Clinical Aspects of Human Circadian Rhythms

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Abstract Circadian rhythmicity can be important in the pathophysiology, diagnosis, and treatment of clinical disease. Due to the difficulties in conducting the necessary experimental work, it remains unknown whether ~24-h changes in pathophysiology or symptoms of many diseases are causally linked to endogenous circadian rhythms or to other diurnal factors that change across the day, such as changes in posture, activity, sleep or wake state, or metabolic changes associated with feeding or fasting. Until the physiology is accurately known, appropriate treatment cannot be designed. This review includes an overview of clinical disorders that are caused or affected by circadian or diurnal rhythms. The clinical side effects of disruption of circadian rhythmicity, such as in shiftwork, including the public health implications of the disrupted alertness and performance, are also discussed.

Key words circadian rhythms, clinical disorders, clinical medicine, sleep disorders

The clinical aspects of human circadian rhythms are potentially important, but much rigorous scientific work remains to be performed. Scientists interested in circadian rhythms began their study of these rhythms by focusing on the behavioral, anatomic, cellular, and molecular aspects of circadian rhythms. Now that there have been significant advances of knowledge in these areas, the effects of circadian rhythms on clinical medicine should and can be more thoroughly investigated.

One problem in understanding the effects of circadian rhythms on clinical medicine is the distinction between circadian and diurnal rhythms. A *circadian* rhythm is causal; it is generated by an endogenous circadian (~24-h) oscillator. Circadian rhythms are present in neuronal and nonneuronal cells, including neuronal cells in the frontal cortex, Purkinje cells in the cerebellum, liver cells and fibroblasts (reviewed in Schibler and Sassone-Corsi, 2002), and in the SCN of the mammalian hypothalamus (Klein et al., 1991). The SCN is the site of the central pacemaker capable of synchronizing these cellular rhythms to produce observable circadian rhythms in different physiologic measures. Other stimuli, such as cycles of food availability, may also be capable of entraining some peripheral rhythms (Stokkan et al., 2001). A *diurnal* rhythm is descriptive; it refers to an observed 24-h pattern. This pattern can be caused by an endogenous circadian pacemaker and/or by the other events within the 24-h day, such as sleep-wake patterns, activity, meals, social contacts, postural changes, or light exposure. Due to the difficulty in conducting human protocols in which circadian rhythmicity can be studied, most clinical reports are based on diurnal studies. Therefore, whether the pathophysiology, symptoms, or treatment tested have a circadian or diurnal basis is fre-

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quently unknown but needs be determined for effective treatment design: changing the phase or amplitude of an endogenous circadian rhythm requires different interventions than changing a diurnal event, such as posture or timing of meals.

The central circadian pacemaker can exert control in at least 2 different ways: (1) determine a changing "set point" around which homeostasis is maintained for some physiologic functions (e.g., core body temperature) or (2) initiate specific changes (e.g., onset of melatonin secretion). The former may be valuable both for conservation of resources (e.g., have high concentrations of digestive enzymes only around the time of expected meals) or may be related to effective regulation of a physiologic process. Down-regulation of response is known to occur in some hormone systems if there is a constant level of stimulus (e.g., a constant pulse frequency of gonadotropin-releasing hormone across the menstrual cycle results in anovulatory cycles; Filicori et al., 1989). It is therefore possible that there could be down-regulation of end-organ response if there is no circadian variation in stimuli. Both mechanisms—varying set point or initiating a process—can be involved in clinical disease and treatment.

There are 2 possible types of interaction of the circadian system with clinical pathophysiology (Fig. 1): (1) primary circadian, in which abnormalities in the circadian system cause the pathophysiology, and (2) secondary circadian, in which the underlying pathophysiology is not circadian based, but the expression of this pathology is altered by circadian or diurnal events.

While sleep and circadian rhythmicity are interconnected, this review will not discuss sleep disorders or sleepiness, except as they relate to clinical aspects of circadian rhythms. Sleep is reviewed elsewhere in this issue.

