Circadian (24-h) rhythms are important to the practice of medicine. The phasing and amplitude of key physiologic and biochemical circadian rhythms contribute to predictable-in-time patterns in the manifestation and exacerbation of most medical conditions. Moreover, body rhythms can significantly affect responses of patients to diagnostic tests and medications. Rhythmicity in the pathophysiology of medical conditions is the rationale for chronotherapeutics—that is purposeful variance of the concentration of medicines in synchrony with biologic rhythm determinants of disease activity—to optimize treatment outcomes. This article discusses the concept of biologic time structure and its relevance to the practice of medicine, with a focus on hypertension and cardiovascular issues.

Key Words: Human circadian rhythms, medicine, hypertension, chronopharmacology, chronotherapeutics.

Search of the medical literature reveals just how important body rhythms—especially, circadian rhythms—are to clinical medicine.1–5 Circadian rhythms can determine when the symptoms of medical conditions flare and how patients respond to diagnostic tests and medications. This article highlights the relevance of the body’s 24-h biologic time structure to medicine with a focus on hypertension.

Biologic Rhythms and Clocks

A biologic rhythm is a self-sustaining oscillation. It is defined by its period, amplitude, and phasing. The period is the duration of time required to complete a single cycle. A rhythm with a period close or equal to 24 h is termed circadian. Shorter period rhythms are called ultradian and longer ones infradian (Table 1). High-frequency oscillations in electrical impulses of the brain and heart, and the pulsatile secretion of hormones are common examples of ultradian rhythms. Menstrual and seasonal oscillations are familiar examples of long period rhythms. Amplitude is a measure of predictable-in-time variability due specifically to rhythmicity. The amplitude differs in magnitude between biologic variables and by age and health status. The amplitude of the circadian rhythm in heart rate and BP is moderate, whereas that in serum epinephrine and cortisol is large. The amplitude of the circadian rhythm in the spirometric measures of peak expiratory flow rate (PEFR) and 1-second forced expiratory volume (FEV$_1$) in persons with healthy lungs is small, about 5% of the 24-h mean level. In asthma, it is typically 25% in mild cases and generally 50% or more in severe cases.6,7 Phase, or stage, refers to the clocking of specific features, such as the peak and trough, of rhythms relative to the time scale of the 24-h day or the week, month (menstrual cycle), or year. The staging of the circadian rhythm in cortisol is defined by a prominent morning peak and sleep-time trough.

Biologic rhythms are viewed as adaptive adjustments of our ancestors to cyclic changes in their environment during the 24-h day, the month, and the year. Human beings inherit, by genetic transmission, unique biologic clock mechanisms. The dominant pacemaker clock of circadian rhythms resides in the anterior hypothalamus, in the suprachiasmatic nuclei (SCN).8 –11 The inherited period of the human circadian clock is not precisely 24 h; in most people it is slightly longer and some slightly shorter.5,12 The light–dark and other cyclic environmental and societal time cues entrain the period of the SCN to precisely 24 h, and stage the peaks and troughs of circadian rhythms to support the diurnal activity–nocturnal sleep routine characteristic of humans.13,14 The same environmental time cues also are responsible for adjusting the phasing of 24-h rhythms when the sleep–activity routine is suddenly altered, for example, in workers who rotate between day and night shifts and in travelers who are rapidly displaced by jet aircraft across several time zones.15–17 Both situations require the adjustment of the 24-h time structure through the gradual restaging of the peaks and troughs of

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the body’s circadian rhythms. jet lag, complaints such as sleep irregularities and mental and biologic fatigue, is common in travelers. it is caused by the disparity in phasing of endogenous circadian rhythms in relation to the staging of environmental and societal demands in the new setting. jet lag symptoms dissipate with adjustment of the circadian time structure to the new environment, generally within 3 to 4 days.

