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Time in biology with particular reference to humans

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Organisms possess an internal 'body clock' that measures the passage of the day, although they respond directly to the influences of the sun. The site of this clock, its properties, and its molecular and genetic mechanisms are now beginning to be discovered. In humans, the clock enables the processes required for daytime activities and nocturnal sleep to be separated; but the system can go wrong or cause difficulties, as in the blind, anybody after a time-zone transition or during night work

Rhythmicity in living organisms

Humans, like all other species, have evolved to meet the demands of their environment. These demands vary widely but include the effects of currents and salinity for aquatic dwellers, of periodic inundation and desiccation for those dwelling in the inter-tidal zone, of temperature changes and water availability for those who live on the land surface, and of the effects of gravity and wind for those who stand upright or fly. A whole range of physiological and biochemical mechanisms has evolved for protection from such environmental forces.

There is another all-pervasive influence in all environments except, possibly, deep within caves or at the bottom of the oceans. This is the influence of time, whether it be the cycle of the seasons (lasting a year), of the solar day (about 24 h), or of the tides (generally about 12.4 h). That plants and animals respond to such cycles has been recorded from classical writers onwards, and there is the charming example of Linnaeus' flower clock (18th century), which related times of opening and closing of different species of flower to the time of the day. Ancient records of astrological and calendrical tables, together with the alignment of some of the stone henges in Northern Europe and pyramids in Egypt, all point to a human awareness of these cycles that stretches back to an early time in human development.

In all these cases, it seems that the plants and animals (and humans) were believed to be responding to the environment (and/or the gods) – that is, the causes were external, and the living organism was responding passively (or at the behest of the deities). The comparatively modern study of chronobiology has changed that view, indicating that plants and animals have an internal timing mechanism (or clock) that, at least to some extent, enables them to show an intrinsic rhythmicity in their physiology and biochemistry that is independent of environment. One of the earliest demonstrations of this was by de Mairan who reported, in 1729, that the daily movement of the leaves of the sensitive plant, Mimosa, continued if the plant were kept in constant conditions. Extensive research in the past 50 years has indicated that an endogenous mechanism contributes to the rhythmicity observed in nearly all species of plant and animal so far studied, including humans. The exceptions to this are animals and primitive members of the plant kingdom that live deep in caves, where rhythmicity in the environment is almost non-existent and, possibly, those that live on the ocean floor, although they have not so far been studied,.

Biological rhythms in humans show a wide range of periods: in the order of seconds (heart rate, brain electrical activity, respiration), hours (hormone release, food intake), day (activity, sleep), month (the menstrual cycle) and year. Some of the best understood are those with a period of about a day, called circadian (from the Latin: circa, about; diem, a day), and it is upon these that we will concentrate.

Circadian rhythms in humans

Studies of humans living their normal routines have shown that almost all physiological and biochemical variables have regular daily rhythms, each with its own characteristic timing. For many of these variables, such as activity, heart rate, mental activity, physical activity, subjective alertness, digestive processes and plasma adrenaline, the rhythms peak during daytime and show troughs during nocturnal sleep. For others, including the hormone melatonin, growth hormone and the sex hormones, the peak is during the hours of darkness. Still other variables have rhythms that peak near to the time of rising (the hormone cortisol is an example) or retiring (such as immune responses). These rhythms correspond to those in many other animals – provided they are diurnal rather than nocturnal creatures, active in the daytime and recuperating at night.

However, these rhythms are not just a response to our habits and rhythms in our environment. Evidence for this comes from both laboratory studies and field observations. Staying awake and sedentary in a constant environment (with regard to lighting, social factors, temperature, noise and food) for at least 24 hours does not cause the rhythms to disappear. For instance, in the first few days after a flight to another continent across several time zones, a traveller feels tired during the night on ‘old’ time and cannot sleep during the new night-time. During a spell of night work, workers feel tired and tend to make more mistakes and, during the daytime, sleep is shorter and more fractionated than normal. The explanation common to these examples is that our daily rhythms are partly due to a ‘body clock’, which can run independent of the environment and which continues to reflect the timing of our old habits for some days after we have changed them.