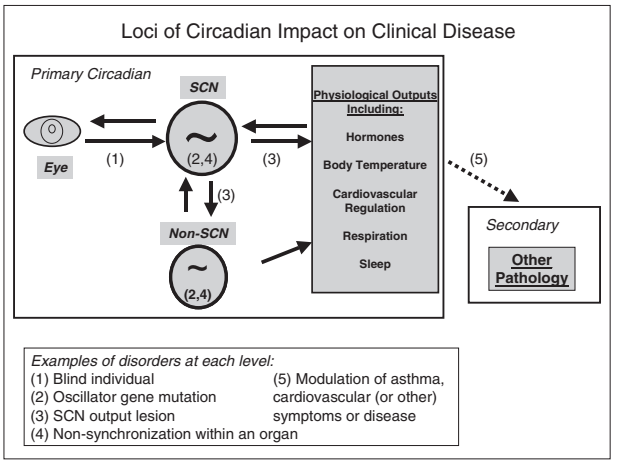

Figure 1. Schematic of physiological loci at which circadian rhythmicity could cause or modulate clinical disease.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Alterations in the Anatomy or Physiology of the Circadian System Causing Clinical Disease

There are 3 possible levels of purely circadian abnormalities. The first level is within the cell: abnormalities prevent or alter the generation of circadian oscillation within each cell. The generation of a ~24-h circadian rhythm is the result of multiple biochemical and genetic processes (Reppert and Weaver, 2002). When the mutations in genes associated with the circadian pacemaker, such as the *Per* family of genes and the *Clock* gene, were first studied, the focus was on changes in purely circadian parameters, such as presence or absence of rhythmicity, amplitude of rhythmicity, or period length. Such pathology has been both observed spontaneously and experimentally induced in animals but not in humans. These circadian rhythm–generating biochemical and genetic processes can be modulated by other chemicals (e.g., heme; Kaasik and Lee, 2004); however, no clinical disorders related to a modulation mechanism are currently known.

Physiological abnormalities associated with circadian gene mutations in a variety of different systems have been described, including cancer, metabolism, and sleep. Since the circadian oscillator gates cytokinesis to defined time windows within the cycle (Nagoshi et al., 2004), it is not surprising that mutations in some circadian clock genes are associated with increased cancer risk in animals, presumably through a mechanism of changes in the regulation of the cell cycle, including cell division (Fu et al., 2002; Lowrey and Takahashi, 2004). A polymorphism in *Per3* has been linked with early onset breast cancer in young women (Zhu et al., 2005), and abnormalities in *Per1*, *Per2*, and *Per3* gene regulation in tumors but not normal cells have been observed (Chen et al., forthcoming). Homozygous circadian *Clock* mutant mice have altered feeding rhythms and develop key components of the "metabolic" syndrome, including obesity,

hyperlipidemia, hyperglycemia, and hypoinsulinemia (Turek et al., 2005). In another example, a circadian *per2* mutation is associated with an alteration of circadian phase and impaired circadian resetting and lowered expression of a glutamate transporter, resulting in increased alcohol intake in mice (Spanagel et al., 2005). In humans, variation of the *PER2* gene is associated with regulation of alcohol consumption (Spanagel et al., 2005), suggesting that *PER2* may contribute to the development of or be associated with individuals with alcoholism. More such interactions will probably be discovered in the next few years, even though the implications and links of circadian oscillator function with these diseases are currently not clear. As expected from the known interactions of the circadian pacemaker and sleep, changes in clock and clock-related genes may alter sleep. Deletion of *BMAL1/Mop3* alters sleep patterns before and after sleep deprivation (Laposky et al., 2005), and a mutation in *NPAS2*, a paralog of the transcription factor *CLOCK* that is not located in the SCN, results in altered patterns of sleep, locomotor activity, and response to light and feeding-related entrainment cues (Dudley et al., 2003).

The second level of circadian abnormalities is caused by abnormalities within an organ (e.g., liver, kidney, SCN), such that the normal intracellular circadian rhythms cannot synchronize to produce a rhythm for the organ. These abnormalities can be detected in vitro. However, clinically, this may be difficult to distinguish from the loss of intracellular circadian rhythm generation.

