ating the action of growth hormone in stimulating incorporation of sulfate into cartilage. J Clin Invest 1956; 35:733. abstract.
8. Chochinov RH, Daughaday WH. Current concepts of somatomedin and other biologically related growth factors. Diabetes 1976; 25:994-1004.
9. Zapf J, Schoenle E, Froesch ER. Insulin-like growth factors I and II: some biological actions and receptor binding characteristics of two purified constituents of nonsuppressible insulin-like activity of human serum. Eur J Biochem 1978; 87:285-96.
10. Rinderknecht E, Humbel RE. The amino acid sequence of human insulin-like growth factor I and its structural homology with proinsulin. J Biol Chem 1978; 253:2769-76.
11. Rinderknecht E, Humbel RE. Primary structure of human insulin-like growth factor II. FEBS Lett 1978; 89:283-6.
12. Zapf J, Walter H, Froesch ER. Radioimmunological determination of insulin-like growth factors I and II in normal subjects and in patients with growth disorders and extrapancreatic tumor hypoglycemia. J Clin Invest 1981; 68:1321-30.
13. Hintz RL, Liu F, Marshall LB, Chang D. Interaction of somatomedin-C with an antibody directed against the synthetic C-peptide region of insulin-like growth factor–I. J Clin Endocrinol Metab 1980; 50:405-7.
14. Van Wyk JJ, Svoboda ME, Underwood LE. Evidence from radioligand assays that somatomedin-C and insulin-like growth factor-I are similar to each other and different from other somatomedins. J Clin Endocrinol Metab 1980; 50:206-8.
15. Hintz RL, Liu F, Rinderknecht E. Somatomedin-C shares carboxy-terminal antigenic determinants with insulin-like growth factor-I. J Clin Endocrinol Metab 1980; 51:672-3.
16. Zapf J, Waldvogel M, Froesch ER. Binding of nonsuppressible insulin-like activity to human serum: evidence for a carrier protein. Arch Biochem Biophys 1975; 168:638-45.
17. Zapf J, Morell B, Walter H, Laron Z, Froesch ER. Serum levels of insulin-like growth factor (IGF) and its carrier protein in various metabolic disorders. Acta Endocrinol (Copenh) 1980; 95:505-17.
18. Daughaday WH, Mariz IK, Blethen SL. Inhibition of access of bound somatomedin to membrane receptor and immunobinding sites: a comparison of radioreceptor and radioimmunoassay of somatomedin in native and acid-ethanol-extracted serum. J Clin Endocrinol Metab 1980; 51:781-8.
19. Kennedy AL, Mehl TD, Merimee TJ. Nonenzymatic glycosylated serum protein: spurious elevation due to free glucose in serum. Diabetes 1979; 29:413-5.
20. Glick SM, Roth J, Yalow RS, Berson SA. Immunoassay of human growth hormone in plasma. Nature 1963; 199:784-7.
21. Horner YM, Kemp SF, Hintz RL. Growth hormone and somatomedin in insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1981; 53:1148-53.
22. Winter RJ, Phillips LL, Klein MN, Traisman HS, Green OC. Somatomedin activity and diabetic control in children with insulin-dependent diabetes. Diabetes 1978; 28:952-4.
23. Cohen MP, Jasti K, Rye DL. Somatomedin in insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1977; 45:236-9.
24. Tamborlane WV, Hintz RL, Bergman M, Genel M, Felig P, Sherwin RS. Insulin-infusion-pump treatment of diabetes: influence of improved metabolic control on plasma somatomedin levels. N Engl J Med 1981; 305:303-7.
25. Yde H. The growth hormone dependent sulfation factor in serum from patients with various types of diabetes. Acta Med Scand 1969; 186:293-7.
26. Blethen SL, Sargeant DT, Whitlow MG, Santiago JV. Effect of pubertal stage and recent blood glucose control on plasma somatomedin C in children with insulin-dependent diabetes mellitus. Diabetes 1981; 30:868-72.
27. Salmon WD Jr. Interaction of somatomedin and a peptide inhibitor in serum of hypophysectomized and starved, pituitary-intact rats. Adv Metab Disord 1975; 8:183-99.
28. Van den Brande JL, Van Buul S, Heinrich U, Van Roon F, Zurcher T, Van Steirtegem AC. Further observations on somatomedin activity in children. Adv Metab Disord 1975; 8:171-81.
29. Phillips LS, Vassilopoulou-Sellin R, Reichard LA. Nutrition and Somatomedin. VIII. The somatomedin inhibitor in diabetic rat serum is a general inhibitor of growing cartilage. Diabetes 1979; 28:919-24.
30. Phillips LS, Belasky DC, Reichard LA. Nutrition and somatomedin. V. Action and measurement of somatomedin inhibitor(s) in serum from diabetic rats. Endocrinology 1979; 104:1513-8.
31. Raymond L, Jacobson B. Isolation and identification of stimulatory and inhibitory cell growth factors in bovine vitreous. Exp Eye Res 1982; 34:267-86.

MEDICAL PROGRESS

CIRCADIAN TIMEKEEPING IN HEALTH AND DISEASE

Part 2. Clinical Implications of Circadian Rhythmicity

MARTIN C. MOORE-EDE, M.D., PH.D., CHARLES A. CZEISLER, PH.D., M.D., AND GARY S. RICHARDSON, M.D.