The body clock

Humans have been studied in isolation chambers and in underground caves (for up to about nine months) in attempts to learn something of the properties of the body clock when uninfluenced by external time cues. Figure 1 shows the successive times of rising and retiring of an individual who lived alone in a cave for a period. The cave had no light or temperature

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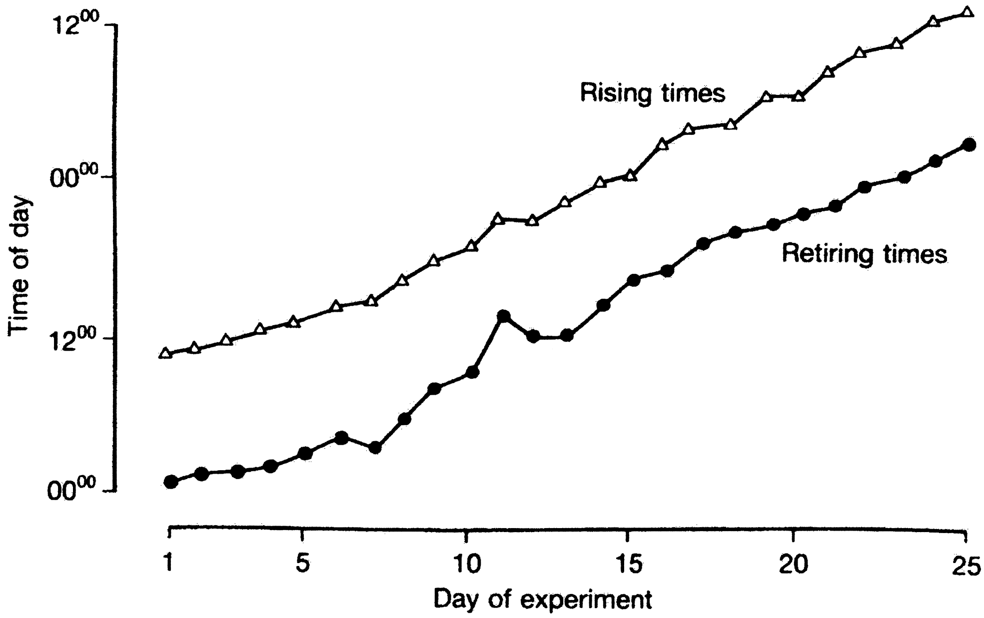

Figure 1. This man was in a cave with no access to knowledge of time outside. This is a record of the time of his retiring and rising. It can be seen that both drift by 24 hours over a period of about 23 days (Waterhouse *et al.* 1998).

fluctuations to indicate the time outside. The subject was allowed his own source of light and cooking facilities. He was free to rise, eat meals and retire when he chose, and could choose the activities that he pursued when awake, but he was not allowed a clock or a watch or to have access to the radio. His timing of these events was determined by his perceived need. All his activities were recorded, so that their timing could be ascertained, but such information was not made available to the individual himself.

Note that three points can be inferred from Figure 1.

(1) The sleep–wake cycle did not disappear and, with only minor changes, the different rhythms (though not shown here) continued to show their normal phasing with regard to it.

(2) The rhythms run slower than the solar day; in this case, the average period of his clock was about 25 h, which is why the rhythms are described as 'circadian'. This meant that rising and retiring times were about 1 h later each day.

(3) On day 7, the subject went to bed slightly earlier, and on day 11, slightly later than the general trend. These slight irregularities could have been due to boredom or finishing something before retiring, respectively. However, rising times did not follow suit, and so a longer waking period than usual was not followed by a longer sleep than usual on day 11 – as would be predicted if the time of waking were determined wholly by having slept long enough to recuperate.