The third level is loss of the ability of the central circadian pacemaker in the SCN to synchronize the peripheral tissue rhythms to produce an organismal level of synchronized rhythms. One example would be loss of overt rhythms of protein synthesis for metabolic pathways, including glycolysis, gluconeogenesis, fatty acid metabolism, and cholesterol metabolism (Lowrey and Takahashi, 2004). This state has been induced experimentally in animals through lesions of the outputs of the SCN. There is a report of 1 individual with very weak or absent circadian rhythmicity in core body temperature and sleep rhythms (Czeisler et al., 1986); the level of disruption of the circadian system in that individual is not known. Internal desynchrony (forced or spontaneous) in humans is not an example of the loss of influence of the central circadian pacemaker on overt rhythms. Although the timing relationships between the circadian pacemaker and some of the overt rhythms (such as activity) change, there is still circadian influence on these rhythms during desynchrony.

In addition to these 3 levels of oscillator function, circadian rhythm abnormalities can also exist due to changes in the inputs and outputs of the circadian pacemaker. Ocular light exposure is the strongest input signal to the mammalian SCN. The existence of blind persons with normal entrained circadian rhythms (Sack et al., 1992; Czeisler et al., 1995) supported animal evidence that 2 systems of photoreceptors exist in the retina. In humans, while none have yet been reported, there are likely to be "sighted" individuals with abnormalities of the photosensitive retinal ganglion cells or retino-hypothalamic tract between the retina and the SCN. In these individuals, normal conscious vision may exist while circadian-based photoreception is diminished or absent. These people would be expected to have abnormally entrained or free-running circadian rhythms, as many totally blind persons do, though there may be some individuals with apparently entrained circadian rhythms, as is seen in some blind individuals. In older individuals, changes in light transmission through the eye to the relevant photoreceptors (e.g., because of cataracts) may affect the circadian response to light without a change in the pacemaker itself.

Relevant changes in outputs of the circadian pacemaker include changes in amplitude or phase of the rhythms. The circadian pacemaker in healthy older individuals exhibits a decreased amplitude (Czeisler et al., 1992). Theoretically, the decreased amplitude of the circadian pacemaker should result in increased ease of phase shifting, but this is not uniformly the case. Dampening of the amplitude of the endogenous circadian rhythm may cause clinical symptoms. For example, more antidiuretic hormone (ADH) is usually secreted at night than during the day in humans, causing decreased urine production during the usual sleep episode. In older persons and in individuals with spinal cord injuries (Szollar et al., 1997; Bodo et al., 1998), there is a loss of the usual nocturnal increase in ADH, resulting in a dampening of the diurnal rhythm, which causes increased urine production at night (nocturia) and disrupted sleep. In another example, Scheer and coworkers have hypothesized that SCN functions are disturbed in patients with essential hypertension (Scheer et al., 2003). Treatment of these individuals with nighttime melatonin to "support" the SCN was associated with decreased blood pres-

sure (Scheer et al., 2004). Further research into whether SCN function itself is altered in some cardiovascular disease is warranted.

Abnormalities of phase or entrainment of the circadian pacemaker are implicated in some sleep disorders (reviewed in Baker and Zee, 2000). These disorders include advanced sleep phase syndrome, delayed sleep phase syndrome, and non-24-h sleep disorder. In advanced sleep phase syndrome, individuals go to sleep and awaken at much earlier hours than normal for the population. In 1 family with this disorder, there was an abnormality in the *casein kinase I (CKI)*–binding domain of *Per2* (Toh et al., 2001), a gene involved in the generation of circadian rhythms. A mutation in a *CKI*δ gene, causing decreased kinase activity in vitro and altered circadian period lengths in animals, has been found in another family with advanced sleep phase syndrome (Xu et al., 2005). In delayed sleep phase syndrome, sleep and wake times are much later than normal for the population. Some individuals with polymorphisms in *Per3* (Robilliard et al., 2002; Lowrey and Takahashi, 2004) have this disorder. The circadian system phase-delays during adolescence relative to that of younger children, although the change does not reach the level of a clinical disorder (Carskadon et al., 2004). The effect of this change in relative circadian phase on performance and schoolwork is reviewed in Wolfson and Carskadon (2003).