Part 1 of this review outlined recent advances in characterizing the properties of hypothalamic circadian pacemakers. In Part 2 we describe the implications of this rhythmicity for clinical medicine.

CIRCADIAN RHYTHMS IN MEDICAL DIAGNOSIS

Almost every physiologic variable that is used as a diagnostic indicator has been shown to exhibit a circadian rhythm.[3] One consequence of this has been the gradual alteration of the common perception that physiologic variables are tightly regulated to a fixed set point and that any movement away from this value is equivalent to disease. Such an oversimplification of the concept of homeostasis must be modified in the light of the demonstration that the internal milieu waxes and wanes with a diurnal rhythm. The consequences for medical diagnosis are obvious; every laboratory value and physiologic measurement must now be interpreted in the light of the circadian phase at which it was obtained.

In some cases, the variation from peak to trough is small — as little as 10 per cent of plasma potassium concentration,[73] for example — but in others it can be extremely large. The rate of urinary potassium excretion, for example, has been shown to vary fivefold in normal subjects across the day, independently of any day–night variations in posture, activity, or food intake.[73] For plasma cortisol, there is a large difference between the normal levels seen just before subjects awaken and those seen a few hours before they go to sleep.[74,75] It is now commonly appreciated that the diagnostic criteria for Addison's disease and Cushing's disease must take into account the time of day at which the plasma cortisol value was obtained.

One approach to the problem of accounting for circadian variability in medical diagnosis has been the creation of circadian "normograms"[3] — plots of the range of normal values for a given variable as a function of time of day. Unfortunately, there are problems

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with this direct approach. As discussed in Part 1, disruptions of the phase relations of circadian rhythms are increasingly common in modern society. For jet travelers, shift workers, and even students on unconventional sleep–wake schedules it is inappropriate to assume that internal circadian time is equivalent to clock time. The hospital environment itself may be one of the most serious offenders. With relatively constant levels of noise, light, and activity around the clock, particularly in intensive-care facilities, even patients with normal phase orientation at the time of admission will probably have some disruption of that orientation after a few days in such an environment. However, it is usually possible for the physician to estimate the circadian phase of his or her patient on the basis of the history, time in the hospital, and other obvious factors. When the situation is unclear, multiple measurements of an easily obtained index, such as body temperature, may provide useful information about the general circadian organization. Taking these steps to allow an accurate assessment of the contribution of circadian variation may improve the precision of any diagnostic test.

Circadian Rhythms in Disease

Another consequence of circadian rhythmicity in physiology is that the body is more susceptible to challenges at certain phases of the circadian cycle than at others. A number of authors have documented a circadian rhythm in the timing of death for both surgical[76] and nonsurgical[77,78] patients. That this represents a real variation in susceptibility to ongoing disease processes is supported by animal experiments that have shown a marked variability in the median lethal dose of a variety of toxins and injuries.[79,80] Of course, diurnal rhythms in such complex events — death due to bacterial infection, for example — are themselves the reflection of circadian variation in several component physiologic rhythms, such as those in leukocyte function[81] and in hepatic detoxification of bacterial toxins.[79]

One recent finding of tremendous interest is the discovery that certain disease states may be associated with abnormal rhythms of susceptibility to otherwise benign insults. For example, the circadian rhythm of lung-airway resistance in normal persons is of such low amplitude that it usually does not produce a noticeable effect on respiratory performance. However, certain patients with respiratory failure secondary to bronchial asthma have been shown to have a greatly exaggerated rhythm of bronchial constriction.[82] Maximal constriction was seen early in the morning (around 6 a.m.). Respiratory arrests in these patients were most frequent at this time of day. The direction of the cause–effect relation in this case has not been elucidated; it is not yet clear whether increased amplitude of airway-resistance rhythms contributes to or results from asthma-related respiratory failure. In either case, the relation suggests the advisability of concentrating therapy and observation at the predictable times of increased risk.

Drug Effectiveness and Toxicity

The effectiveness or toxicity of a variety of drugs has been shown to have a circadian rhythm. A number of extensive reviews of this subject have been published,[83-85] and an exhaustive catalogue is beyond the scope of this presentation. However, like rhythms in disease susceptibility, rhythms in drug effectiveness appear to be a function of multiple-component physiologic rhythms. First of all, circadian rhythms are apparent in the rate of drug absorption. For medications that are administered orally, rhythms in absorption are secondary to several other components, including gastric contents,[86] gastric acid production,[87] and intestinal enzyme activity.[10] Secondly, there are well-documented rhythms in the rates of drug metabolism. The activities of several hepatic enzymes capable of inactivating several drugs have been shown to vary in a clear circadian fashion.[88,89] Hexobarbital oxidase, for example, has been shown to have markedly greater activity at 2 a.m. than at 2 p.m.[90] Thirdly, rates of drug excretion also vary. Reinberg et al.[91] have shown, for example, that salicylate excretion is lowest early in the morning — a pattern similar to that seen for sulfonamide excretion.[92] Conversely, Beckett and Rowland[93] have demonstrated that methylamphetamine excretion is maximal in the early morning. At least for the sulfonamides and salicylates, rhythms in the rate of drug excretion appear to be principally a consequence of circadian variation in urinary acid excretion,[94] with urine excreted at night being markedly more acidic than that excreted during the day.