These kinds of finding strongly support the view that we possess some internal timing

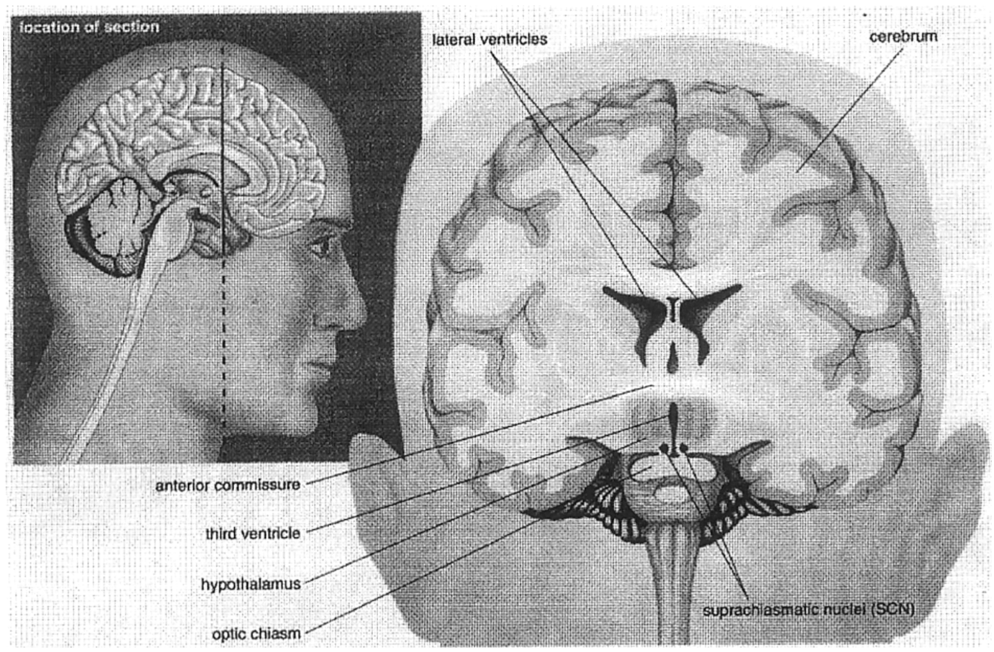

Figure 2. Section through the human brain, showing the suprachiasmatic nuclei at the base of the hypothalamus. (Waterhouse and Akerstedt 1998).

mechanism independent of the environment – a 'body clock' – but a clock that does not keep exactly in time with the solar day and varies a little between individuals.

In experiments with other animals and plants, the same kind of results are found, but in some species the clock runs slightly faster than 24 h (it is unclear what determines whether this circadian period should be greater, or less than the solar day in a particular species). Equally, for organisms responding to the tides, the clock runs with a period that is slightly less or more than 24.8 h (the lunar day).

Studies on the site and mechanism of action of this body clock in rodents have clearly pointed to the importance of paired groups of cells, or nuclei, at the base of the hypothalamus, just above where the optic nerves cross over on entering the brain (Figure 2). These cells, are known as the suprachiasmatic nuclei (SCN), and are the only mammalian brain tissue discovered so far that can continue to show circadian rhythms in electrical activity and the secretion of neurotransmitters when studied *in vitro* under constant conditions. These nuclei probably send their output to widely different areas of the brain, especially to other regions of the hypothalamus, the region of the brain with key functions in the control of hormone release, the autonomic nervous system, appetite and body temperature. This is why circadian rhythms are so widespread throughout the body; they influence our metabolism and ability to sleep, as well as our physical and mental performance when awake.

