

Biological clocks and the practice of psychiatry

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Endogenous biological clocks enable living species to acquire some independence in relation to time. They improve the efficiency of biological systems, by allowing them to anticipate future constraints on major physiological systems and cell energy metabolism. The temporal organization of a given biological function can be impaired in its coordination with astronomical time or with other biological functions. There are also external conditions that influence biological clocks. This temporal organization is complex, and it is possible that a series of psychiatric disorders and syndromes involve primary or secondary changes in biological clocks: seasonal and other mood disorders, premenstrual syndromes, social jet lag, free-running rhythms, and several sleep disorders are among them. In this review, we describe the main concepts relevant to chronobiology and explore the relevance of knowledge about biological clocks to the clinical practice of psychiatry.

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Dialogues Clin Neurosci. 2007;9:237-255.

Keywords: *chronobiology; circadian rhythm; ultradian rhythm; human study; psychiatric disorder*

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The view that living organisms are three-dimensional beings, with height, length and depth, might be correct when applied to gross anatomy, but represents a simplified and misleading description of most aspects of physiology and biochemistry. Biology operates in the fourth dimension, ie, time, and the number and extent of time-related and oscillating bodily functions is huge: most physiological functions are coded or structured in time. This conclusion comes from clinical studies of a descriptive nature, as well as from in-vitro studies on isolated cells or cell groups from multicellular organisms, and on unicellular organisms.¹ For example, in endocrinology, the extent of a cell secretory response depends on the interspike and interburst intervals from afferent axons.²

Physiological mechanisms have diverse durations and oscillation frequencies, from nanosecond changes in membrane ion channel shifts or enzymatic reactions and protein synthesis, to electroencephalographic or electrocardiographic waves, to ultradian rhythms of a few minutes or hours, to longer circadian rhythms, and up to cycles that last a month, a season, a year, or even more.

It has long been recognized that the incidence of disease in humans can show annual fluctuation. Meteorological conditions favor the spread of many infections during either the cold or hot or damp months. Centuries ago in France, the lack of vitamins in food during winter was a cause of visual impairment during early spring, described in poor people such as the French peasants. More recently, clinical and epidemiological studies have shown that given syndromes or disorders tend to occur more frequently at given astronomical times, for example myocardial infarction during the very early hours of the morning.³

Although the role of astronomical time in the occurrence and the incidence of various disorders was recognized centuries ago, basic and medical research on biological clocks is only recent. In the 18th century, the French scientist Jean-Jacques Dortous de Mairan (1678-1771) described a circadian rhythm in plant leaf movements

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Selected abbreviations and acronyms

BRAC	<i>basic rest-activity cycle</i>
EEG	<i>electroencephalogram</i>
GnRH	<i>gonadotrophin-releasing hormone</i>
LH	<i>luteinizing hormone</i>
PMDD	<i>premenstrual dysphoric disorder</i>
REM	<i>rapid eye movement</i>
RNA	<i>ribonucleic acid</i>
SAD	<i>seasonal affective disorder</i>
SCN	<i>suprachiasmatic nuclei</i>
TSH	<i>thyroid-stimulating hormone</i>

that was independent of the lighting schedule. Then, in the early 20th century, studies on the capacity of the honeybee to remember the time of day when a given food was available led to the idea of a *memory of time*. Whether this was more than a mere memory, and whether it reflected an endogenous *production of time* was then evaluated, leading to the discovery of *biological clocks*, a concept very different from that of memory of time. Biological clocks are defined by the fact that they generate a rhythm with cycles that exist independently of any exogenous cycles, such as the influence from astronomical time (also named clock time or external light/dark cycle). Circadian rhythms (*circa* means around or approximately and *dies* means day) occur in activity-rest cycles as well as in body temperature and in the secretion of many hormones, even when a subject lives without any external clues about time. This was clearly demonstrated by the French researcher Michel Siffre, who lived in an underground cave during 1962 and then in 1972. At the end of the first experiment, he believed that 43 days had passed rather than 60, and at the end of the second experiment, he believed that only 175 days had passed instead of 205. He had had a few rest-activity cycles that extended up to 50 hours, of which he had remained unaware.^{4,5}

Early studies in chronobiology covered many fields, from circadian organization,^{6,7} to erythrocyte enzyme activity in vitro,⁸ to functions such as memory or verbal reasoning, to free-running experiments,⁹ to the extent to which a *Zeitgeber* (see definition in *Table I*) could shorten or prolong the circadian period, ie, studies on limits of entrainment.¹⁰ Other studies were on the synchronizing role of environmental factors and nonphotic stimuli such as magnetic fields,¹¹ exercise, melatonin, or even acute noise.¹² Recent studies have been done on the molecular genetics and biology of clocks.¹³

A short presentation of chronobiology

A biological rhythm was defined by Nathaniel Kleitman (1949) as “a regularly recurring quantitative change in some particular variable biological process, irrespective of whether or not it takes place in a cell, tissue, structure, organism or population.”¹⁴ Biological rhythms often reflect the functioning of a biological clock, but this is not an absolute rule, since cycles can occur as a consequence of some complex nonlinear system.

Table I summarizes the available information on mammalian biological clocks, with a short list of facts and definitions.

Studies in animals have indicated that the functional characteristics of biological clocks are genetically determined,^{15,16} that specific lesions can disrupt biological rhythms,¹⁷ and that these rhythms are restored after embryo neuronal tissue graft in mammals¹⁸ or gene transfer in insects.¹⁹ There is also a polymorphism in the genes responsible for the period of endogenous rhythms, and clock gene transfer can modify the period of the receiver insect. Genes involved in the generation of endogenous rhythms have been identified. The biochemical mechanism of biological clocks consist of cycles of clock gene transduction into ribonucleic acid (RNA) and then translation of RNA into specific proteins that exert a feedback. This mechanism is described in detail in another article in this issue.¹³ Phosphorylation and dephosphorylation of proteins also play a role.

Circadian rhythms and the suprachiasmatic nucleus

The suprachiasmatic nucleus (SCN) is the main biological clock in mammals, while it is the pineal gland that has such a role in reptiles and birds. The SCN receives information on lighting conditions directly from the retina. It influences the pineal gland secretion of melatonin and also many peripheral clocks in tissues other than the brain. Indeed, there are biological clocks in almost all tissues, in the sense that isolated cells from different tissues kept in culture maintain a cyclical pattern of their biochemical activities. Thus there is a hierarchy of interacting clocks. These clocks can themselves regulate the SCN through feedback or feed-forward effects.²⁰

When isolated in vitro, SCN neurons have a spontaneous and persisting rhythm of a period of about 24 hours and each neuron represents an oscillator, with its individual parameters. Overt circadian rhythms result from the

coordination of neurons from the SCN, but how this can occur remains unresolved. Also, there might exist specialized groups of neurons within the SCN, each group being aimed at the regulation of a given organ, ie, targeting the pineal gland, the liver, or other organs.²¹

Ultradian rhythms

Nathaniel Kleitman, a pioneer in sleep and chronobiological research, proposed the existence of a basic rest-activity cycle, or BRAC, as early as the 1960s.²² The BRAC was considered to be clearly expressed clinically

early after birth and then, within weeks or months, to become less evident during daytime and mostly seen during sleep, with the alternation between rapid eye movement (REM) and nonREM sleep. Apart from sleep, several physiological functions have an ultradian periodicity of approximately 90 min in man. The period of the BRAC might be species-specific since, for example, luteinizing hormone (LH) blood concentrations oscillate with periods of 20 minutes to 2 hours in different animal species.²³ In mice, there is an ultradian rhythm for avoidance behavior that is of 9 min in young mice, near the period of REM/nonREM sleep, while in adult mice it is