The last component of the circadian rhythm of drug effect is the rhythm of tissue susceptibility. It seems likely that some variation in drug response will prove to be secondary to changes in the concentration of cell-surface receptors or to changes in the rates of synthesis of intracellular enzymes. However, very little work has yet been done in this area, and the importance of this factor remains unclear.

One of the most intriguing possibilities arising from this research stems from evidence that the toxicity and effectiveness of drugs may have circadian rhythms that are separately timed. Thus, attention to the circadian timing of drug administration in cancer chemotherapy may minimize the toxic effects and enhance the therapeutic effects of the medication.[95] Cardoso et al.[96] have demonstrated that the lethality of high doses of cytarabine, a drug that inhibits DNA synthesis, varies between 74 and 15 per cent of treated mice, depending solely on the phase of the circadian cycle at which the dose is administered. This variation is apparently the result of circadian variation in the rates of DNA synthesis in susceptible tissues[97] — e.g., hematopoietic elements in bone marrow. If the phase orientation of tumor tissue proves to be different, or can perhaps be induced to be different, from that of the host, correct timing of chemotherapeutic doses may make it possible to maximize therapeutic effects while simultaneously minimizing toxicity.

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Disorders of Circadian Timekeeping

Like any physiologic regulatory system, the circadian system occasionally malfunctions. The consequent pathologic process can, however, be rather subtle. Although it has been demonstrated that merely disrupting normal internal phase relations can compromise, for example, the capacity to defend core temperature against hypothermic stress,[98,99] it is not yet clear whether such disruptions are associated with serious disease.[100] Furthermore, current diagnostic procedures are not designed to identify abnormalities in temporal organization; physicians typically take one blood sample or one blood-pressure measurement. Thus, objective evidence of temporal disarray is rarely obtained, even in the presence of subjective symptoms.

One area where temporal organization is an obvious feature of normal function is the sleep–wake cycle. If a patient cannot sleep at night or falls asleep in the daytime, he or she is inevitably aware of this difficulty and often goes to the physician with these subjective symptoms. These disruptions are often debilitating, interfering with normal daytime function and causing secondary psychological disturbances. It thus seems logical to assume that many disorders of the circadian system may first appear as sleep–wake disturbances. One of the most provocative lines of evidence supporting this hypothesis comes from the observation that many patients with neuropathological evidence of hypothalamic tumors that may have damaged the suprachiasmatic nuclei have a history of sleep–wake disturbances.[101,102]

As disorders of circadian timekeeping are increasingly recognized, the need arises for a system of classification. One possibility is that they be classified according to the mechanistic component of the circadian system that is defective. Thus, one could ascribe specific symptoms to a disordered perception of environmental cues, disorders of the clock itself, or disordered connections between the clock and the driven rhythms. Such a system would ultimately allow correlation between the symptom and specific anatomic sites or physiologic mechanisms. Unfortunately, the anatomy and physiology underlying each function of the circadian system are not sufficiently understood to allow classification of all known disorders. Instead, for now, a more symptom-based classification must be used in which circadian disorders are grouped according to the abnormal features of the rhythm. Thus, three categories of rhythm disorder are recognized, which depend on the major effects observed when the subject is studied under standard 24-hour conditions: phase-relation disorders, entrainment failure, and amplitude disorders.

Phase-Relation Disorder: Delayed-Sleep-Phase Insomnia

The most common circadian sleep disorder is characterized by difficulty falling asleep at night followed by corresponding difficulty awakening in the morning. When the problem is sufficiently chronic in nature as to rule out the transient effects of a changed schedule or jet lag, when actual sleep time is relatively constant, and when sleep at the delayed time is essentially normal, the diagnosis of "delayed-sleep-phase insomnia" is made.[7,103] Delayed-sleep-phase insomnia is common, affecting as many as 10 per cent of all patients reporting difficulty in sleeping.[103,104] However, since disordered sleep–wake schedules can often be accommodated by adjustments of social or work schedules, many more persons with this condition probably do not seek medical help. Those who do are often treated ineffectively with hypnotic medications.[104,105]

We have hypothesized that the basis of delayed-sleep-phase insomnia appears to be a reduced phase-advance capability corresponding to a low-amplitude advance portion of the phase-response curve.[7] Although patients with this problem are capable of achieving the daily shortening of the endogenous circadian period to accomplish entrainment to a 24-hour period, they have a markedly limited ability to achieve larger phase advances. Thus, once their circadian period has been delayed to an abnormal phase by late bedtimes over a weekend or travel to a different time zone, patients with delayed-sleep-phase insomnia cannot advance the timing of sleep to accommodate their preferred schedule. A non-drug treatment of such patients has been developed that consists of sequentially delaying the patient's sleep–wake schedule around the clock until the desired orientation is reached.[7] This approach uses the presumably normal phase-delay capability of the patient with delayed-sleep-phase insomnia and also exploits the more than 24-hour endogenous period of the human circadian rhythm, making it relatively easy to accomplish large adjustments of phase in the delay direction with a minimum of discomfort. This therapy has been consistently successful in the treatment of such patients. The sleep–wake history of a representative patient with delayed-sleep-phase insomnia is shown in Figure 5A.