In non-24-h sleep-wake syndrome, individuals do not keep a regular 24-h sleep-wake schedule. Free-running circadian rhythms have been documented in these individuals, some of whom are blind and some of whom are sighted (Hashimoto et al., 1998). Many of these individuals have self-imposed irregular schedules, causing irregular patterns of light exposure. No reports have documented the absence of circadian rhythmicity in these individuals. The pathophysiology of this syndrome may include decreased stimuli capable of entraining the circadian system. Such pathology can be found in blind persons with no light stimuli reaching the SCN, individuals with decreased sensitivity to entraining stimuli, and individuals with irregular light-dark patterns because they work nights or rotating schedules or otherwise choose irregular sleep-wake schedules. Reports of successful treatment of this syndrome with regularly timed melatonin and/or bright-light stimuli (Hayakawa et al., 1998; Watanabe et al., 2000) support this hypothesis. A relatively high percentage of the sighted individuals with this syndrome have psychiatric disorders (Yamadera et al., 1996); the relationship between psychiatric disease and these sleep abnormalities is unknown.

There is a debate whether the annual depressions seen in seasonal affective disorder (SAD) are related to circadian rhythms and/or changes in light exposure to individuals predisposed to depression. Three lines of evidence suggest that this disorder has a circadian component: (1) improved outcomes in individuals exposed to light during the morning rather than the evening, (2) the association between the timing of the light and phase shifts (Eastman et al., 1998; Lewy et al., 1998; Terman et al., 2001; Avery et al., 2001), and (3) a report of a difference in *NPAS2* genes, another gene family involved in circadian rhythm generation, between SAD patients and healthy controls (Johansson et al., 2003). On the other hand, inpatient intensive circadian studies using forced desynchrony or constant-routine techniques do not show significant differences in circadian amplitude or period or timing of core body temperature or melatonin (2 markers of the human circadian pacemaker) relative to sleep, variations in mood, or sleep parameters between the 2 groups (Dahl et al., 1993; Wirz-Justice et al., 1995; Koorengevel et al., 2002a, 2002b). The positive effect of light therapy in the treatment of both seasonal and nonseasonal mood disorders has recently been reviewed in Golden et al. (2005).

Normal Circadian or Diurnal Variation Affecting Clinical Disease

A secondary-level relationship between circadian rhythms and clinical disease occurs when normal circadian or diurnal variations or the loss of these variations contribute to pathophysiology of another system in predisposed individuals. For example, while a myocardial infarction may be caused by loss of blood flow to a portion of the heart muscle, circadian variations in factors affecting blood flow or clotting may modulate the time at which a myocardial infarction occurs. The following is a nonexhaustive list of such conditions, organized by clinical area.

Cardiovascular and Respiratory Disease

Hypertension and cardiovascular-related events are significant sources of morbidity in developed countries. The interactions of circadian/diurnal