the timing of the peaks and troughs of circadian rhythms is quite predictable from 1 day to the next in the majority of people who adhere to a fairly regular sleep–activity schedule. however, the staging of 24-h rhythms in those who work rotating shift schedules or follow variable rest–activity routines is less predictable. this has clinical importance. the activity–sleep routine determines when the peaks and troughs of circadian rhythms occur with reference to the 24-h time scale. the phasing of the circadian time structure in turn determines when the symptoms of diseases are likely to flare, and they can affect responses to diagnostic tests and therapeutic interventions according to their timing, as discussed below.

the circadian time structure

the results of numerous biologic rhythm studies help to define the temporal organization of human beings.1,3,18 one means of illustrating the human circadian time structure is to depict the peak time of 24-h rhythms on a clock-like diagram. fig. 1 shows the peak time of a number of circadian rhythms with reference to the sleep (approximately 10:30 pm to 6:30 am) activity cycle.19 the peak in basal gastric acid secretion, white blood cell count (wbc), and calciotin gene–related protein and atrial natriuretic peptides (both exerting bp–lowering effects) is late at night or early in sleep. growth and thyroid stimulating hormone (tsh), blood lymphocyte and eosinophil number, and plasma concentration of melatonin and prolactin crest later in sleep, as do adrenocorticotropic hormone (acth), follicle stimulating hormone (fsh), and luteinizing (lh) hormone. plasma cortisol, renin activity, angiotensin, and aldosterone crest in the morning as do arterial compliance, vascular resistance, platelet aggregation, and blood viscosity. hemoglobin and insulin are greatest in the afternoon, as are the spirometric measures of fev1 and pefr. serum cholesterol and triglycerides and urinary diuresis are highest early in the evening. the information conveyed in this and other such figures clearly shows the biochemistry and physiology of human beings are not constant; rather, they are variable in a predictable manner during the 24-h period.

diagnostic tests: circadian rhythm dependencies

several diagnostic tests are affected by circadian rhythms (table 2). the erythema and induration reaction to intradermal allergen testing is two- to threefold greater late in the afternoon and early evening than in the morning.20,21 the diagnosis of reversible airway disease, as well as its severity and differentiation from the fixed airway diseases of chronic bronchitis and emphysema, is best accomplished when spirometric tests are done at the start of the clinic day. in diurnally active chronic obstructive pulmonary disease (copd) patients, this is when fev1 and pefr are most like the lowest values that occur in sleep. in addition, this is when the airway response to β-agonist bronchodilator aerosol medication is greatest.6,7,22 thus, early morning spirometric reversibility studies best determine whether there is a reversible component in copd. moreover, the airway reaction to aerosol provocation by antigens as well as histamine and methacholine exhibits marked circadian rhythmicity; reactivity is least in the early afternoon and near peak early in the morning.23 intraocular pressure is highest between 2 and 4 am and lowest in the late afternoon.24,25 persons at risk for glaucoma should be seen as early as possible in the morning during office hours, because this is when intraocular pressure is likely to be highest during the daytime. the diagnosis of normal tension glaucoma (ie, evidence of visual
field damage in the presence of normal eye pressure) might be due to the assessment of intraocular pressure at the wrong biologic time.26

Determination of blood pressure (BP) level is affected by time of measurement.4,27 Systolic blood pressure (SBP) and diastolic blood pressure (DBP) vary considerably during the 24 h (Fig. 2). With the commencement of morning activity, SBP rises rapidly typically by 20 to 25 mm Hg and DBP by 10 to 15 mm Hg. Both SBP and DBP are highest late in the afternoon. In the evening they begin to decline, attaining lowest levels in sleep.27,28 This variation is attributable to temporal patterns in activity, stress, and