Phase-Relation Disorders in Affective Illness

A comprehensive and consistent picture of circadian disruption appears to be emerging in patients with primary depression and related affective disorders. Depression has long been associated with early-morning waking.[106] In addition, the finding of a consistently phase-advanced rhythm of rapid-eye-movement sleep has been suggested as a useful adjunct to the differential diagnosis of affective illness.[107] Body-temperature rhythms and a variety of neuroendocrine rhythms are also shifted to earlier times,[108-110] suggesting that the phase of the circadian system is advanced in patients with such illness.

Perhaps the most provocative finding in this area is that of Wehr and his colleagues at the National Institute of Mental Health, who have shown, in a study of manic-depressive patients with rapidly oscillating mood swings,[111] that the phase of the rhythms of sleeping and waking and of body temperature were advanced during the patients' depressive periods and

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delayed during their hypomanic periods. In addition, Wehr and his colleagues have shown that short-term phase advances of the environmental schedule can temporarily correct the abnormal timing of the depressed patients' circadian rhythms and induce a transient remission of symptoms, lasting until the abnormal phase relation is restored.

The hypothesis that depressive illnesses may somehow be etiologically related to disorders of the circadian system is further supported by the evidence that conventional psychotherapeutic agents affect the function of the circadian pacemaker. Lithium salts, which are often effective in the treatment of depressive symptoms, have been reported to lengthen the period of the body-temperature rhythm markedly in healthy subjects.[22] Lengthening the period of the entrained rhythm while the period of the entraining rhythm is held constant results in a delayed phase of entrainment.[112] Thus, lithium would be expected to have the same effect as the transient environmental phase advances studied by Wehr.

Entrainment Failure

A small population of patients appears to be unable to entrain their endogenous circadian rhythms to the 24-hour period of the external environment. Their rhythms thus oscillate with a period longer than 24 hours, despite the presence of normal synchronizing information from the environment. Some of these patients are blind,[113] but the majority of reported cases have been in normally sighted persons.[114-116] A sleep–wake history from one such sighted patient is shown in Figure 5B. Although light–dark cycles alone have been shown to be an effective synchronizer of the human circadian system,[54] electric lighting now allows considerable control over environmental illumination. Thus, failure of the system to entrain to the 24-hour day in normally sighted persons could be due to a malfunctioning of the retinohypothalamic tract, an inadequate intrinsic resetting capacity of the circadian pacemaker, or a pattern of chosen behavior that interferes with the normal reception of periodic cues from the external environment. It is interesting to note that one year after the recording depicted in Figure 5A was made, the patient in question was found to have had a pituitary tumor (unpublished data), which may have compromised the functioning of either the retinohypothalamic tract or the suprachiasmatic nucleus itself.

Recent studies in blind subjects have shown that persons with no light perception at all appear to be divided into three groups with respect to the circadian rhythm of melatonin secretion: those with normal, stable entrainment and an appropriate phase relation to the 24-hour day; those with a normal, stable period but an abnormal phase relation to the 24-hour day; and those with a period longer than 24 hours whose rhythm does not synchronize with the 24-hour day (Lewy A: personal communication). The fact that at least some persons with total retinal blindness are able to entrain stably to a 24-hour day indicates that there must be other, non-retinal synchronizing cues capable of entraining the human circadian system. These could include either social contacts, as has been suggested in human beings[117] and animals,[118] or behavioral scheduling (e.g., bedtimes, waking times, and mealtimes), as Webb and Agnew have suggested in human beings.[119] The definitive explanation will have to await a greater understanding of the physiologic basis of entrainment in human beings.

Disorders of Rhythm Amplitude

The third general type of disorder of circadian timekeeping is characterized by a reduction in rhythm amplitude or, in the extreme case, by a complete loss of overt rhythmicity. Theoretically, causes of amplitude disorders could include chronic disruption of environmental time cues, failure of the pacemaker, breakdown of the link between pacemaker and effector organ, or disease of the effector organ itself.

Populations living near or above the Arctic Circle are exposed to continuous dark or continuous daylight for several months of the year. Eskimos living in these conditions have been shown to have circadian rhythms of abnormally low amplitude.[120] This is apparently a direct consequence of long-term exposure to abnormal environmental time cues and not a genetic feature of these populations, as evidenced by the restoration of normal rhythm amplitude in Eskimos exposed to artificial light–dark cycles[121] and the gradual decline in rhythm amplitude seen in acclimatized visitors.[122] It is not yet clear what meaning should be attached to the reduced rhythm amplitude itself. However, it has been documented that these same populations have a markedly increased incidence of sleep–wake disturbances[122,123] (and Lingjaerde B: personal communication).

