN are more active during the day than during the night, in both diurnal and nocturnal species—a finding that allowed investigators to demonstrate SCN rhythmicity in fetal and neonatal animals long before any physiological and behavioral rhythms are expressed);
- The use of the expression of immediate early genes to map the molecular cascade of events that occur in neural tissue between stimulation and a change in brain function,
We take the position that the field of neurology has not paid sufficient attention to the importance of sleep and circadian rhythms in the etiology and/or treatment of neurological disorders. Of course as sleep and circadian rhythm researchers, we obviously have a biased perspective. Nevertheless, as discussed in this review, sleep and rhythm disorders are characteristic of many neurological disorders, and these temporal disturbances may in themselves be responsible for some of the symptoms that are a part of neurological diseases. In addition, it is likely that associated sleep and rhythm disturbances will have a negative effect on the quality of life of the patients and their caregivers, and thus, for optimal treatment of the neurological disorder, improving sleep and circadian organization should be of high priority.

In the 1970s and 1980s, the discovery and the discovery process that the SCN was the site of the master circadian clock in mammals ushered in an era during which the study of circadian rhythms became one of the subdivisions of the neurosciences. Indeed, except for meetings at which the central focus is biological rhythms (such as the meeting of the Society for Research on Biological Rhythms), it is likely that more papers are presented on circadian rhythms at the Annual Meeting of the American Neuroscience Society than at any other broad-based biomedical scientific meeting. Given that the “home” basic science discipline of the field of biological rhythms is the neurosciences, one might expect that the “home” clinical discipline for the clinical components of the field of circadian rhythms would be neurology. Despite neurology being the natural clinical and intellectual base for the field of rhythms, this has not occurred in practice. While there are certainly many historical reasons for this, perhaps an overriding one has to do with the position of sleep clinics in the United States. Since the majority of patients visiting at sleep clinics are diagnosed and treated for sleep apnea, sleep clinics have commonly been dominated by clinicians interested and focused on respiratory problems. With sleep disorders being one of the most obvious links between the neural circadian clock and human health and disease, the clear clinical connection for circadian biomedical researchers is with those clinicians interested in the neural basis of sleep and its neuronal interactions with the circadian system. Thus, there is a disconnect between the home of the basic researchers and the clinical practitioners. The study of the central mechanisms underlying sleep and rhythmicity is in the neurosciences, while the clinical home for sleep disorders (and the revenues generated by the treatment of these disorders) is often in the field of pulmonary physiology. However, the central nervous system control of the sleep-wake and circadian clock systems is rarely the intellectual focus of respiratory physiologists. We hope and anticipate that greater awareness of the important role played by sleep and circadian disturbances in the causes and treatment of neurological disorders will lead to a heightened interest in the discipline of neurology for the study of sleep and circadian rhythms that matches that found today in the neurosciences.

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