<table>
<thead>
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<th>Table 2. Circadian rhythms: impact on the diagnosis of medical conditions</th>
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<td><strong>Allergy</strong>: Cutaneous reaction to intradermal antigen tests two- to threefold greater in evening than in morning.</td>
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<tr>
<td><strong>COPD</strong>: Airway patency best in the afternoon and poorest overnight. Morning best time to assess severity of asthma and differentiate between fixed and reversible airway disease.</td>
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<td><strong>Glaucoma</strong>: Intraocular pressure highest during sleep and lowest in afternoon. Early morning eye exams best for assessing at-risk patients; false-negative diagnosis more of a risk in the afternoon.</td>
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<td><strong>Circadian rhythm sleep disorders</strong>: Sleep phase delay syndrome (abnormally retarded sleep onset and offset times), sleep phase advanced syndrome (abnormally advanced sleep onset and offset times) and non–24-h sleep–wake syndrome (period of the sleep–wake cycle considerably different from 24 h) best diagnosed by wrist actigraphy.</td>
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<tr>
<td><strong>Diabetes</strong>: Results of glucose tolerance test different in the morning than in afternoon, different times of the menstrual cycle, and different seasons of the year.</td>
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<td><strong>Laboratory chemistries</strong>: Plasma cortisol, melatonin, testosterone, and certain other hormone concentrations differ radically over the 24 h as do certain other commonly assessed blood constituents and parameters in hematology, such as the number of circulating granulocytes, lymphocytes, and their subtypes.</td>
</tr>
<tr>
<td><strong>Blood pressure assessment</strong>: SBP and DBP rapidly rise in the morning by at least 15 to 25 mm Hg and reach highest levels late in the day. Typically SBP and DBP decline in sleep by 10% to 20% from daytime level. In uncomplicated essential hypertension, the pattern is similar, but the BP amplitude and/or 24-h mean abnormally elevated. In secondary hypertension, SBP and DBP may be normal or near normal in the day but abnormally high in sleep.</td>
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BP – blood pressure; COPD – chronic obstructive pulmonary disease; DBP – diastolic blood pressure; SBP – systolic blood pressure.
posture during the 24 h, as well as to circadian rhythms in autonomic nervous and endocrine systems.\textsuperscript{27,29,30} The temporal picture of BP in uncomplicated essential hypertension is similar to that in normotension; however, the 24-h mean and/or amplitude of variation is abnormally elevated. The BP profile of secondary hypertension, for example in renal insufficiency, dysautonomia, mineral corticoid excess and diabetes, is often different.\textsuperscript{27,30,31} Typically there is a blunting of the nocturnal decline or even an increase in BP during sleep relative to the daytime level. The extent of the circadian variation plus the differential phasing of the BP rhythms in primary compared to secondary hypertension can complicate the accurate assessment of BP and make difficult the clinical differentiation of hypertension from normotension. In-home BP measurements made at different times of the day and night and 24-h ambulatory monitoring are useful strategies to complement office assessments, especially in those who display a “white coat” effect.\textsuperscript{27,29}

The results of several other medical tests may be affected by rhythms. Patient response to the glucose tolerance test (GTT) is greater in the morning than in the evening.\textsuperscript{32,33} The findings of certain hematology, coagulation, and hormone studies can vary greatly with the time.
when blood samples are withdrawn. Even the accuracy of genetic screening tests (for example, that for Tay-Sachs disease) has been reported to depend on the time of blood withdrawal.

**Circadian Rhythms of Disease**

The symptom intensity of most medical conditions, including ones that involve the cardiovascular system, and occurrence of life-threatening medical emergencies exhibit rather precise timings (Fig. 3). Gout, gallbladder, and peptic ulcer attacks are most frequent at night. Acute pulmonary edema, congestive heart failure, and asthma worsen nocturnally. Sudden infant death syndrome occurs most frequently in the middle of the night. Symptoms of allergic rhinitis and rheumatoid arthritis are most intense in the morning. Migraine headache typically is triggered during rapid eye movement (REM) episodes toward the end of nighttime sleep or early in the morning. Angina pectoris, acute myocardial infarction, sudden cardiac death, ventricular arrhythmia, stroke, fatal pulmonary embolism, and hypertensive crises are most frequent in the morning, as are certain other cardiovascular conditions. Depression is most severe in the morning. Symptoms of osteoarthritis worsen during the course of daily activity, usually being most bothersome in the evening. Perforated and bleeding ulcer is most common in the afternoon. Some seizure disorders are triggered in specific sleep stages and/or by transitions between sleep and wakefulness.