Genetic and molecular biochemical studies indicate that the clock mechanism itself depends on a set of genes that are translated in sequence. The protein produced by the first gene (a 'clock protein') is transported back to the nucleus to initiate translation of the next gene in the sequence, and so on. Since the last protein then re-activates the first gene, a cycle is produced. The length of this cycle is determined by the number of base pairs in the genes, as well as by the time taken for the gene product to be manufactured and transported, after any necessary modifications, back into the nucleus. Much of the genetic information for the body clock is conserved between species, which indicates the fundamental importance of the clock during the process of evolution.

'Clock mutants' – organisms in which the circadian period is abnormally short or long – have been identified in animals, plants and fungi. As far as can be judged at the present, they appear either to have altered numbers of base pairs or changed kinetics for the transport of the clock protein back to the nucleus, and such changes are believed to account for the changed period of the clock. If foetal SCN tissue from a mutant golden hamster is transplanted into a 'wild-type' host, after recovery from the operation, the host shows a circadian period equal to that of the mutant. The transplantation can also be performed in the reciprocal manner, with the mutant host then taking up the 'wild-type' period (Figure 3). The SCN tissue appears to contain all the information about clock function. (The reason that foetal tissue is transplanted is that adult brain tissue has lost the power to grow and divide).

Even though the culture of individual cells of the SCN has shown that each can act as a circadian oscillator, the cells are normally connected to each other, and so function as a single clock. In some nocturnal animals kept in constant light, the circadian rhythms begin to 'split' into more than one component, probably due to a failure of all the cells of the SCN to act in unison. In healthy human babies, circadian rhythms are poorly developed (as demonstrated by their tendency to wake frequently at night and sleep often in the daytime), and this also is believed to reflect the lack of functional connections between cells of the SCN at this stage of life.

Adjusting the body clock

As the clock in humans would be expected to run slow in the absence of time cues, by about one hour a day, this would render it useless as a timekeeper if uncorrected. However, it will be noted that this error is only of the order of 4%, an error that is small for biological phenomena in general. The observations that the circadian rhythm is normally adjusted to the environment indicate that adjustment of the endogenous pacemaker must take place. In practice, there is a continual adjustment of the body clock by rhythmic processes in the external environment, by mechanisms that are called *zeitgebers* (German: *zeit*, time; *geber*, giver). What the zeitgebers are depends upon the species under consideration and, in some cases, upon the stage of its life that has been reached. Some examples of zeitgebers are:

(1) the alternation of light–dark in green plants and many animals;
(2) the alternation of food availability–unavailability in new-born mammals;
(3) changes in environmental temperature in some invertebrates;
(4) social influences (behavioural) in animals;
(5) buffeting, and the effects of hydrostatic pressure, from the tides in shore-dwelling creatures.