Alternatively, a reduction in rhythm amplitude or a complete arrhythmicity could result from damage to the circadian pacemaker itself. As mentioned above, patients documented on post-mortem examination to have tumors involving the region of the suprachiasmatic nuclei were shown retrospectively to have had a high incidence of disturbances of the sleep–wake cycle early in the course of their illness.[101,102] In addition, patients with clinically documented hypothalamic disease were shown to have disrupted urinary electrolyte rhythms,[124] and patients with elevated third-ventricle pressure secondary to outlet obstruction have been shown to have abnormal body-temperature rhythms.[125]

Circadian Rhythms and Public Health

The limited range of entrainment of the human circadian timing system often becomes an issue for persons with round-the-clock schedules of work and rest.[2,126,127] Since World War II the number of people staffing continuous 24-hour-a-day industrial plants, utilities, and health-care, computer, and military facilities has been rapidly increasing. As a result, the introduction of extended hours for transportation, security protection, radio and television entertainment,

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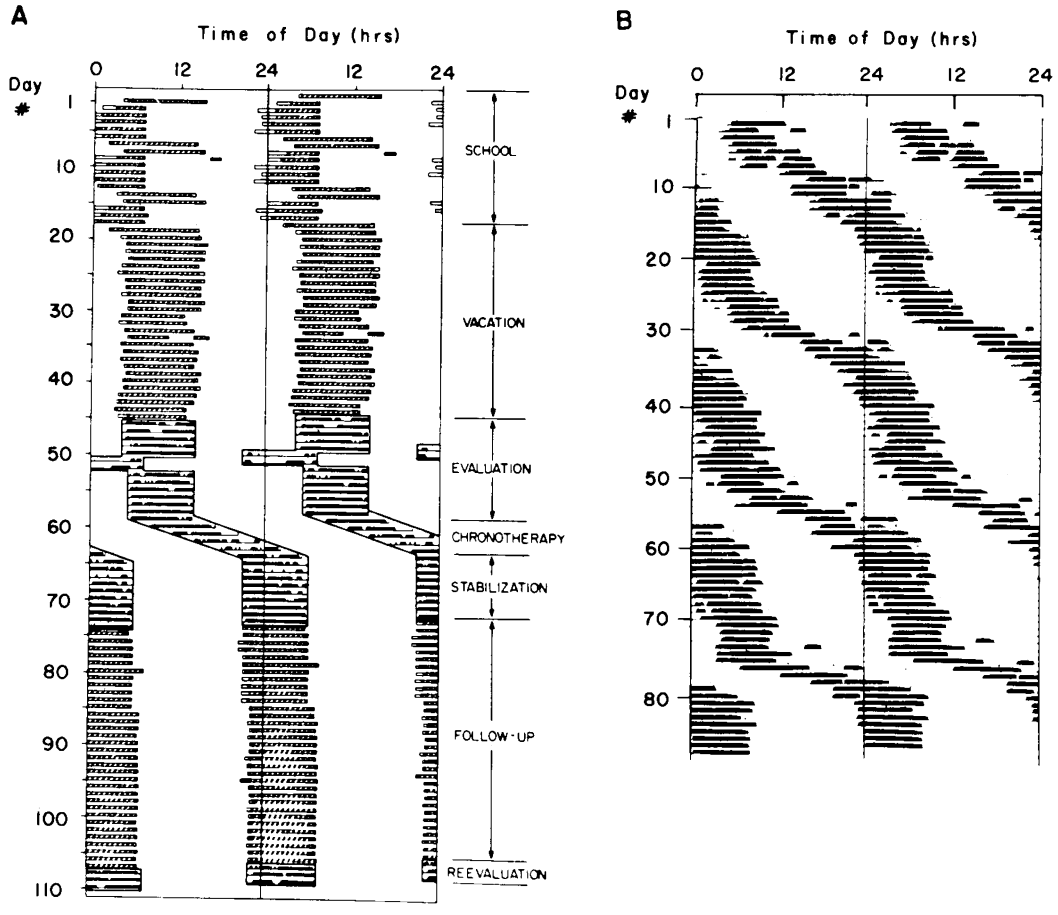

Figure 5. Evaluation, Treatment, and Follow-up in a Patient with Delayed-Sleep-Phase Insomnia (A) and Failure to Entrain to Normal 24-Hour Environmental Time Cues in a Normally Sighted Person (B).

In both graphs the abscissa is "double-plotted" over 48 hours (top line, Day 1 to Day 2; next line, Day 2 to Day 3). The ordinate represents successive 24-hour days.

Days 1 to 45 (Part A) are reconstructed from the patient's sleep–wake diary (striped bar denotes sleep, open bar time spent awake in bed). Despite repeated attempts to advance the sleep schedule abruptly to conform with weekday school requirements, an abnormally delayed sleep phase persists, especially on weekends and during vacation. In laboratory evaluation, polygraphic determination of sleep showed normal sleep expression but at a delayed phase (thick horizontal line indicates sleep), but when the phase was abruptly advanced (Days 51 and 52), sleep was markedly disturbed. Therapy consisted of sequential delay of the rest–activity cycle phase in three-hour increments, followed by stabilization at the intended new phase. After a 30-day at-home follow-up, a 2-day recording ("reevaluation") showed persistence of a normal sleep pattern at the normal phase.

Dark bars (Part B) represent estimated sleep time from the subject's sleep–wake diary. Periods in which sleep onsets cluster around midnight (e.g., Cycles 36 to 48) alternate with periods in which entrainment fails completely, and the time of sleep onset progresses rapidly around the clock.