- Three parameters are sufficient to describe any cyclical function. They are the frequency, the phase, and the amplitude. The **frequency** is the number of cycles per unit of time. In chronobiology, the **period**, or the duration of a complete cycle, is often mentioned. It is the reciprocal of the frequency. The **amplitude** is the extent of change in the variable value over one cycle, ie, the difference between the maximal and the minimal value. The **phase** is the relation between endogenous rhythms and astronomical time, or between rhythms themselves.
- The **acrophase** is the time when the maximal value of the variable is observed.
- **Synchrony** refers to the temporally coordinated occurrence of functions.
- **Ultradian** rhythms have periods of less than a day, **circadian** rhythms of approximately a day, **infradian** rhythms of more than a day. There are also very short rhythms, as well as weekly, seasonal, and annual rhythms.
- Rhythms are labeled as **endogenous** when cycles in activity levels do not occur as a result of environmental influences.
- Endogenous **biological clocks** are groups of cells that show cycles in activity levels even in vitro. The bilateral suprachiasmatic nucleus (SCN) in the hypothalamus is the major biological clock in mammals. The SCN generates circadian rhythms with a mean cycle length (period) of slightly more than 24 hours in most mammals.
- The endogenous period of a biological rhythm can be measured when the subject receives no information from environmental factors, ie, no information about astronomical time, no regular social stimuli, or no regular feeding schedule. These factors are labeled **Zeitgebers**, which translates literally into *time givers*, or synchronizers or timekeepers. The main *Zeitgeber* in mammalian and most other animals is light.
- In the presence of *Zeitgebers*, the endogenous rhythm is constrained to a period of 24 hours, it is **entrained** to astronomical time. In the absence of *Zeitgebers*, the SCN is no longer constrained to a 24-hour periodicity, and circadian rhythms are said to be **free-running**, or nonentrained, ie, they show no synchrony with astronomical time (unless the subject has an endogenous period of circadian rhythms of exactly 24 hours).
- In mammals, the nocturnal secretion of melatonin by the pineal gland is under the command of the SCN. Light leads to the interruption of melatonin secretion. The organization of the biological clocks varies between species, but in all species light is the major external factor influencing the secretion of melatonin.
- The biological clock or clocks generating ultradian rhythms, such as those of secretion of several hormones, is still a theme of research.
- Environmental influences (light, food, social activities, etc) can also influence the shape of the endogenous rhythms. This phenomenon is called **masking** or the **masking effect**.
- A short exposure to a *Zeitgeber* such a light flash can advance or delay the next circadian cycle, in either free-running or entrained conditions. When this is studied in free-running conditions, one can construct a **phase response curve**: at some moment of the cycle, the *Zeitgeber* advances the next cycle, while at other moments, it delays it. There can be a singularity point, a time when the influence of the *Zeitgeber* is not determined, or when the regularity of the cycles disappears if the *Zeitgeber* is administered.

Table I. Facts and definitions in chronobiology.

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of 20 min.²⁴ In humans, a mean period of the BRAC of around 90 min was found in endocrine studies or in studies on dreaming and sleep.²⁵ For example, the secretory pulses of prolactin into blood in humans have a mean period of 95 min and are closely associated with the secretory pulses of LH.²⁶ There is an ultradian rhythm of nasal permeability, with a shift between nostrils that correlates with changes in contralateral electroencephalogram (EEG) wave amplitude.²⁷ The BRAC has the hypothetical role of coordinating bodily functions, hormones, sleep phases, and perceptual and cognitive capacities. This hypothesis raises several questions, few of which have yet been solved. First, there have been subsequent negative findings, for example regarding the absence of ultradian rhythms in the cognitive task of the sentence-verification test.²⁸ Also, many variables show more than one ultradian period and have superimposed circadian components. Finally, the existence of groups of neurons that govern ultradian periodicities has been demonstrated for gonadotrophin-releasing hormone (GnRH, also called LHRH, for luteinizing hormone-releasing hormone) in the preoptic area of the hypothalamus and for the sleep architecture, but not for other rhythms; moreover, a few authors have suggested that evidence for the existence of BRAC might result from artifacts in protocols and calculations.²⁸ Ultradian clocks have not yet been as clearly delineated, as is the case for the circadian clock in the SCN.

Reciprocal influences and coupling between biological clocks

Many biological functions show more than one rhythm and have superimposed ultradian and circadian components. Moreover, many tissues express endogenous rhythms. This raises the following questions: how do these many biological rhythms and clocks interact, and how do they influence each other (or how are they subject to the temporal message of a higher-order clock)? The relationship between biological clocks remains unclear, but lesions of the SCN influence ultradian rhythms in many animal experiments, indicating that the SCN might influence ultradian clocks,²⁹ although its presence is not conditional to the existence of ultradian rhythms. Also, mutations in circadian rhythms can alter ultradian rhythms.³⁰ Several hormones are secreted in peaks coincident with sleep stages. For example, growth hormone (GH) is secreted shortly after falling asleep, often as a large pulse,

followed later at night or not by other secretory pulses. Shifting the time of sleep by 8 hours will shift the secretion of GH in the same direction, as of the first night. A sleep-dependent shift of hormone secretion is also observed with prolactin. In contrast, there is little modification in cortisol's nocturnal secretion pattern when sleep is shifted by 8 hours, indicating that this hormone is more dependent on the circadian biological clock than on sleep initiation.³¹ When pulses of cortisol and thyroid-stimulating hormone (TSH) secretion occur, the power of EEG delta waves, that parallels the depth of sleep, is at the lowest. This is in contrast to what is observed with GH and prolactin.³²

In a study in normal subjects who were able to live on a self-selected schedule (but not in time isolation), 4 out of 10 subjects developed activity/rest cycles that differed from 24 hours, with a mean of 36.8 hours, but the core body temperature maintained a circadian rhythm with a mean of 24.6 hours. In this condition of internal desynchronization, the REM propensity increased during the time when body temperature was rising, suggesting that the circadian rhythm of REM propensity could cycle independently of the activity-rest cycle, but that it was closely associated with the body temperature cycle.³³

A challenging question about the relation between biological clocks was raised decades ago, through the work of Ernst Knobil.^{34,35} His work concerned the relationship between the ultradian rhythm of GnRH and LH and the monthly rhythm of menstruation. For this, he studied female monkeys who had a surgically destroyed hypothalamic GnRH ultradian pulse generator. GnRH was then given intravenously for several weeks, with different schedules of administration, to find a rhythm of administration that would reinstate a menstrual cycle. GnRH administered in pulses with a period of 60 min reinstated a menstrual cycle, while constant administration of GnRH did not suppress the amenorrhea. Thus, an ultradian rhythm of about 1 hour can govern a monthly rhythm. This discovery led to the first efficacious treatment of human infertility of hypothalamic origin. Obviously, the GnRH ultradian periodicity is not the sole origin of menstrual rhythms, since sex steroids have a feedback influence on the GnRH ultradian generator that varies during the cycle.³⁶ Further, amenorrhea in anorexia nervosa, in stress conditions, and in opiate consumers might be linked to an inhibitory effect of these conditions on the GnRH pulse generator. An *in vitro* study of the episodic secretion of GnRH showed that

cells with altered circadian clocks genes lost the ultradian rhythm of GnRH release.³⁷ Interactions between cells and cell groups capable of generating endogenous rhythms remains an interesting field of research.