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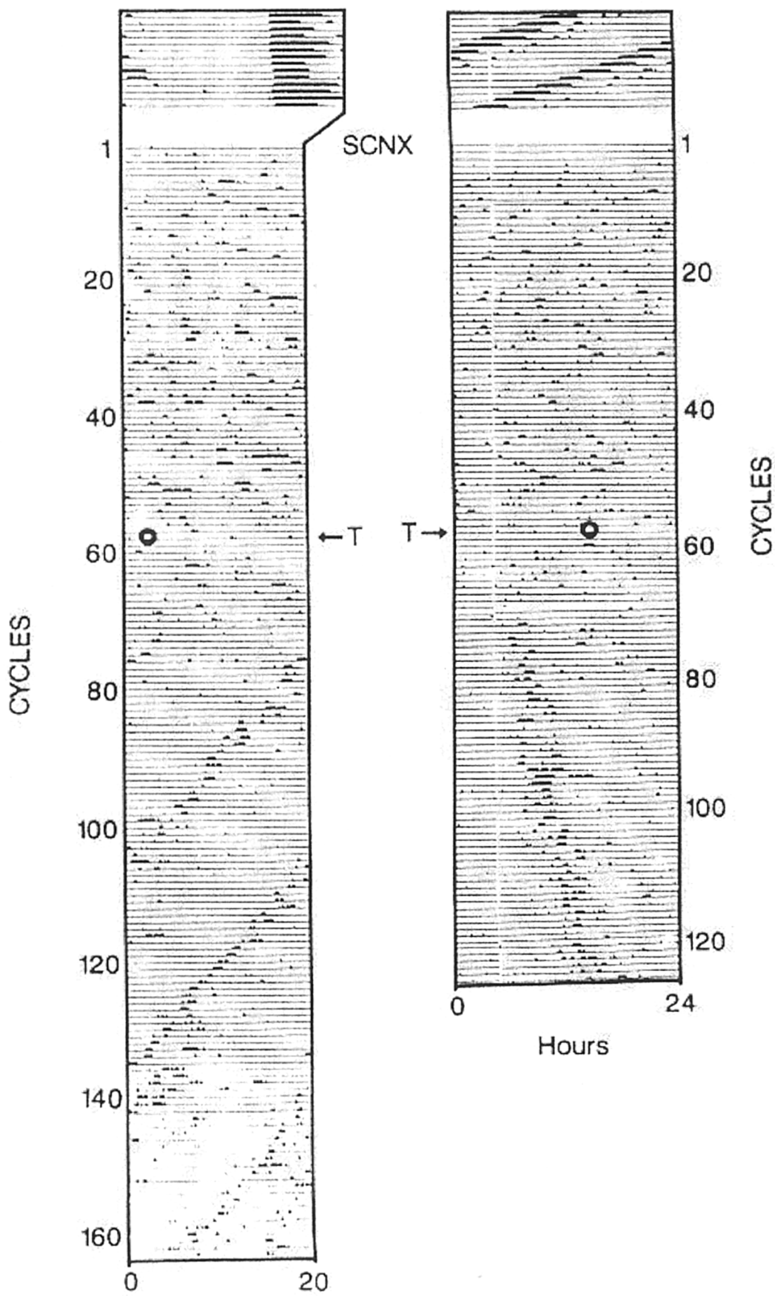

Figure 3. Left: activity rhythm of a 'wild-type' golden hamster kept in darkness (the period is about 24 h). On day 1, the suprachiasmatic nucleus was removed (SCNX), resulting in a loss of rhythmicity. On day 58, foetal SCN tissue from a mutant hamster whose period was 22 h was transplanted (T). Following this a new activity rhythm of 22h was established. Right: this is the reverse situation. A mutant hamster with a period of 22 h received foetal SCN tissue from a wild-type donor and a period of about 24h became established. (Ralph *et al.* 1990).

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Table 1. A daily timetable for humans

20–24 h. Evening:		
	falling temperature falling adrenaline rising melatonin	prepare for sleep
	falling cortisol	broncho-constriction and? asthma attacks
	?	foetus kicks most
24–04 h. Early night:		
	rising growth hormone	deep (SWS) sleep fat metabolism
04–08 h. Late night-		
	rising temperature rising adrenaline falling melatonin rising cortisol	dream (REM) sleep and prepare for waking
08 h. On waking:		
	'sleep inertia'	
	rising BP rising activity platelets stickiest	greatest load on heart and risk of cardiac problems
09–12 h. Morning:		
	higher temperature	best mental activity
	rising insulin sensitivity	glucose metabolism
12–14 h. Early afternoon:		
	transient fall in adrenaline	time for siesta?
15–20 h. Late afternoon:		
	highest temperature	best physical activity
	effects of fatigue begin	complex tasks worsen

More speculative possibilities include:

(6) changes in osmotic pressure in estuarine dwellers;
(7) social influences (pheromones?) in social insects.

In each case, the zeitgeber adjusts the plant or animal to the environmental time cues, and it will be noted that this will be a lunar, rather than a solar, cycle in cases 5 and 6 above.