**Alteration of Circadian Time-Keeping in Disease**

Certain sleep disorders result from abnormalities of biologic time-keeping systems. Delayed sleep-phase syndrome (DSPS) is characterized by severe sleep-onset insomnia. Typically sleep is impossible until 3 AM or later, and consequently there is great difficulty in awakening at the normal time in the morning. The cause of DSPS may be abnormal sensitivity to evening light, causing the biologic clock controlling the sleep–wake cycle to reset to a later staging. The non–24-h sleep–wake syndrome is characterized by complaints of difficulty in initiating and terminating sleep at consistent clock times every day. Diagnostic studies show that sleep onset and offset times are progressively delayed by 2 to 3 h from day to day. The period of the inherited biologic clock controlling the sleep–wake cycle is abnormal, being as long as 26 or 27 h. Other medical conditions, such as seasonal affective mood disorder (SAD), premenstrual dysphoric disorder (PMDD), and even regular depression, at least to some extent, might be the consequence of abnormalities of circadian time-keeping. Weekly, monthly menstrual cycle, and annual patterns in disease are also known; however, their discussion is beyond the scope of this review.

**Biologic Rhythms and Medications**

Chronopharmacology, the study of how biologic rhythms affect medications, has led to new understandings and concepts about the behavior of therapeutic agents.
Chronokinetics refers to biologic rhythm effects on drug absorption, distribution, and elimination. Circadian changes in gastric hydrogen ion secretion, stomach emptying/gastrointestinal transit time, liver enzyme activity, and organ blood flow, for example, can cause treatment-time differences in the pharmacokinetics of medications. Chronokinetic phenomena may be specific to the chemical nature of the medication itself or to the physiochemical attributes of tablet, capsule, and aerosol drug-delivery technology. β-adrenergic receptor antagonists, theophylline, and nonsteroidal anti-inflammatory drugs (NSAID) are but a few examples of prescribed medications that show administration time (circadian rhythm) dependent differences in kinetics.

Chronesthesia is another new concept in pharmacology. It refers to rhythm-dependent differences in the effects of medications that cannot be explained by their pharmacokinetics. Chronesthesies result from rhythms in drug-free-fraction and rhythms in receptor number and conformation, second messenger dynamics, and rate-limiting steps of metabolic pathways in drug-targeted tissues. Analgesics, anticoagulants, β-adrenergic receptor agonists and antagonists, corticosteroids, and NSAID are some examples of therapies that differ in effect according to their biologic time of administration.

Chronotoxicity refers specifically to rhythm-dependencies in the manifestation and intensity of drug-related side effects. Medications that have a narrow therapeutic window and high risk of adverse effects (eg, NSAID, synthetic corticosteroids, and antitumor agents) commonly display significant circadian chronotoxicities.

Some antihypertensive medications are affected by body rhythms. As shown in Fig. 4, the duration of the BP-lowering effect of 4 mg of the angiotensin converting enzyme (ACE) inhibitor perindopril is 24 h when ingested consistently in the morning at 9 AM, whereas it is only 12 h when ingested in the evening.

**FIG. 4.** Duration of the blood pressure (BP) lowering effect of 4 mg of perindopril, an angiotensin converting enzyme (ACE) inhibitor, consistently ingested either in the morning at 9 AM (top graph) or evening at 9 PM (bottom graph) for 4 weeks. The duration of the blood pressure-lowering effect is a full 24 h when the ACE inhibitor is ingested in the morning. However, it is only 12 to 14 h when ingested in the evening and, moreover, the drug effect on sleep-time blood pressure is markedly enhanced. Adapted with permission from Morgan T, et al: The effect on 24-hour blood pressure control of an angiotensin converting enzyme inhibitor (perindopril) administered in the morning or at night. J Hypertens 1997;15:205-211.
Table 3. Chronotherapies currently in clinical use