Masking

Changes in the environment (temperature or light intensity and duration), and changes in internal states and behaviors such as movement and immobility, fatigue and sleep, hunger and eating, can modify the pattern of biological rhythms.³⁸ These are known as *masking effects*,³⁹ to indicate that the circadian or ultradian rhythms would differ in the absence of these factors. For example, going to sleep is accompanied by a decrease in core body temperature, while the contrary occurs at the time of physical or mental effort. Also, the circadian rhythm of TSH is more marked if subjects maintain their usual feeding schedule and professional activities rather than staying in bed and receiving no food.⁴⁰ Masking effects could in part explain the decreased amplitude in temperature and TSH circadian rhythms described in depressed patients by several authors,⁴¹ since these patients might have had a lower level of physical activity within the hospital. Social and lifestyle factors also play a role in the measurable phenotype of biological clock physiology.⁴² The so-called constant routine studies enable to overcome or neutralize masking effects; in such studies, subjects lie recumbent in constant light and receive frequent snacks. These protocols are complex, but they are necessary to explore the functioning of the biological clock in manners that separate the endogenous and exogenous components of rhythms.

Ontogeny and senescence of endogenous rhythms

Biological clocks play a role at the cellular level by modulating the rate of mitosis.⁴³ At the macroscopic level, preterm infants of 35 weeks already have bouts of activity and sleep⁴⁴ and, based on extrapolation from animal research, the human SCN might become sensitive to light around the sixth month of pregnancy,⁴⁵ and even low levels of light, of 200 lux, entrain the SCN.⁴⁶ After birth, a circadian periodicity of body temperature and other variables is present at 1 month and develops over the following month.⁴⁷ Children stabilize a circadian rather than an ultradian rhythm of wake-sleep around the age of 3 to 6 months,⁴⁸ although differences in activity and

sleep can be detected very soon after birth in some infants.

Of note is the fact that the prenatal development of biological clocks is sensitive to fetal exposure to teratogens and other toxins, such as alcohol.⁴⁹ Circadian clock physiology can also be altered by postnatal maternal deprivation in rodents, and the changes persist into adulthood.⁵⁰

According to the results of a survey of 25 000 inhabitants in Europe, there is a sudden change in sleep habits that marks the end of the tendency to sleep later during childhood and adolescence. Indeed, around the age of 20, most young adults tend to go to sleep and wake up earlier. Roenneberg and collaborators even suggested that this change could be a marker of the end of adolescence.⁵¹

The regulation of sleep and wakefulness might be altered in elderly people,⁵² explaining the awakenings during sleep and the decrease in slow-wave sleep. Elderly persons tend to go to bed earlier, and the duration of their sleep is often decreased. This has been interpreted as secondary to a lesser secretion of melatonin, as found in many studies,⁵³ or to the fact that cell death in the SCN leads the remaining neurons to generate a shorter endogenous circadian rhythm with age. Indeed, experiments with partial destruction of the SCN in laboratory rodents have shown that the circadian period becomes shorter under these conditions, but there are also negative findings. In elderly persons, the secretion of melatonin is decreased, and this decrease could in part be due to the lack of exposure to daytime light, since a trial in a small population of subjects indicated that exposure to light could increase the nocturnal secretion of melatonin with a concomitant improvement in sleep.⁵⁴ There are, however, studies reporting no changes in melatonin with age in humans.⁵⁵ The neurodegeneration of the nucleus basalis of Meynert, a major source of cholinergic innervation, might explain sleep alteration in dementia, since this group of cells is involved in rest/activity and is among the structures that send efferent messages to the SCN.⁵⁶

Measurements in human chronobiology

Chronobiological protocols can be cumbersome for two reasons. First, because of the necessity to study several biological cycles. Indeed, one cannot conclude that a change occurred in the frequency of any phenomenon when the study duration is too short for repetitions of the

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phenomenon to have occurred. This is a challenging issue for psychiatry, where many disorders show recurrent decompensations. An observation lasting 1 to 2 times the theoretical duration of a cycle is necessary to infer that one has indeed identified a periodic change and to measure the duration of that cyclic change. A clinical observation of a patient during a time equivalent to 3 to 4 times the theoretical duration of a cycle is necessary to conclude that a treatment has influenced the course of a recurrent disorder. When the manifestation recur in shorter cycles, such as with 48-h rapid cycling bipolar disorder, or with the premenstrual syndromes, the duration of studies becomes a lesser constraint.

The second reason for which chronobiological protocols are complex is the nature of the measured phenomena. Indeed, biological rhythms are found in brain waves, in hormone concentration in blood, and in cognitive abilities. Measuring these phenomena can be difficult and necessitate more or less invasive methods, while less invasive techniques only allow long-term studies. Among these, the simplest one remains the repeated use of questionnaires to evaluate subjective biological functions such as mood, energy, or pain. Visual analogue scales can be used, but small portable computerized devices that regularly ask for the person's evaluation are a definite advance, in terms of compliance. Another technique for long-term studies is actigraphy, ie, wearing an actometer that measures the movements of the wrist. This is a simple and practical method to study sleep disorders and the rest-activity cycle, and this can be done over weeks or even months.⁵⁷ Practice parameters for the use of actigraphy have been regularly updated.^{58,59} Actigraphy is also useful in recurrent mood disorders, since it records the rest-activity cycle. This method has also shown that adults with attention deficit disorder show high levels of motor activity during the day and the night, and that methylphenidate shortens their total sleep time, but improves sleep fragmentation.⁶⁰ Ambulatory continuous monitoring of blood pressure can be useful for the treatment of hypertension; measurement over only 24 hours was sufficient to confirm that hypertensive patients who do not show a decrease in blood pressure at night are at higher risk of cardiovascular complications.^{61,62} Long-term temperature measurement can be carried out using rectal probes, a somewhat impractical method. Multichannel recorders have been developed for cardiac, pulmonary, and other variables, with detectors placed in a special shirt. This device is useful for studying ultradian or cir-

cadian rhythms in research and in the routine of clinical work.⁶³ As mentioned above, protocols with constant routine are technically cumbersome, but they represent the golden rule for exploring the endogenous functional characteristics of clocks without masking effects. Few human disorders have been studied in constant routine up to now.