Part A is reproduced from Czeisler et al.,[7] and Part B from Kokkoris et al.,[115] with the permission of the publishers.

and shopping is growing to meet the demands of people who work evening and night shifts. A recent national health survey by the National Center for Health Statistics indicates that over 27 per cent of male workers and 16 per cent of female workers now rotate between day and night shifts.[128] In these persons, serious health consequences are becoming apparent. Over 80 per cent of shift workers have serious sleep disruption (insomnia at home and sleepiness at work),[126] and there is evidence of increased levels of cardiovascular risk factors and gastrointestinal disorders among shift workers.[2]

An important element in the pathogenesis of these conditions is the schedule to which rotating shift workers are assigned. One of the most common schedules in American industry is a sequential weekly rotation of eight-hour night, evening, and day shifts so that workers are required either to phase-delay by eight hours every week or — more problematic for the circadian system — to phase-advance by eight hours weekly. Since even in the phase-delay direction of rotation it is possible to shift by only one or two hours per day, it takes the better part of the week for workers to adjust to the new rotation; and as soon as they do adjust, they are immediately rotated to the next shift.

Schedules that are even more disruptive are followed by the men who operate nuclear submarines in the U.S. Navy. They are typically assigned to 6 hours

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of duty and 12 hours of rest, which puts them on an 18-hour day–night cycle (although their officers keep a regular 24-hour day–night schedule).[129] Similarly, Swedish policemen have traditionally worked a schedule in which duty hours advance by four hours each day (Åkerstedt T: personal communication). Both these schedules are outside the range of entrainment of the circadian system, and the people affected are thus constantly in a state of desynchrony with the imposed schedule. The men on the naval watch schedule have problems with insomnia, emotional disturbance, and impaired coordination, and their sleep is highly fragmented as compared with that of shore-based naval personnel.[1,130] As Schaeffer and colleagues[129] have pointed out, there would be considerable advantages to adopting a 24-hour work–rest schedule for the whole crew rather than just for officers, as is the current practice.

A demonstration project conducted at a potash mining and processing facility in Utah has shown the advantages of redesigning an industrial work-shift schedule to make it less disruptive of the circadian system.[126] Workers who had been on a weekly phase-advance rotation schedule were placed on a schedule that rotated in the phase-delay direction once every three weeks. Hence, they were required to shift phase in the optimal direction and were allowed to become stabilized on that new schedule for three weeks before rotation. This intervention was associated with an improvement in health indexes, a reduction in personnel turnover, and a marked increase in the productivity of the shift workers.

It is particularly ironic that the work schedules followed by members of the health professions (particularly house officers, nurses, and technical personnel who must care for patients around the clock) are among the most disruptive as far as the circadian sleep–wake cycle is concerned. They are not easy to improve, however, partly because of the unique responsibilities of the physician and also because of the deeply entrenched traditions of the medical profession. The weight of evidence both from the laboratory and from field studies suggests it is now time to address the problems of the disruption of the sleep–wake cycle in medical personnel.[131,132] In addition, the continuous illumination of the hospital environment, especially in both general and neonatal intensive-care units, should also be reconsidered with an eye to determining what elements of normal temporal structure can be introduced. The ultimate benefit will be to the patient, for the rapid strides that have been made in understanding the pathophysiology of the circadian system offer great promise for the future if the iatrogenous risks of the hospital's temporal environment can be reduced.