rhythms with hypertension are reviewed in Smolensky and Haus (2001). A series of epidemiological studies has shown that cardiovascular-related events—such as myocardial infarctions (heart attacks), angina, strokes, arrhythmias, sudden cardiac death, and deaths associated with congestive heart failure—are more common in the morning hours (Cohen et al., 1997; Elliott, 1998). Potential causes include higher blood pressure in the morning (White, 2003), the peak in the timing of rupture of coronary artery plaques between 6 a.m. and noon, changes in activated carotid baroreceptor reflex, heart function and respiratory resistance in older men (Klawe et al., 2004), loss of diurnal variation in endothelium-dependent vasodilation in early morning (so blood vessels cannot widen normally when tissues need more blood) (Shaw et al., 2000; Otto et al., 2004), and changes in heartbeat dynamics (Hu et al., 2004). In addition, adrenaline, cortisol, and testosterone, each of which can alter cardiovascular function, all have endogenous circadian rhythms with peak levels in early morning, and there is increased sympathetic autonomic activity during the day and increased parasympathetic autonomic activity at night (Furlan et al., 1990). Waking up is stressful: both the change in conscious state and the changes in posture and activity cause changes in autonomic levels (Furlan et al., 1990; Muller, 1999). There is also a circadian variation in heart rate response to awakening (Hilton et al., 2001). It is therefore not unexpected that cardiovascular events are more likely around the time of awakening, and this increase may be due to both endogenous and exogenous factors. A recent report documented that the peak in sudden death from cardiac causes is higher during habitual sleep time, rather than around the time of awakening, in individuals with obstructive sleep apnea (Gami et al., 2005); the risk was even higher with individuals with more severe symptoms and may be related to the physiologic changes associated with sleep apnea symptoms occurring while the individual is asleep.

The diurnal variation in cardiovascular risk is altered in individuals with diabetes mellitus. Individuals with diabetes have a loss of the normal nocturnal decrease in blood pressure (Bernardi et al., 1992; Monteagudo et al., 1996), loss of the normal diurnal variation in fibrinolytic activity and plasminogen activator inhibitor (Aronson et al., 1999), and decreased parasympathetic activity during sleep (Bernardi et al., 1992). These changes may contribute to the absence of a diurnal pattern in the risk of myocardial infarction in individuals who have had diabetes more than 5 years (Rana et al., 2003). The clinical implications of the loss of diurnal rhythmicity of risk, in the presence of an overall increased cardiovascular risk in these individuals, are not known.

Diurnal and circadian variation in respiratory function, including respiratory control—specifically, hypercapnic ventilatory response, O_2 uptake, and CO_2 production—but not in tidal volume, respiratory frequency, or ventilation (Spengler et al., 2000) may affect some respiratory disease symptoms. Nocturnal worsening of asthma has been related to increased response to increased reactivity of the airways and inflammatory cells (Kelly et al., 2004). Asthma diagnosis and treatment guidelines now reflect the known diurnal rhythmicity in pathophysiology and symptoms (Smolensky et al., 1999).

Endocrine and Rheumatological Disease

The circadian variation in metabolic response has implications for diabetes care and for obesity. In a recent study in which individuals were fed frequent meals while remaining awake, circadian rhythms in glucose, insulin, and leptin were described that had peak levels around the usual time of awakening. Sleep—normally associated with fasting and usually at night—resulted in additional decreases in leptin, glucose, and insulin, whereas wakefulness—associated with food intake and daytime hours—resulted in an increase in leptin (Shea et al., 2005). Other studies have found a diurnal variation of response to a constant glucose infusion: increased blood glucose levels (decreased glucose tolerance) were observed from approximately midnight to 6 a.m. and during sleep (Van Cauter et al., 1997). When volunteer subjects were awake during usual nocturnal sleep time, a lower increase in glucose and insulin secretory rates occurred than during sleep; when the subjects were asleep during usual wake time, increases in glucose and insulin secretory rates were observed. Therefore, both circadian and sleep-wake regulatory factors affect glucose tolerance and insulin secretory rates (Van Cauter et al., 1997). Older people had a decreased postsleep rise in insulin secretion, suggesting that more insulin resistance (worse glucose tolerance) arises with aging (Frank et al., 1995). The problem of nocturnal hypoglycemia in individuals with insulin-dependent diabetes mellitus has been

recognized for years (Matyka et al., 1999; Allen and Frier, 2003). What remains unclear, however, is how much of nocturnal hypoglycemia is due to circadian variation in glucose and insulin and how much to patterns of exogenous insulin administration relative to meals (Van Cauter et al., 1997).