Frontiers of chronobiology

Several themes concerning time might be included in the domain of chronobiology, although research on these themes, from molecular biology to psychology, is generally not labeled as chronobiological. The physiology and the genetics of aging is one of these themes. The time structure in societal and individual life organization is another.⁶⁴ The perception of time is yet another. This perception varies from moment to moment, and is quite different during sleep or wakefulness. The perception of time is relative, and there are illusionary perceptions of time, as there are illusions in the visual system. For example, a given musical rhythm sounds more rapid if it follows a slow rhythm (an illusion of a similar nature occurs when the temperature of hot and cold objects is successively felt). Could this relative dimension of time be measured? There are indices that it could, based on the suggestions of Karl Ernst von Baer⁶⁵ that subjective time perception is species-specific. A basic unit of time is defined by the shortest time during which the subject cannot identify a change in the environment. In humans, this time might be around 1/18th of a second, while in agile carnivorous fishes that catch fast prey, it might be up to 1/50th of a second and in snails it might be 1/4th of a second. These interspecies differences in time perception seem to allow correction for the pace of actions occurring in their environment: for snails, the world might seem to go as fast as it does for us, but who knows?⁶⁶

In conditions of emergency, the perception of space can become widened, as described by the Swiss geologist Albert Heim (1849-1937) who mentioned that, while falling, mountain climbers see from far above minute details of the ground where they will land. In these conditions, the perception of time can also widen, memories of events of long duration might be evoked in a few seconds, and complex decisions can be made very rapidly.⁶⁷ This system of time perception expansion might have evolved for survival purposes.

Also, social exchanges are of better quality when the subjects synchronize their behavioral rhythms and this capacity to synchronize appears early in ontogeny.⁶⁸ Finally, the subjective sensation of time (time estimation), or the capacity to give an indication of time (time production) are of interest for psychiatry and neurology.

Chronomics

Many studies show that the rhythmic properties of biological phenomena can be characteristic of the individual subject, organ, or even cell. For example, the fact that the EEG waves had subject-specific patterns was recognized 70 years ago.⁶⁹ Recently, at a molecular level, it was shown that the expression of *clock* gene messenger RNA (mRNA) in peripheral tissues from a group of men and women differed manifold and that these differences were stable over an 8-week study.⁷⁰

Subjects have their own peculiar and personal rhythmic organization, and the idea of individually determined configurations of biological variables applies to chronobiology, as it does to genes (genomics) or to proteins (proteomics), or to intermediate metabolism (metabolomics). The word *chronomics* has been proposed by a few authors and it is found, albeit rarely, in the literature. However, what chronomics exactly is and what a *chronome* might be remains unclear because authors do not provide the same definition of these terms.^{71,72} They might refer to the idea of the individual configurations in the temporal organization of biological variables, for example a map of the acrophases of circadian rhythms or rhythms with shorter or longer periods.⁷¹ Another meaning refers to the epidemiology of clinical acute events such as stroke, myocardial infarction, or suicide as a function of time within a day, a month, a year, or decades. Still another meaning of chronomics is synonymous with chronotherapy, ie, changes in efficacy and toxicity, and therefore in therapeutic index, as a function of the time of treatment administration. Here, we propose defining chronomics as the field of quantifying the physiological functions that show changes over time. According to this definition, chronomics would differ from genomics or proteomics by the existence of several levels for its description, from changes in gene expression to changes in overt behaviors. This makes it necessary to choose a scale for the variables to be included: chronomics can be constructed from the polymorphism of genes that relate to biological clocks, from blood lev-

els of hormones (ultradian rhythms), from a rapid rhythm such as the electroencephalogram, or from clinical data (period of circadian rhythms, amplitude and phase position of rhythms, ie, synchronization between rhythms). In the field of endocrinology, chronomics can be constructed using variables such as mean concentrations, number of pulses, pulse height, pulse intervals, phase position of the rhythm, stability over time, and under different conditions.

Normal versus abnormal changes in human chronobiology

Einstein (1879-1955) wrote that “the only reason for time is so that everything doesn’t happen at once.” This applies to biology, where the dimension of time is as vital to life as is the production of energy by cells. Indeed, *things* should not happen all at once, and they should happen at the right moment, ie, when the biological environment is in the right state. Thus, an adequate synchronization characterizes a healthy organism, while a faulty temporal regulation, ie, lack of synchronization, can induce clinical manifestations of different types. For example, when the muscle relaxation that characterizes REM sleep occurs at other times than during REM, an awake subject may have a short period of inability to move, labeled waking sleep paralysis, or suffer a sudden drop attack, or act out their aggressive dreams if no muscle relaxation occurs during REM.⁷³

As discussed above, biological rhythms show interindividual differences in frequency, amplitude, or phase, as well as in their mutual synchronization. Subjects also differ in their sensitivity to external events acting as *Zeitgebers*. These interindividual differences observed in humans raise two questions pertinent for the practice of medicine. The first concerns the definition or the limits of chronobiological health or normality, not in statistical terms, but in terms of the adequacy in the biological and mental functioning of the person: the question is whether or not the differences in chronobiological parameters are accompanied by subjective or objective clinical impairment. The second question relates to whether significant interindividual differences in chronobiology are linked to modifications of biological clocks, or whether they are secondary to other aspects of syndromes or disorders. These questions are theoretical, but it might be that answering them will have relevance for therapeutic approaches.

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Table II indicates a series of chronobiological changes in humans, going from a clinical to a molecular level of postulated mechanisms. These changes are not independent, and desynchronization, phase advance or delay, and abnormal entrainment may influence the amplitude of rhythms.⁷⁹

A series of changes in chronobiology are clear alterations (Table III), yet they are not accompanied by clinical dysfunction and might still be within the norms of human biology (although several of these changes are also observed in cases of mental and physical disorders). There is also a series of neurological or psychiatric disorders in which biological clocks are dysfunctional.

Diagnosing chronobiological changes

From a clinical point of view, there are several uncertainties when diagnosing changes in chronobiology. First, a defect in the biological clock might not manifest itself by recurring clinical manifestations that have irregular cycles. Second, a disorder that does not a priori imply biological clock dysfunctions might nevertheless manifest itself in regular cycles. This is the case of many disorders that show premenstrual exacerbations. Third, and more importantly, most psychiatric disorders seem to have composite mechanisms, and chronobiological mechanisms might be associated with other pathophysiological changes. Fourth, a precise and repeated measurement of symptoms is needed in order to evaluate a periodic exacerbation of a syndrome.

Free-running circadian rhythms

The term “free-running” refers to situations where the circadian rhythm differs from 24 hours and is not entrained to astronomical time. The most frequent cases of free-running in everyday conditions have been described in blind people.⁸⁰

Free-running in healthy subjects

A small number of physically and mentally healthy subjects have been described who had a free-running circadian rhythm. Wirz-Justice⁸¹ described the 9-month sleep log of a healthy student who occasionally had very long rest-activity cycles, with no deleterious consequences. Yet, persons with a non-24-hour sleep-wake syndrome can present clinical manifestations when they attempt, as most do, to force their activity/rest cycle to the astronomical 24-hour cycle, as was illustrated in the case of a 43-year-old man who complained of recurring days, every 4 weeks, of disabling fatigue and sleep difficulties. He was instructed to live with no time constraints (albeit with the knowledge of time and under the influence of light) for 8 weeks and his circadian rhythm took on a period of 25.8 hours, with the disappearance of the episodes of fatigue.⁸²

Free-running, personality, and psychiatric disorders

In a study in 110 subjects isolated from time cues during a month, about 1 in 5 subjects showed the phenomenon

- Frequency of the circadian rhythm. Short or long periods might occur in mood disorders and in sleep disorders.
- Amplitude of circadian or ultradian rhythms. Decreased amplitude of body temperature and thyroid-stimulating hormone (TSH) rhythms was described in major depressive disorder.⁴¹
- Sensitivity to *Zeitgebers*. Sensitivity to the influence of light on the secretion of melatonin might differ in seasonal affective disorder (SAD) patients.⁷⁴
- Cellular activity. Overactivity may occur when too many cell groups are simultaneously active, as in the physical disorder of hydarthrosis.⁷⁵
- Stability of biological rhythms over time. A less stable biological rhythm organization might lead to a greater tendency to desynchronize during shift work.
- Synchronization between rhythms. Desynchronization occurs in shift work, and may occur in mood disorders.⁷⁶
- Phase shift. Phase advance might occur with circadian rhythms in aging. Phase delay might characterize SAD.⁷⁷
- Complexity of biological rhythms. Loss of complexity in biological rhythm organization and in other central nervous system functions probably occurs in neurodegenerative disorders.
- Mutation in one or more of the genes of the circadian clock. Such mutations have been described in several sleep disorders,⁷⁸ and may occur in mood disorders or in schizophrenia.