References

73. Moore-Ede MC, Brennan MF, Ball MR. Circadian variation of intercompartmental potassium fluxes in man. J Appl Physiol 1975; 38:163-70.
74. Midgeon CJ, Tyler FH, Mahoney JP, et al. The diurnal variation of plasma levels and urinary excretion of 17-hydroxycorticosteroids in normal subjects, night workers and blind subjects. J Clin Endocrinol Metab 1956; 16:622-33.
75. Weitzman ED, Fukushima DK, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. J Clin Endocrinol Metab 1971; 33:14-22.
76. Frey S. Der Tod des Menschen in seinen Beziehungen zu den Tages-und Jahreszeiten. Dtsch Z Chir 1929; 218:366-9.
77. Jenny E. Tagesperiodische Einflüsse auf Geburt und Tod. Schweiz Med Wochenschr 1933; 14:15-7.
78. Jusatz HJ, Eckardt E. Die häufigste Todesstunde. Munch Med Wochenschr 1934; 81:709-10.
79. Halberg F, Johnson EA, Brown BW, Bittner JJ. Susceptibility rhythm to *E. coli* endotoxin and bioassay. Proc Soc Exp Biol Med 1960; 103:142-4.
80. Reinberg A. The hours of changing responsiveness or susceptibility. Perspect Biol Med 1967; 11:111-28.
81. McGovern JP, Smolensky MH, Reinberg A, eds. Chronobiology in allergy and immunology. Springfield, Ill.: Charles C Thomas, 1977.
82. Hetzel MR, Clark TJH. The clinical importance of circadian factors in severe asthma. In: Reinberg A, Halberg F, eds. Chronopharmacology. New York: Pergamon Press, 1979:213-21.
83. Reinberg A, Halberg F. Circadian chronopharmacology. Annu Rev Pharmacol Toxicol 1971; 11:455-92.
84. Moore-Ede MC. Circadian rhythms of drug effectiveness and toxicity. Clin Pharmacol Ther 1973; 14:925-35.
85. Walker CA, Winget CM, Soliman KFA, eds. Chronopharmacology and chronotherapeutics. Tallahassee, Fla.: Florida A&M University Foundation, 1981.
86. Fingl E, Woodbury DM. General principles. In: Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. 5th ed. New York: Macmillan, 1975:1-44.
87. Johnston RL, Washeim H. Studies in gastric secretion. II. Gastric secretion in sleep. Am J Physiol 1924; 70:247-53.
88. Radzialowski FM, Bousquet WF. Circadian rhythm in hepatic drug metabolizing activity in the rat. Life Sci 1967; 6:2545-8.
89. *Idem.* Daily rhythmic variation in hepatic drug metabolism in the rat and mouse. J Pharmacol Exp Ther 1968; 163:229-38.
90. Jori A, Di Salle E, Santini V. Daily rhythmic variation and liver drug metabolism in rats. Biochem Pharmacol 1971; 20:2965-9.
91. Reinberg A, Zagula-Mally ZW, Ghata J, Halberg F. Circadian rhythm in duration of salicylate excretion referred to phase of excretory rhythms and routine. Proc Soc Exp Biol Med 1967; 124:826-32.
92. Dettli L, Spring P. Diurnal variations in the elimination rate of a sulphonamide in man. Helv Med Acta 1967; 33:291-306.
93. Beckett AH, Rowland M. Rhythmic urinary excretion of amphetamine in man. Nature 1964; 204:1203-4.
94. Mills JN, Stanbury SW. Rhythmic diurnal variations in the behaviour of the human renal tubule. Acta Med Scand [Suppl] 1955; 307:95-6.
95. Scheving LE, Burns ER, Pauly JE, Halberg F, Haus E. Survival and cure of leukemic mice after circadian optimization with treatment of cyclophosphamide and 1-β-D arabinofuranosylcytosine. Cancer Res 1977; 37:3648-55.
96. Cardoso SS, Scheving LE, Halberg F. Mortality of mice as influenced by the hour of the day of the drug (ARA-C) administration. Pharmacologist 1970; 12:302. abstract.
97. Halberg F, Halberg E, Carandente F. Chronobiology and metabolism in the broader context of timely intervention and timed treatment. In: Diabetes research today: meeting of the Minkowski prize-winners. New York: FK Schattauer Verlag, 1976:45-95.
98. Fuller CA, Sulzman FM, Moore-Ede MC. Thermoregulation is impaired in an environment without circadian time cues. Science 1978; 199:794-6.
99. *Idem.* Effective thermoregulation in primates depends upon internal circadian synchronization. Comp Biochem Physiol [A] 1979; 63:207-12.
100. Moore-Ede MC. Hypothermia: a timing disorder of circadian thermoregulatory rhythms? In: Pozos RS, eds. The nature and treatment of hypothermia. Minneapolis: University of Minnesota Press, 1983:69-80.
101. Fulton JF, Bailey P. Tumors in the region of the third ventricle: their diagnosis and relation to pathological sleep. J Nerv Ment Dis 1929; 69:1-25, 145-64, 261-77.
102. Gillespie RD. Sleep and the treatment of its disorders. New York: William Wood, 1930.
103. Weitzman ED, Czeisler CA, Coleman RM, et al. Delayed sleep phase syndrome: a chronobiological disorder associated wth sleep-onset insomnia. Arch Gen Psychiatry 1981; 38:737-46.
104. Dement WC, Guilleminault C, Zarcone V. The pathologies of sleep: a case series approach. In: Tower DB, ed. The nervous system. Vol. 2. The clinical neurosciences. New York: Raven Press, 1975:501-18.
105. Sleeping pills, insomnia, and medical practice. Washington, D.C.: National Academy of Sciences, 1979.
106. Mendels J, Cochrane C. The nosology of depression: the endogenous-reactive concept. Am J Psychiatry 1968; 124: Suppl:1-11.
107. Kupfer DJ, Foster FG, Coble P, McPartland RJ, Ulrich RF. The application of EEG sleep for the differential diagnosis of affective disorders. Am J Psychiatry 1978; 135:69-74.
108. Sachar EJ, Halpern F, Rosenfeld RS, Gallagher TF, Hellman L. Plasma