The circadian rhythm in hormones in the adrenocorticotropic hormone (ACTH)/cortisol family has been used by endocrinologists for diagnosis (Krieger et al., 1968; Krieger et al., 1976). One example is the overnight dexamethasone suppression test for Cushing's syndrome, a disease characterized by increased levels of cortisol; dexamethasone blocks the normal nighttime increase in ACTH and cortisol in normal individuals but not those with Cushing's syndrome. In addition, the relative circadian amplitudes, as well as the relative pulse amplitudes of cortisol and of ACTH, are lower in Cushing's disease than in pseudo-Cushing's disease (Cunningham et al., 2002). There are also changes in 24-h cortisol release in patients with Alzheimer's and Parkinson's diseases (Hartmann et al., 1997).

Clinical symptoms of rheumatoid arthritis show diurnal variation: joint stiffness and pain are present more in the early morning. This pattern is different from the diurnal pattern of the evening pain of "wear and tear" osteoarthritis, which may be related to the patient's activity during the day. One potential cause of rheumatoid arthritis symptoms is the diurnal rhythm of human cytokine production, which contributes to inflammation, which has peak levels during night and early morning, when cortisol (anti-inflammatory) is lowest and melatonin (pro-inflammatory) is highest (Cutolo and Masi, 2005), although other mediators are also involved.

Psychiatric and Neurological Disease

Disturbed sleep and circadian rhythms have been observed in patients with schizophrenia and depression (Anderson and Wirz-Justice, 1991; Boivin, 2000; Martin et al., 2005), although it is unclear if the circadian and sleep disorders are causal or related to the disease and/or its medications. Mood improves during the waking day in patients with depression; extension of waking/sleep deprivation has an antidepressant effect (King, 1980). Sleep deprivation can also induce mania in some individuals with bipolar affective disorder. Some other features of depression, such as early morning awakening, decreased REM latency, and shifted cortisol and prolactin rhythms, are also suggestive of a circadian phase advance relative to the sleep-wake cycle. However, despite many studies, this hypothesis has not been causally proven (Anderson and Wirz-Justice, 1991; Boivin, 2000).

The time of occurrence of seizures has a diurnal variation. There are significantly more first febrile seizures between 6 p.m. and midnight, with a peak between 5 and 8 p.m. (Manfredini et al., 2004). There is also a day/night variation in different types of seizures, with a peak from 3 to 6 p.m. in patients with temporal lobe epilepsy and from 7 to 11 p.m. in patients with extratemporal lobe epilepsy (Pavlova et al., 2004).

Other

Diurnal sleep patterns change across the life cycle. Infants have multiple short sleep episodes, toddlers have 2 sleep episodes, children and most adults have 1 sleep episode, and some older individuals have 2 sleep episodes per day. In older adults, the interaction of the circadian pacemaker with sleep regulatory mechanisms causes decreased sleep at certain phases of the circadian system (Dijk et al., 1999), as if the awakening signal from the SCN is stronger and earlier in older than younger individuals. It is not clear whether increased midday napping in older adults is a direct consequence of changes in circadian rhythmicity (e.g., from the decreased circadian amplitude) or from the increased early awakening signal from the circadian pacemaker or from lifestyle, disease, or medication changes. Some, all, or none may be factors in different individuals.

The daily patterns of some hormones and sleep depend on the duration of prior light exposure (Wehr, 1991). Annual rhythms of fertility in individuals whose indoor and outdoor light exposures change with the seasons persist in some populations and may be related to this photoperiodic response (e.g., Becker, 1991).

There may be a circadian variation in pain thresholds. In a review of biological rhythms of pain and treatment of pain (Labrecque and Vanier, 1995), the time of peak pain depended on the type and location of pain and on the methods used, suggesting that the pain may be related to both the underlying disorder(s) and to diurnal or circadian rhythms in pain perception. There is a diurnal distribution of breakthrough analgesia required in advanced cancer patients

(Gagnon et al., 2001), and labor pain (associated with childbirth) by self-report is least in morning (7 a.m. to 1 p.m.) compared to 8-h time bins in the afternoon, evening, and night (Aya et al., 2004). Gout pain is most likely in the middle of the night, and the pain of kidney stones begins early morning.