Table II. Possible changes in human chronobiology.

of internal desynchronization, where the period of the temperature rhythm deviates from that of rest-activity, for example a rest-activity period of 19 hours and a temperature period of 24.4 hours in 1 subject, or of respectively 33.2 and 24.9 in another. When it occurred, this desynchronization generally persisted for several days. Subjects with such desynchronization had higher scores of neuroticism ($P < 0.001$) and of bodily preoccupations ($P < 0.05$).⁸³

Overall, free-running seems to occur more frequently in neurological or psychiatric patients. It has been proposed that a defect in entrainment to social *Zeitgebers* might play a role in personality disorders.⁸⁴ In a series of 57 sighted adults with free-running circadian rhythms in everyday conditions (or non-24-hour sleep-wake syndrome), the mean period was of 24.9 hours, with a range from 24.4 to 26.5 hours, and there was a suggestion that psychiatric comorbidity was high in these subjects.⁸⁵

Irregular rhythms

Irregular rhythms and personality

Through astute and long-term direct ethological observation in the 1970s, Montagner studied the behavior of children in a kindergarten and described a typology of child behavior into three major categories of children, labeled as leader, dominant/aggressive, or dominated. He also took urine samples for cortisol and 17-hydroxycorticosteroids, called defense steroids. He found lower diurnal levels of defense steroids in leader children, significantly lower at all moments of the day than in dominant/aggressive children. Behavior was more stable in leader children, and the cortisol values remained sta-

ble from one year to the next. He also measured changes in defense steroids in relation to days of the week, and in relation to exchanges with the mother.⁸⁶ Again, the values were more stable in leader children. These findings suggest that there might exist a more or less direct relationship between chronobiology and behavioral tendencies, whatever the mechanisms of this relation might be.

Irregular rhythms and disorders

An irregular and blurred activity-rest cycle is rare, but can be found in demented persons.⁸⁷ The case of a schizophrenic patient, who had a near-arrhythmic rest/activity cycle but a normal (although phase-advance) rhythm of body temperature and 6-sulphatoxy-melatonin was published by Wirz-Justice.⁸⁸ In schizophrenia, the influence of social *Zeitgebers* might be lessened or lost, explaining the occurrence of odd behavior at odd times. In geriatric and other institutions, lighting is often dim and might not be sufficient for it to function as a *Zeitgeber*. In the above situations, lesions in biological clocks could in part explain the clinical observations.

Short or long sleepers

A small proportion of subjects sleep only a few hours each night, while others need more than 7 or 8 hours. The polysomnography of short sleepers shows little time spent in stage 1 or 2 sleep, with about the same or a higher total time as control subjects in stage 3 and 4, but one third to one half less duration of REM sleep.^{89,90} In a constant routine protocol, it was shown that the increase in temperature and the decrease in cortisol and in melatonin occurred earlier in short sleepers, at the time when they would have woken up under usual conditions, indicating that these biological correlates of sleep also differ between short and long sleepers.⁹¹

Over the last decades, a tendency towards fewer hours of sleep has been noted in many countries, with fewer persons who sleep for at least 8 hours and who go to sleep before 11 pm. The consequences of this decrease in sleep hours in terms of mental and physical health might be important. In a cohort of more than 1000 persons, it was found that short sleepers had higher blood levels of ghrelin and lower levels of leptin, as well as a higher body mass index.⁹² Similar changes were found in an experiment in which volunteers were studied under a condition of sleep curtailment.⁹³ Adipocyte biology is linked to

Unusual biological rhythms
• Free-running circadian rhythms and irregular rhythms
• Short or long sleepers
• Jet lag
• Social jet lag
• Shift work
Disorders associated with chronobiological changes
• Advanced or delayed sleep phase syndrome
• Several sleep disorders
• Mood disorders
• Seasonal affective disorder
• Premenstrual syndromes

Table III. Chronobiology and the frontier of disorders.

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peripheral biological clocks.⁹⁴ In fact, a short duration of sleep seems to modify several variables such as glucose tolerance, insulin secretion, tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6) towards values that favor obesity, the metabolic syndrome, and its cardiovascular complications.

Jet lag

Jet lag is a configuration of acute and short-lasting consequences of an ongoing resynchronization to astronomical time (in order that the normal relationship between biological events and external time is regained) after rapid travel across several time zones. The circadian clock can readjust to astronomical time at a rate of about 1 hour or slightly more per day. For example, the secretion of cortisol is normally lowest in the evening and then peaks late at night and early in the morning, and it takes a few days for this secretion to adapt to the new schedule. Other rhythms are quicker to adjust. Thus, there is a transitory state of internal desynchronization (defined as an usual relative phase position of oscillating variables). A single night of good sleep does not suffice to overcome jet lag biologically, although it can do so subjectively. It is postulated that if jet lag symptoms last more than a week, then the resynchronization to astronomical time might not have occurred in the faster direction, regaining the number of hours of the jet lag, but in the other direction, ie, regaining 24 hours minus the number of hours of the jet lag. Strategies to decrease the uncomfortable manifestations of jet lag have been extensively studied, and are easily consulted in the literature.⁹⁵

Social jet lag

When a person has a circadian clock that runs with a few hours of delay, ie, a bit later than that the astronomical day/night cycle, she or he has a chronotype characterized by “eveningness,” a neologism describing difficulty falling asleep before late at night, and the associated difficulty waking up early. These persons do not have a sufficient number of hours of sleep during week days. Roenneberg and his colleagues called this phenomenon a “misalignment of biological time to social time,”⁹⁶ and they have used a specially designed questionnaire, the Munich Chrono Type Questionnaire (MCTQ) about sleep/wake habits. More than 40 000 Europeans have

now answered this questionnaire. The authors have validated the existence of social jet lag as a set of recurrent and permanent consequences of having the tendency to stay awake in the evening, ie, of having a late chronotype. Since professional and social constraints oblige most people to wake up early in the morning, those with a late chronotype develop a debt in hours of sleep during the week. During the weekend, these persons go to sleep even later and do not catch up their sleep debt completely. These persons might have biological clocks that are constantly misaligned in relation to astronomical time (the name “social jet lag” was proposed, despite the fact that there is no jet travel involved). The severity of the social jet lag can be measured by the difference between the sleep schedule during the week and during the weekend. This is done by comparing when the mid-time of sleep occurs (ie, the time when the person has slept half of the total of hours of his or her night) during weekdays versus during weekends. Persons with more social jet lag are more often smokers, consume more caffeinated soft drinks, drink more alcohol, and are more depressed. All these correlations are significant. For example, in a group of 501 persons, those with the lowest social jet lag were smokers in 10% of cases, while the proportion was as high as 65% in persons with higher social jet lag.⁹⁶ Thus the concept of social jet lag, or misalignment of biological and social time, has obvious clinical consequences.