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and urinary testosterone levels in depressed men. Arch Gen Psychiatry 1973; 28:15-8.
109. Sachar EJ, Hellman L, Roffwarg HP, Halpern FS, Fukushima DK, Gallagher TF. Disrupted 24-hour patterns of cortisol secretion in psychotic depression. Arch Gen Psychiatry 1973; 288:19-24.
110. Wehr TA, Muscettola G, Goodwin FK. Urinary 3-methoxy-4-hydroxyphenylglycol circadian rhythm: early timing (phase-advance) in manic-depressives compared with normal subjects. Arch Gen Psychiatry 1980; 37:257-63.
111. Wehr TA, Wirz-Justice A, Goodwin FK, Duncan W, Gillin JC. Phase advance of the circadian sleep-wake cycle as an antidepressant. Science 1979; 206:710-3.
112. Richter CP. Heavy water as a tool for study of the forces that control length of period of the 24-hour clock of the hamster. Proc Natl Acad Sci USA 1977; 74:1295-9.
113. Miles LEM, Raynal DM, Wilson MA. Blind man living in normal society has circadian rhythms of 24.9 hours. Science 1977; 198:421-3.
114. Elliott AL, Mills JN, Waterhouse JM. A man with too long a day. J Physiol (Lond) 1971; 212:30P-1P.
115. Kokkoris CP, Weitzman ED, Pollak CP, Spielman AJ, Czeisler CA, Bradlow H. Long-term ambulatory temperature monitoring in a subject with a hypernychthemeral sleep–wake cycle disturbance. Sleep 1978; 1:177-90.
116. Weber AL, Cary MS, Connor N, Keyes P. Human non-24-hour sleep–wake cycles in an everyday environment. Sleep 1980; 2:347-54.
117. Aschoff J, Fatranská M, Giedke H. Human circadian rhythms in continuous darkness: entrainment by social cues. Science 1971; 171:213-5.
118. Marimuthu G, Chandrashekaran MK. Social synchronization of circadian rhythms in bats. Chronobiologia 1979; 6:129. abstract.
119. Webb WB, Agnew HW Jr. Regularity in the control of the free-running sleep-wakefulness rhythm. Aerospace Med 1974; 45:701-4.
120. Lobban MC. The entrainment of circadian rhythms in man. Cold Spring Harbor Symp Quant Biol 1960; 25:325-32.
121. *Idem.* Seasonal variations in daily patterns of urinary excretion by Eskimo subjects. In: Shephard RJ, Itoh S, eds. Circumpolar health. Toronto: University of Toronto Press, 1976:17-23.
122. Yoshimura H. Review of medical researches at the Japanese station (Syowa base) in the Antarctic. In: Edholm OG, Gunderson EKE, eds. Polar human biology. London: William Heinemann, 1973:54-65.
123. Lewis HE, Masterton JP. British North Greenland expedition, 1952-54: medical and physiological aspects. Lancet 1955; 2:494-500, 549-556.
124. Krieger DT, Krieger HP. Circadian patterns of urinary electrolyte excretion in central nervous system disease. Metabolism 1967; 16:815-23.
125. Page RB, Galicich JH, Grunt JA. Alteration of circadian temperature rhythm with third ventricular obstruction. J Neurosurg 1973; 38:309-19.
126. Czeisler CA, Moore-Ede MC, Coleman RM. Rotating shift work schedules that disrupt sleep are improved by applying circadian principles. Science 1982; 217:460-3.
127. Institute of Medicine. Sleep, biological clocks, and health. In: Hamburg DA, Elliott GR, Parron DL, eds. Health and behavior: frontiers of research in the biobehavioral sciences. Washington, D.C.: National Academy Press, 1982:108-23.
128. Danchik KM, Schoenborn CA, Elinson J Jr, eds. Basic data from Wave I of the National Survey of Personal Health Practices and Consequences: United States, 1979. Hyattsville, Md.: Public Health Service, 1981. (DHHS publication no. (PHS)81-1162).
129. Schaefer KE, Kerr CM, Buss D, Haus E. Effect of 18-h watch schedules on circadian cycles of physiological functions during submarine patrols. Undersea Biomed Res 1979; 6: Suppl:S81-90.
130. Johnson LC. Sleep disturbances in humans. In: Nicholson AN, ed. Sleep, wakefulness and circadian rhythm. Neuilly sur Seine, France: NATO Advisory Group for Aerospace Research and Development, 1979:4.1-4.16.
131. Friedman RC, Bigger JT, Kornfeld DS. The intern and sleep loss. N Engl J Med 1971; 285:201-3.
132. Poulton EC, Hunt GM, Carpenter A, Edwards RS. The performance of junior hospital doctors following reduced sleep and long hours of work. Ergonomics 1978; 21:279-95.

MEDICAL INTELLIGENCE

CURRENT CONCEPTS IN NEUROLOGY

Partial Epilepsy

DONALD L. SCHOMER, M.D.

EPILEPSY was defined by John Hughlings Jackson[1] as a sudden, excessive, rapid, and localized electrical discharge by gray matter from some part of the brain. This definition is still accepted today with respect to partial (or focal-onset) seizures. The physiologic phenomenon associated with partial seizures is the paroxysmal depolarization[2,3] of the neuronal membrane in a local group of neurons, which corresponds temporally to the finding of a focal spike and wave complex on the electroencephalogram. This mechanism differs from those proposed in the primary (or generalized) types of epilepsy, with or without tonic or clonic phases or absences. In the generalized types there appears to be an intermittent abnormal interrelation between the neocortex and the thalamic reticular system rather than a focal process.[4-8] Partial epilepsy probably has a different physiologic mechanism and pathologic basis. The following discussion will review the clinical manifestations, pathologic possibilities, and treatment of partial-seizure states.

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CLINICAL MANIFESTATIONS OF PARTIAL SEIZURES

The current international system of nomenclature[9] for partial seizures has three major divisions. If the seizure starts as a focal discharge and remains focal without alteration in consciousness, it is a simple partial seizure regardless of the clinical manifestation of that event. If the seizure starts as a focal discharge but consciousness becomes impaired during the course of the event, it is called a complex-partial seizure. If, during the course of a focal partial seizure, the patient goes into a generalized tonic–clonic, tonic, or clonic seizure, it is called a partial seizure, either simple or complex, that secondarily generalizes. Difficulty arises in differentiating between a partial seizure that generalizes rapidly and a primary generalized seizure.

Since no one test can absolutely rule out the existence of a partial seizure, a clinical understanding of this entity is of critical importance in making the diagnosis. The clinician must be aware of the various manifestations of focal seizures arising from different parts of the nervous system that either remain restricted or spread. A frontal-lobe discharge confined to the motor strip can produce a contralateral tonic or clonic movement. If it progresses locally, a Jacksonian march with gradual incorporation of additional muscle groups may ensue. If it arises in and is confined to

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