Night sweats or fever at night are prominent in some illnesses, such as tuberculosis, HIV, Still's disease, and lymphoma. To what degree the fevers are related to the thermoregulatory systems involved in the endogenous circadian variation in core body temperature or to other factors is not known. Some human parasites have diurnal periodicity in their activity (Hawking, 1975), including the malaria parasite (Magesa et al., 2000), which may be related to diurnal changes in the parasite itself or in the human host.

CLINICAL IMPLICATIONS OF NIGHTWORK AND ROTATING SHIFTWORK

Health disorders of shift workers have been reviewed recently (Knutsson, 2003; Costa, 2003). Individuals working night/rotating shifts have 2 types of clinical disorders: effects on their health, including accidents, and effects on others, including family and social stress, errors and accidents, and workplace performance. The causes of both types of disorders are multiple and may include disruption in circadian rhythms, sleep deprivation, stress, poor eating habits or eating at unusual times, other behavioral changes, and changes in social support (Knutsson, 2003). It is difficult to isolate individual factors responsible for these changes or calculate risk statistics for nightwork- and shiftwork-related disorders since there are many different work shift patterns experienced, even within 1 individual, and many different workplace conditions and settings (lights/other environmental, stress, workplace load). Clinically, disorders of sleep—difficulty getting to sleep, shortened sleep duration, and sleepiness when wanting to be awake—are the most common complaints (Akerstedt, 2003), followed by digestive disturbances (peptic ulcer disease), cardiovascular disease (Knutsson et al., 1986; Bøggild and Knutsson, 1999), and fertility issues (miscarriage, preterm birth) (Axelsson et al., 1989; Xu et al., 1994). Disturbed glucose regulation (reviewed in Knutsson, 2003) and altered metabolic response to meals at nonstandard times (Ribeiro et al., 1998) have also been documented. There may also be psychological symptoms such as anxiety and irritability. There is a question about whether these disorders are more common in shift workers or if the severity is worse for preexisting conditions in these individuals (Knutsson, 2003). There is increased risk of breast cancer in women working the nightshift, which has been hypothesized to be due to light exposure during work at night (reviewed in Stevens, 2005).

The circadian disadvantages of nightwork or shiftwork can also affect others besides the worker. Performance decrements, accidents, and injuries have been documented in shift workers, health care workers, and transportation workers (Folkard and Tucker, 2003; Barger et al., 2005). Accidents can happen at work or when traveling from work. The accident risk is related, as expected, to both time of day and length of time driving or at work. The interaction of these 2—longer time awake is associated with adverse circadian phases for performance—worsens the accident or poor performance rate. Accidents at the Chernobyl and Three Mile Island nuclear power plants, the NASA *Challenger* disaster, and the Exxon oil spill in Valdez, Alaska, were all partially caused by decrements in performance due to the effects of nightwork, circadian phase, and length of time awake.

Shift workers also have differential health care patterns: they have increased visits to health care providers and increased use of medications to stay awake or fall asleep (reviewed in Moore-Ede and Richardson, 1985). These medications may have side effects, especially with long duration use. The treatment of circadian disorders of shiftwork and nightwork, including a discussion of sleeping, napping, and light exposure strategies, is discussed elsewhere in this issue. Education of the worker about sleep, light exposure, and drug-related strategies to aid working on these schedules is important.

TREATMENT

Clinical diseases due to some circadian phase abnormalities, such as shiftwork, irregular sleep cycles, or jet lag, have been treated with appropriately timed light stimuli, although a few nonphotic stimuli, including melatonin, may affect circadian rhythms (Lockley et al., 2000; Sack et al., 2000; Rajaratnam et al., 2004; Wirz-Justice et al., 2004). Recent reviews of multiple studies found no evidence for melatonin's effectiveness in most sleep disorders but some effective-

ness in jet lag and shiftwork (Herxheimer and Petrie, 2002). The fact that some mice species do not have endogenous melatonin and still have circadian rhythms similar to species with endogenous melatonin does not exclude the possibility that melatonin may affect the circadian clock.