Shiftwork

Irregular hours of work, with hours of waking and sleep at odds with the circadian clock, have detrimental effects on health and can lead to psychological and cardiovascular problems, but the exact size of these effects needs to be further evaluated.

Many persons do not resynchronize their rhythm to their work schedule, particularly because they are exposed to daylight after a night of work. Overall, persons who have irregular hours of work seem to get a smaller number of hours of sleep during the week. They can develop difficulty falling asleep, poor sleep, fatigue, psychiatric symptoms, and gastrointestinal complaints⁹⁷ Interindividual variability in sleepiness secondary to shift work is found even in highly trained jet pilots.⁹⁸ Among the many factors that determine the tolerance to shiftwork, persons of the morning chronotype and those over 45 years do not adjust easily to shift work,⁹⁹

while persons with temperature rhythms of high amplitude seem to adjust more easily.⁸

Shiftwork can alter some endogenous rhythms, but the internal relationship between rhythms might be maintained. For example, cortisol secretion partially adapts to shiftwork, and the onset of melatonin secretion remains entrained, with a time-lag of 1 hour and a half, to the period when no cortisol is secreted (the quiescent phase), as it is entrained in subjects who work regular hours.¹⁰⁰

Approaches to minimize the deleterious consequences of nighttime work are many. Shift work should ideally be organized in such a manner that the biological clock can resynchronize each day to the work schedule. This could happen if the daily delay was of 90 min approximately,

and no more, since entrainment limits are such that consecutive daily 2-hour phase delays are still too much for the biological clocks to adapt to by resynchronizing.¹⁰⁰ Periods of work shorter than 12 hours in a row are beneficial; beginning work each evening a couple of hours later during a shift of several days of night work can be helpful (so that workers slowly adapt to the night work), but it is not very practical, although it has been used for railroad drivers. Light treatment efficacy is well demonstrated in experimental studies, with the treated persons showing a shift in their temperature circadian rhythm that was not obtained in controls¹⁰²; bright light also improves nocturnal mental performance independently of its effect on synchronization.¹⁰³ Unfortunately, many work places are only dimly lit at night. Melatonin is of little utility, both in terms of improving sleep quality and mood¹⁰⁴ (melatonin is not available on the market in some countries, while in other countries, it can be found in health food stores, in formulations of a quality that cannot be guaranteed). Hypnotics are probably more efficacious, as far as the subjective quality of sleep is considered. However, since most persons working night shifts have such a schedule during months, even years, hypnotics should not be prescribed to them if the prescriber follows the guideline recommendations to limit the prescription to a few weeks only, because of the risk of dependence. Multimodal approaches with scheduled bright light and darkness, sunglasses, and melatonin have been proposed to improve adaptation to shift work.¹⁰⁵

Sleep phase shift syndromes

The two situations of delayed or enhanced sleep phase syndromes are extremes where the circadian clock is locked to earlier or later astronomical time than socially well accepted. In the sleep delay syndrome, persons prefer to go to sleep very late at night, for example after 2 or 3 am and sleep late in the morning. In the sleep advance syndrome, the opposite situation is found. These conditions can be familial and hereditary.^{78,106} Subjects with the delayed sleep phase syndrome might also show a particular personality profile, with manifestations from the domains of anxiety and mood disorders, as well as hypochondriasis.¹⁰⁷ Techniques have been proposed to treat the extreme cases of sleep phase syndromes by modification of lighting,¹⁰⁸ of sleeping schedule, or by a progressive shift of the time to go to sleep of 2 hours each night.¹⁰⁹

- Many functions that are altered during depression are regulated by biological clocks, for example sleep⁷⁹ or feeding.
- The severity of depressive symptoms changes with a daily regular pattern.
- A few affective disorder patients suffer from regular cycles of relapse.
- The existence of SAD, and the beneficial role of light in SAD and in nonseasonal depression.^{110,111}
- The observation that a number of totally blind subjects have free-running periods and feel depressed when the rhythms are out of phase in relation to the astronomical time, eg, when hormones that should be secreted during nighttime are secreted during the day.
- The efficacy of sleep deprivation, and the possible benefits of advance in sleep phase.^{112,113}
- The changes in the circadian rhythm of many variables during depression.
- The modified sensitivity to the melatonin suppressing effect of light in bipolar patients,¹¹⁴ and in their descendants.¹¹⁵
- Most antidepressants and mood stabilizers influence endogenous rhythms in free-running conditions in animals.¹¹⁶ Sleep deprivation and light therapy also modify biological clocks physiology. Lithium might act on biological clocks through its effect on glycogen synthase kinase 3 (GSK3).¹¹⁷
- Circadian genes might be associated with bipolar disorder.¹¹⁸
- Polymorphism of the *Clock* gene might correlate with some aspects of sleep in depressed bipolar patients.^{119,120}
- Mutation of the *Clock* gene in mice renders these animals hyperactive, with little need to sleep and a high threshold for anxiety, ie, they resemble somewhat a manic patient.¹²¹

Table IV. Arguments in favor of chronobiological changes in mood disorders.

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Mood disorders

It was observed more than a hundred years ago that a few mood disorder patients have regular (periodic) recurrences of depression (with or without episodes of mania). For more than 50 years, hypotheses have been proposed for the biological mechanisms of mood disorders, but none is as yet accepted. This is in contrast to the fact that many causes of depression are well recognized, such as loss and grief, endocrine disorders (Cushing's disorder, hypothyroidism, hyperparathyroidism, etc), differences in season, and the menstrual cycle.

There are several arguments that are in favor of a role of biological clocks in mood disorders (*Table IV*). Some arguments which speak against such a role, notably concerning the absence of a relationship between low levels of melatonin and depression, are shown in *Table V*.

Clinical cases in favor of chronobiological changes

Case reports of periodic changes in mood can be spectacular. Richter⁷⁵ proposed the shock-phase hypothesis to explain these observations, as well as observations in fields other than psychiatry. According to this hypothesis, groups of cells that are normally active in succession become synchronized and active all at the same time. He quoted a case of intermittent hyarthrosis in a 43-year-old man who had regular cycles of 9 days of swollen and normal knees over 4 months of daily recording in 1905.

- A single administration of a compound such as corticotropin-releasing hormone (CRH) to animals acutely induces behaviors homologous to human anxiety and depression.
- Most animal models of depression do not primarily involve biological clocks (however, the chronic mild stress model does include perturbation in the rhythm of *Zeitgebers* exposure).
- Most humans who have grossly perturbed rhythms, for example during jet lag, do not develop clinical depression.
- Melatonin secretion pattern does not show important changes during depression.¹²²
- Most subjects with low melatonin levels (ie, cardiac patients on β -blocking drugs, tetraplegics) are not depressed.

Table V. Arguments against chronobiological changes in mood disorders.