In humans, it has been established that light, particularly bright light outdoors, will adjust the body clock, but dimmer light, of an intensity found domestically, can also affect it. Melatonin also appears to play a role; it is a hormone that is secreted from the pineal gland from around 9 pm to around 8 am, provided that bright light is absent (bright light inhibits melatonin secretion). It shifts the clock in the opposite direction to bright light, advancing the body clock in the evening and delaying it in the morning and, for this reason, melatonin has been called an 'internal zeitgeber'. The rhythms of melatonin secretion and light intensity act together to adjust the human to the light–dark cycle.

The cells of the SCN receive neural and chemical inputs from widespread regions of the body, and it is through some of these that the zeitgeber signals reach the body clock. There is a direct pathway in mammals from the retina to the SCN, the retino-hypothalamic tract, through which visual information leads to the expression of a group of genes within the SCN, called the 'immediate early genes'. In some way, these genes or their products act upon the cyclic mechanisms that constitute the clock itself, sometimes causing it to advance, at other times, to delay. Recent work indicates that there might be a special type of receptor cell in the retina that is responsible for signalling information about light intensity, and that the photopigment might be based on vitamin B2 rather than rhodopsin (vitamin A) which is concerned with ordinary photoreception. There is also the possibility that light information can be picked up by cryptochromes in the skin (substances widely distributed through the plant and animal kingdoms) and be transmitted to the brain, presumably, via the blood stream.

Another neural input to the SCN comes from the intergeniculate leaflet. This could be the pathway by which information about physical, social and mental activity reaches the master clock. Finally, there are melatonin receptors on the SCN, through which plasma melatonin probably exerts its effects.

The role of the body clock

There are several roles of the body clock (see Table 1).

(1) It enables the body to switch between 'active' (ergotropic) and 'inactive' (trophotropic) modes, in synchrony with the solar or tidal changes in the environment. There are many differences between these two modes, which are most obvious in a species such as the human, where there is one consolidated sleep per day and these differences are reflected throughout the physiology and biochemistry of the individual.

(2) The body clock enables the organism to change its biochemistry and physiology in preparation for this 'switch'. In humans in the evening, for example, our body clock prepares us for sleep by reducing the concentration of adrenaline in the plasma, reducing blood pressure and body temperature, and increasing plasma melatonin and the sense of fatigue. Before the end of sleep, these processes are reversed.

In many cases, such changes must begin before the environmental changes take place, and so cannot be a response to the environment. Consider, for example, a creature living in the inter-tidal zone that forages for food when the tide is in, but needs to hide in its burrow to resist desiccation when the tide is out. Clearly, some way of knowing that the tide is about to go out but before this actually happens is needed, so that the animal can return to its burrow in time. This use of a body clock to foretell environmental changes has been called 'predictive homeostasis' to distinguish it from the more usual 'reactive homeostasis'. It is interesting that an additional method for predicting changes that will follow from environmental changes has been evolved in some cases. For example, heat-loss mechanisms are stimulated by warming the skin, through inputs from cutaneous

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thermal receptors; by this means, the body can lose heat before the 'error' in core temperature has arisen.

(3) If the circadian clock is adjusted to the time of sunrise (or sunset), it then becomes possible to establish, by considering the position, say 12 h later, if the length of daylight (or night-time) is increasing or decreasing. This can become the stimulus – for example in preparing for the rigours of winter or the opportunities of springtime – in deciduous trees, pupating insects, hibernating amphibians, migratory birds and seasonally breeding mammals.

It will be noted that points (2) and (3) above bear out the old adage, 'To be forewarned is to be fore-armed'.

Difficulties associated with a body clock

For most of the time, the body clock effectively integrates us into the rhythmic patterns in the environment, but there are some circumstances where this does not happen.

There is a Gaussian distribution of the time of peak of the core temperature, with a mean at about 18:00 h. and about two-thirds of the population have their peak within an hour of this mean. Five percent of the population at each extreme are about 2 h earlier or later then this, these sub-groups are commonly called 'larks' (morning-types) or 'owls' (evening-types), respectively. These differences do not normally cause any problems, but even more extreme differences exist. Since all circadian rhythms are affected, these extremes result in individuals wishing to sleep at hours that are too late (about 04:00–12:00 h, for example) or too early (20:00–04:00 h) to be compatible with a conventional lifestyle.