For other diseases for which basic pathophysiology may not be diurnal or circadian, appropriate timing of standard therapeutic interventions may be useful. Reviews of the concepts and practical aspects of chronotherapeutics/chronopharmacology are found in Smolensky et al. (1999) and Elliott (2001). The underlying principle is that if there are diurnal changes in the physiology or drug metabolism or drug clearance rates, if there are diurnal patterns of activities that may affect the disease, or (in the case of cancer) if there may be different times of vulnerability to treatment and side effects of medications, then there may be optimal times to administer drugs or other therapies. For example, if cardiovascular risk is highest in the early morning and at approximately wake time, then medications affecting blood pressure, platelet aggregability, and other factors affecting cardiovascular risk should be administered so that they are at their peak effectiveness at that time. Giving cancer therapy at times when the cancer cells might be most vulnerable but the healthy cells are less vulnerable, thereby improving the ratio of benefit/side effects, has been effective in some but not all reports (Kobayashi et al., 2002; Mormont and Levi, 2003; Gallion et al., 2003; Hrushesky et al., 2004).

IMPLICATIONS FOR HEALTH CARE DELIVERY AND FOR PUBLIC HEALTH

Circadian or diurnal symptom patterns may not coincide with the way medical services are usually delivered. Single convenient-to-the-clinician testing times may not be optimal for disease diagnosis for 2 reasons: the symptom or the key diagnostic feature may be most prominent at a specific time outside office hours, or the loss or change of a diurnal variation may be the relevant feature of the disorder. For example, 24-h ambulatory blood pressure monitoring may reveal information about an individual's likelihood to both have significant high blood pressure present and what the pattern of high blood pressure is (White, 2003), including whether the normal variation is lost, as in diabetes (see references above) (Spallone et al., 1996). Or, fever or levels of hormones or other physiologic measures may be abnormal at night (see above). Diagnostic testing should include these non–office hour measurements. The clinician first must be aware that such measurements are beneficial, and the equipment (e.g., Holter monitors) and personnel must be available.

Of importance for health care planning, there are diurnal rhythms in symptoms in many disorders. For example, calls to emergency rooms have diurnal rhythms, with a morning peak for cardiologic, respiratory, and neurology symptoms and an afternoon peak for trauma, neoplastic, and acute poisoning symptoms (Manfredini et al., 2002). Spontaneous childbirth occurs most often in late morning/early afternoon hours (Anderka et al., 2000; Mancuso et al., 2004).

Other public health issues for clinical implications of circadian rhythms are safety related—both for workers and for others. As noted above in the discussion of nightwork and shiftwork, there are increased accidents affecting both these workers and others. Multiple governmental and nongovernmental agencies are tracking these measures.

FUTURE WORK

This review has concentrated on circadian rhythms. However, circadian rhythms also interact with shorter/ultradian (e.g., REM sleep, hormonal) and longer/infradian (e.g., menstrual, annual) rhythms. The circadian rhythms in the SCN cells are created from shorter cycles (e.g., changes that occur in less than a second) and their interactions (Reppert and Weaver, 2002). Altered interactions of circadian with ultradian and infradian cycles are other possible sources of clinical disease.

Our knowledge of the molecular and genetic mechanisms underlying circadian rhythmicity is rapidly expanding. However, the functional outputs of these mechanisms are largely unknown, especially in humans. Documenting these outputs of the circadian pacemaker will be crucial to understanding the interactions between the basic science of the circadian system and their clinical aspects.

Future work in clinical aspects of circadian rhythms should also focus on differentiating circadian from diurnal aspects of disease pathology, symptoms, and treatment. Unfortunately, experiments to differentiate diurnal from circadian effects usually require inpa-

tient conditions and are therefore difficult and expensive. Much also can be learned from patients with symptoms suggesting specific mutations of the circadian system such as photoreceptor, gene mutation, or abnormal link to observable output rhythms. Medicine and basic research have frequently learned about normal and abnormal physiology from individuals with disease; therefore, vigilance for individuals with symptoms suggesting circadian abnormalities will be vital. Finally, education and other public health activities concerning circadian rhythms and their clinical implications and disorders should be pursued.

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