- Once-daily and alternate-day morning corticosteroids dosing minimizes risk of adrenal suppression and other side effects.
- Bedtime corticosteroid dosing controls excessive hormone secretion in congenital adrenal hyperplasia.
- Asymmetrical morning high and late-afternoon low-dose corticosteroid substitution chronotherapy for Addison's disease best corrects fatigue and abnormal circadian time structure.
- Evening ingestion of certain HMG-CoA reductase antagonist medications optimizes cholesterol-lowering effect.
- Nitroglycerin transdermal patch medication worn during the portion of the 24 h to protect against angina adverse effects. These goals are achieved either through the desired effects of medications and control of their cine. The goals of chronotherapeutics are enhancement of asymmetrical morning high and late-afternoon low-dose corticosteroid substitution chronotherapy for congenital adrenal hyperplasia. The morning prednisolone dosing or the evening half-dose substitution for the morning dose is a relatively new concept in medicine. It is a means of special drug technology to purposely vary the concentration of medications in synchrony with circadian rhythms in disease activity and patient tolerance to treatments. The principal goal of this treatment schedule is to ensure that the highest concentration of the synthetic hormone coincides in time with the morning peak of cortisol. In diurnally active individuals, this is when the hypothalamic-pituitary-adrenocortical axis is least vulnerable to suppression by exogenous corticosteroids. A list of other chronotherapies that are now in use in clinical medicine is presented in Table 3.

<table>
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Chronotherapeutics can also involve the application of physical agents. The successful management of certain conditions such as non-24-h sleep–wake disorder, seasonal affective disorder, and premenstrual dysphoric disorder, can be achieved by bright-light chronotherapy. The efficiency of radiotherapy for solid tumors is best when it is timed to coincide with the peak in tumor metabolism during the 24 h. The best known and most extensively used chronotherapy is the daily and alternate-day morning dosing schedule of corticosteroid medications. The principal goal of this treatment schedule is to ensure that the highest concentration of the synthetic hormone coincides in time with the morning peak of cortisol. In diurnally active individuals, this is when the hypothalamic-pituitary-adrenocortical axis is least vulnerable to suppression by exogenous corticosteroids. A list of other chronotherapies that are now in use in clinical medicine is presented in Table 3.

Homeostasis Versus Rhythms: Issue of 24-Hour Blood Pressure Control

Improper BP control throughout the entire 24 h can increase the risk of end-organ injury and cardiovascular...
events. Indeed, 24-h BP control is the goal of antihypertensive therapy, and a large variety of different classes of medications are available to choose from to reach it. Most of the medicines are intended for morning ingestion, and most aim at maintaining near-constant plasma drug concentration during the day and night. From a regulatory perspective, 24-h BP control means that the magnitude of the BP-lowering effect at the end of the daily dosing interval (when drug level is lowest) is 50% or more of the peak BP-lowering effect (when drug level is highest). However, this seems to be an inadequate clinical definition, because it fails to take into account all the relevant features of the circadian BP rhythm as they relate to risk for cardiovascular events and end-organ injury.

Population-based studies clearly document association between daytime SBP and DBP measured in the office and coronary heart death. However, other features of the circadian pattern that are less discussed, such as the extent of the sleep-time BP decline and level and the morning BP rate of rise, also are associated with end-organ injury and cardiovascular risk. Too great a rate of rise in BP at the onset of daily activity has been linked to angina pectoris and is hypothesized to play a causal role in myocardial infarction, sudden cardiac death, and stroke in the morning. Too small a decline in BP during sleep (<10% of the daytime level) is associated with elevated risk for left ventricular hypertrophy as well as cardiovascular events. Too great a decline in BP during sleep (>20% from the daytime mean), particularly in elderly hypertensive individuals with small-vessel disease of the brain, increases the risk for stroke. In addition, in elderly glaucoma patients, too great a reduction of sleep-time BP is associated with neuropathy of the anterior optic nerve, resulting in visual field deterioration. These observations imply that true 24-h BP control should involve attenuation of the morning BP rate of rise plus normalization of both daytime and sleep-time BP levels.