He also mentioned a 1931 description of a woman who had suffered from parkinsonism secondary to encephalitis. She was unable to talk or feed herself. We quote from his publication: "During each day up to nine o'clock in the evening the patient was bed-ridden, unable to walk, or to feed herself because of a marked rigidity and tremors of her legs and arms. Her handwriting was indecipherable, her speech unclear; but she was euphoric. Quite sharply near nine o'clock in the evening, she showed a sudden change in her whole personality. Rigidity and tremors disappeared to leave in their place a state of apathy. These 24-hour cycles were present during the nine-year observation period in the hospital."

Another example of a spectacular case report is the case of a woman of 43 years of age who had manic-depressive cycles of 48 hours and was studied over 2 years.¹²³ The peak incidence of the 173 switches into mania was between 4 AM and 6 AM, and most of the 171 switches out of mania occurred between 10 PM and midnight and between 6 AM and 8 AM. Another striking case report was that of a patient who had a 19.5 hour period for body temperature with intervals of 10 days between psychiatric decompensations.¹²⁴ Such cases are certainly rare. Of the few patients who were studied longitudinally for days to months, some showed changes in circadian rhythms while others did not. The latter situation is illustrated by a study by Wehr and collaborators where 4 bipolar patients were isolated from external cues for 1 month.¹¹² In 3 patients, the free-running period was within the norm, whereas in the fourth patient it had a period of 22 hours. Case reports of rapid, even ultradian cycling bipolar disorders, have appeared in the recent literature.¹²⁵

Clinical studies

There have been population studies on biological rhythm abnormalities in mood disorders, mostly in depression. A phase advance was found for body temperature,¹²⁶ for the latency of the first phase of REM sleep,¹²⁷ for cortisol secretion,^{128,129} for several other hormones, and monoamines or their metabolites. These findings were not always confirmed in other studies, for example the absence of a phase advance of temperature in depression.¹³⁰ Other chronobiological changes that have been identified are phase-delay,¹³¹ decreased amplitude of variables,⁴¹ and possible changes in ultradian rhythms.¹³² Some facts cannot be interpreted either in favor or

against the hypothesis of changes in chronobiology in mood disorders. For example, only a very small proportion of subjects became depressed during free-running experiments. Also, severe psychiatric manifestations during jet lag occur only very rarely. Finally, electroconvulsive therapy can have acute and immediate beneficial effects in melancholia, either by a release of endogenous compounds or by a form of resetting of cerebral or biological clocks activities. There are also arguments against a direct role of biological clocks in mood disorders.

Seasonal affective disorder

Seasonal affective disorder (SAD) is among disorders with a circannual period. This was recently described by Rosenthal and his collaborators.¹³³ They defined it as a syndrome characterized by recurrent depression that occurs annually, generally at the same time each year, for several years. They described 29 patients, most of them presenting depression from early fall during all winter, with hypersomnia, hyperphagia, and carbohydrate craving. The temperature pattern was normal during depression,^{134,135} or showed a decrease in amplitude.¹³⁶ This mood disorder is considered to have a high prevalence, which somehow does not correspond to the impression of some psychiatrists, perhaps because they do not recognize SAD, or because SAD patients consult psychiatrists less than do other depressives. The pathophysiology of SAD might involve a phase-delay of circadian rhythms.⁷⁷ Light therapy is useful,¹³⁷ as are selective serotonin reuptake inhibitors (SSRIs).

Premenstrual syndromes

The DSM-III-R label of late luteal phase dysphoric disorder was replaced by the actual wording of premenstrual dysphoric disorder (PMDD) in the *DSM-IV*.¹³⁸ In the *ICD-10*,¹³⁹ premenstrual tension or premenstrual syndrome is listed under the disorders of the genitourinary system. The term premenstrual syndrome is often used to describe the less severe presentations of the syndrome. These different terms describe a series of symptoms and signs in women of reproductive age that occur during the luteal phase of their cycle and disappear on the first day or days of menstruation. In some women, these symptoms are limited to a few days before menstruation, while in others, they start at the time of ovulation. The clinical manifestations vary in severity, PMDD being character-

ized by quite severe changes in mood, with depression, anxiety, and suspiciousness; women tend to be irritable, cry, and feel desperate, with the impression of losing control of their existence. One of the diagnostic criteria for PMDD is impairment of quality of life. There are also atypical cases, where somnambulism, psychosis, or self-mutilation occur regularly during the days before ovulation, as well as neurological signs such as clumsiness in the hands. In many cases, it is unclear whether the diagnosis should be PMDD or whether the clinical presentation consists of an aggravation of other psychiatric entities during the luteal or late luteal phase.

The prevalence of PMDD is estimated to be in the order of 3% to 5% of women of childbearing age, but it might be higher. Minor forms of premenstrual syndrome are present in 20% to 50% of women. PMDD can start at adolescence, but it is more manifest in women of 20 to 35 years; it is very rare after the menopause has ostensibly occurred. PMDD is a risk factor for the development of other mood disorders, particularly during the post-partum period.

The mechanism of PMDD quite certainly involves the endocrinology of reproduction, despite several negative findings. No difference has been clearly proven to exist between PMDD and control women in LH, gonadotrophin, melatonin, estrogen, and also anxiolytic neurosteroids such as allopregalone.¹⁴⁰ These hormones have been studied as to their mean concentration and as to the temporal circadian organization of secretion at different days of the menstrual cycle, with no significant changes, although Parry and her colleagues did find a lower melatonin secretion in a third of patients, throughout the cycle¹⁴¹; some abnormalities in circulating neurosteroids have also been described.¹⁴² No changes in the genetics of monoamine oxidase A, tryptophan hydroxylase or the serotonin transporter was found.¹⁴³

That the endocrinology of reproduction is involved is attested by the fact that blockade of estrogen and progesterone secretion by an agonist of GnRH leads to cessation of the PMDD symptoms,¹⁴⁴ and giving either estrogen or progesterone to women having received a GnRH agonist leads to the reappearance of symptoms. The change in sex hormone concentration does not explain the changes in mood, because mood alterations were not observed in women who were included in the same protocol but who had no history of PMDD.¹⁴⁵ These findings led Rubinow and Schmidt¹⁴⁶ to suggest that PMDD results from an abnormal response to normal hormonal menstrual changes and probably involves interactions

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between hormones and neurotransmitters. PMDD illustrates that a regularly periodic syndrome might have an origin other than biological clocks. It has been suggested that PMDD might be close to the entity of panic disorder,¹⁴⁷ since there is an increased sensitivity, in terms of panic induction, to several substances such as CO₂, or cholecystokinin,¹⁴⁸ or flumazenil¹⁴⁹; these responses fit with the false-alarm theory of panic attacks.¹⁵⁰ Another suggestion is that PMDD results from the evolutionary selection of immunological changes, resulting in a low probability of early fetal rejection.¹⁵¹ Indeed, cellular immunity would be decreased during the luteal phase of the cycle, while humoral immunity would be raised. Changes in immunity are also found in stress and in mood disorders.¹⁵²

The pharmacological treatment of PMDD is with SSRIs rather than with sex hormones.¹⁵³ However, a meta-analysis confirmed the efficacy of GnRH agonists and suggested that adding steroidal hormones did not decrease the efficacy of therapy.¹⁵⁴ This is an interesting possibility, but it stands in contradiction to the results of earlier controlled trials.¹⁴⁰ It has been proposed that the pharmacological treatment of PMDD should be modulated in relation to the pattern of symptoms of the individual patient.¹⁵⁵ Sleep deprivation is also useful.¹⁵⁶

Chronopharmacology and psychopharmacology

The clinical efficacy of a drug might change as a function of the time of administration, and this is the domain of chronopharmacology. It concerns changes in pharmacokinetics¹⁵⁷ and in pharmacodynamics. Also, exogenous substances might influence the physiology of biological clocks.