In the United States, the chronotherapy of hypertension relies upon sophisticated drug delivery technology to vary the concentration of the calcium channel antagonist verapamil in synchrony with the BP circadian rhythm seen in essential hypertension. Verapamil chronotherapy, ingested at bedtime as recommended, achieves true 24-h BP control. It markedly attenuates the rate at which BP rises in the morning (which is thought to reduce the risk for stroke and other cardiovascular events then), significantly reduces or normalizes daytime BP, and modulates the extent of BP reduction during sleep, thereby attenuating the risk for drug-induced hypotension or BP superdipping seen sometimes with conventional once-a-day medications. Moreover, unlike the dihydropyridine calcium antagonists, verapamil moderates heart rate, particularly in the morning when taken as a chronotherapy. The rate–pressure product, or RPP (SBP × HR), a surrogate measure of myocardial oxygen demand and cardiac workload, is gaining increasing attention because it is predictive of ischemic events. Typically, the RPP increases rapidly in the morning by 25% or more. Initial studies show that verapamil chronotherapy attenuates the morning rise in RPP to a much better extent than conventional long-acting dihydropyridine medication. This finding might be of significance to hypertensive patients with coexisting coronary heart disease, as the sudden rise of RPP in the morning in these patients is commonly associated with episodes of ischemia.

**Summary**

The concept of homeostasis—which dominates the research, teaching, and practice of medicine—infers that there is constancy of the milieu intérieur (internal government). The concept was proposed in the 19th century by Claude Bernard in France and further developed early in the 20th century by Walter Cannon in the US. It was deduced from research mainly performed in the daytime. Laboratory techniques of yesteryear necessitated the withdrawal of very large volumes of blood to assess individual hormones and other constituents. Moreover, instrumenta-
tion enabling around-the-clock measurement of biologic variables did not then exist. Thus, it was seldom possible to assess biologic function more than once a day. Modern laboratory methods require only a minute amount of blood, making it possible to do around-the-clock serial blood and other body fluid samplings. New ambulatory monitoring devices make possible continuous assessment of a variety of variables throughout the 24 h. Data derived from such studies reveal clear evidence of the body’s biologic time structure.

The biologic time structure—that is, the staging of various features such as the peak and trough of body rhythms, over the 24 h, monthly menstrual cycle, and year—along with the temporal patterning of environmental triggers of disease, explain why the risk and symptom intensity of many medical conditions can vary so dramatically over time. Moreover, circadian rhythms can affect the findings of certain diagnostic tests and can influence the behavior of prescription and nonprescription medications according to their timing.

Clinical medicine is primarily concerned with answering the following questions: What is ailing the patient? What diagnostic tests are indicated? Why and how should the patient be treated? And how much medication should be dosed? Chronobiology adds a new dimension—namely, biologic time—to medicine, necessitating answers to an additional set of questions: When are symptoms most troublesome? When is the risk of morbid and mortal events greatest? When should diagnostic tests be conducted? And when should treatment be timed? We need to ascertain information from patients regarding when their symptoms occur or are most problematic, and we need to be aware that the time when patients take their prescription medications can influence their effectiveness and safety.

The findings of a 1996 Gallup poll conducted on American primary care doctors revealed they possessed insig-
significant knowledge of how circadian rhythms determine when symptoms occur or are worse during the 24 h, and how they affect the diagnosis and treatment of medical conditions. Significant advances in medical chronobiology, especially in cardiovascular medicine, have taken place since the 1996 Gallup survey. Yet, the teaching of chronobiology in schools of medicine and its application to patient care still are lacking. The purpose of this article is to bring to the fore the relevance of biologic rhythms to medicine, to illustrate how they affect clinical practice, and to show how they can be incorporated into patient care.

References