Chronopharmacokinetics

In the field of psychotropic agent pharmacokinetics, the renal clearance of lithium is decreased by one third during the night¹⁵⁸; this is explained by the fact that the renal clearance of lithium is about a third of that of creatinine, which is itself lower at night. Aside from lithium, amisulpride, and bupropion, other psychotropic medications are mostly metabolized by the liver, and it could be that their clearance decreases at night, since there are circadian rhythms in the expression of many cytochrome P-450,¹⁵⁹ however, the extent of this nocturnal decrease in hepatic clearance has been too rarely studied. The relevance of

such studies is illustrated by the example of ketoprofen. When administered (after an 8-hour fast) at 07:00, the absorption was very fast, while it was very low at 01:00 (also after an 8-hour fast). The highest clearance was observed after administration at 13:00, and it was twice as high as that at 07:00.¹⁶⁰ High concentrations of carbamazepine after the morning dose have been observed in children,¹⁶¹ which might also reflect circadian changes in absorption or clearance.

Chronopharmacodynamics

Studies in animals have shown an important variation in the dose/response curves according to the clock time of administration. For example, according to a study done during the 1960s, a dose of *E. coli* endotoxin that kills less than 10% of mice at a given clock time, corresponding to the active nocturnal phase of the animal, can kill more than 80% at another clock time, during daytime, when mice rest.¹⁶² In a recent study, the loss of the righting reflex in the mouse induced by several hypnotics varied by a factor of 1.5 to 2 depending on whether the drug was given at the beginning of the active or the inactive phase of the rodents.¹⁶³ In oncology, chronopharmacological studies have shown that a given dose of an anticancer medication can have better efficacy and fewer side effects depending on when it is administered.¹⁶⁴ This is explained by circadian changes in tumor cell characteristics.¹⁶⁵ Other fields where chronopharmacology is of demonstrated relevance are those of asthma and cardiovascular disorders.^{166,167} In the field of psychotropic agents or illegal drugs, aside from research on laboratory animals, and research on alcohol, little is known on circadian changes in pharmacodynamics. In particular, the extent of changes in the concentration/response curve over the course of the day has not been well evaluated in humans.

The pharmacology of alcohol shows circadian changes.¹⁶⁸ Several studies during the last 50 years have shown that alcohol is absorbed more rapidly, with higher blood levels when taken during the morning, but that it is also eliminated faster.¹⁶⁹ Each addicted person has his or her own daily schedule to start the consumption of alcohol.¹⁷⁰ Alcohol given during one day to non-addicted volunteers does not influence the circadian rhythm, nor the concentration of cortisol, but it increases that of testosterone¹⁷¹ and suppresses the nocturnal increase of TSH, and decreases the mean concentration of the later hormone.¹⁶⁸

Clinical consequences of chronopharmacology

There is little information as to whether giving a psychotropic medication once a day or as a divided dose shows any benefit in terms of efficacy or side effects. It might be with substances that themselves influence the physiology of biological clocks that chronopharmacology will find its major application. Benzodiazepines and other sedatives can influence the phase position of circadian rhythms, and lithium, as well as a few antidepressants, might modify the functioning of the SCN.¹⁷² However, lithium and most antidepressants and many benzodiazepines have a half-life of elimination that is longer than 12 hours; thus their effects persist throughout the night. Melatonin has a short half-life and its timing of administration is quite relevant for its efficacy in SAD treatment.⁷⁷

The following general clinical and general rules prevail: a stimulating medication should be given in the morning and not late in the afternoon or in the evening, a medication that is sedative should be given at the time of sleep, and a medication that induces nausea might be better tolerated when given with a meal.

Conclusion

The time structure of biology is as essential as is its spatial structure, yet the relevance of chronobiology for

pathophysiology remains underestimated in internal medicine, neurology, or psychiatry. This might be because measuring the rhythms of most biological variables over the long term is complex, because feedback loops and regulations maintain vital phenomena within apparently stable ranges labeled as norms, and finally because our knowledge about the temporal structure of biology remains incomplete. Indeed, the relation between endogenous biological oscillators is far less well established than are mechanisms in other domains of biology, for example endocrine feedback mechanisms.

New approaches to biology, called high-dimensional approaches, involve multiple measurements to address the physiology at the levels of genes, gene transcription, peptide synthesis, and metabolic states in organs and tissues. These high-dimensional approaches are somewhat technically cumbersome when the aim is to explore the phenotype of biological clocks. However, this will probably be a necessary step in the understanding of several disorders in psychiatry. Indeed, several psychiatric disorders show more or less regular periodicity in their clinical manifestation, and they could be seen as dynamic diseases, in the sense given to this term by Glass and Mackey,¹⁷³ i.e., diseases characterized by abnormal temporal organization of bodily systems. □

The studies by the author were supported by grants 3.599.084 and 3.968.085 from the Swiss Fonds National de la Recherche.

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Los relojes biológicos y la práctica psiquiátrica

Los relojes biológicos endógenos le permiten a los seres vivos adquirir cierta independencia en relación con el tiempo. También mejoran la eficiencia de los sistemas biológicos al darles la posibilidad de anticipar futuras exigencias a los principales sistemas fisiológicos y al metabolismo energético celular. La organización temporal de una función biológica puede deteriorarse en su coordinación con el tiempo astronómico o con otras funciones biológicas. Asimismo existen condiciones externas que afectan los relojes biológicos. La organización temporal es compleja y es posible que algunos síndromes y trastornos psiquiátricos incluyan cambios primarios o secundarios en los relojes biológicos. Entre estos trastornos deben considerarse los trastornos del ánimo estacional y otros trastornos del ánimo, los síndromes premenstruales, el jet lag social, los ritmos de oscilación espontánea y algunos trastornos del sueño. En esta revisión se describen los conceptos principales relacionados con la cronobiología y se explora la importancia del conocimiento acerca de los relojes biológicos para la práctica clínica de la psiquiatría.

Les horloges biologiques et la pratique de la psychiatrie

Les horloges biologiques endogènes permettent aux espèces vivantes d'acquiescer une meilleure indépendance par rapport au temps. Elles améliorent l'efficacité des systèmes biologiques en leur donnant la possibilité d'anticiper les contraintes à venir sur les systèmes physiologiques principaux et sur le métabolisme cellulaire énergétique. L'organisation temporelle d'une fonction biologique donnée peut être altérée dans sa coordination avec le temps astronomique ou avec d'autres fonctions biologiques. Des conditions externes aux espèces vivantes peuvent aussi influencer sur les horloges biologiques. Cette organisation temporelle est complexe et il se peut qu'une série de troubles ou de syndromes psychiatriques impliquent principalement ou secondairement des changements dans les horloges biologiques : troubles de l'humeur saisonniers et autres troubles de l'humeur, syndrome prémenstruel, jetlag social, rythmes en libre cours, plusieurs troubles du sommeil figurent dans la liste. Dans cet article, nous décrivons les concepts principaux se rapportant à la chronobiologie et nous discutons de la pertinence de connaître ces concepts par rapport à la pratique clinique en psychiatrie.

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