For some individuals, there is evidence that the body clock is unable to adjust to a 24 h day. This is not uncommon in blind people, and supports the view that the light–dark cycle is normally an important zeitgeber. In these individuals, free circadian rhythms continue but with a period greater than 24 h. As the body rhythms drift out of phase with a normal lifestyle, the problems of sleep loss and fatigue worsen and are at their most marked when the body rhythms and lifestyles differ by 12 hours (when temperature peaks during the night and melatonin secretion starts at about 9 am). With a continuation of this drift, the body clock and lifestyle come back into synchrony, bringing better sleep at night and more alertness in the daytime, although only temporarily. Presumably this would be the kind of problem experienced by the 'clock mutants' referred to above, if they were placed in the wild and this would put them at a disadvantage.

Interestingly, some blind people do adjust their body clock to the 24 h day. It is assumed, but not yet clearly established, that despite their blindness, their retinohypothalamic pathway has remained intact and functional.

Two other examples showing the difficulties that arise when our body clocks and lifestyle do not match will be familiar to many. Normally, our lifestyle and environmental zeitgebers act in harmony with our body clock and we are rhythmic creatures attuned to our rhythmic world. The stability of the body clock is an advantage as it means that occasional changes, such as a daytime nap or waking briefly at night to micturate, will not disrupt our normal rhythmicity. But this stability can be a disadvantage. For some days after a long-haul flight or during a spell of night work, people have difficulty sleeping, feel tired when they should

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Table 2. The use of bright light to adjust the body clock after time-zone transitions

	Bad local times for exposure to bright light	Good local times for exposure to bright light
Time zones to the west:		
4 h	01:00–07:00 (a)	17:00–23:00 (b)
8 h	21:00–03:00 (a)	13:00–19:00 (b)
12 h	17:00–23:00 (a)	09:00–15:00 (b)
Time zones to the east:		
4 h	01:00–07:00 (b)	09:00–15:00 (a)
8 h	05:00–11:00 (b)	13:00–19:00 (a)
10–12 h	Treat this as 12–14 h to the west (c)	

Notes:
(a) This will advance the body clock.
(b) This will delay the body clock.
(c) Because the body clock adjusts to large delays more easily than to large advances.

be working, lose powers of concentration and have little appetite – in short, they feel 'below par'. Unlike the example of subjects who cannot adjust their clocks to a 24 h day, these problems of 'jet-lag' and 'shift-workers' malaise' are normal responses to an abnormal, imposed lifestyle. They arise because of the stability of the body clock.

Treatment of problems associated with the body clock

Can these problems – whether due to inadequacies of adjustment of the circadian system or to an abnormal lifestyle – be combated? The answer is that, to some extent, they can – by strengthening the zeitgebers that normally adjust the body clock. Thus, by manipulating the times of exposure to, and avoidance of, bright light, the adjustment to time-zone transitions and shift work can be promoted (see Table 2). In the neonatal wards of hospitals, the imposition of dimmed light at night and brighter light in the daytime for routine care has been shown to result in more rapid weight gain and neurological development of the new-born. In addition, people in whom sleep disturbances are common, including the blind, the elderly, and those with depression or senile dementia, have been helped by a combination of therapeutic and behavioural approaches. These strategies include exposure to bright light each morning, organized activities in the daytime, a dose of melatonin in the evening and the discouragement of getting up at night.

Some clinical implications of circadian rhythms

A simple example is that of the timing of blood samples taken for diagnostic purposes. Cortisol and growth hormone show large amplitude circadian rhythms, and so the 'normal' concentration of either hormone depends upon the time of measurement. If this circadian variation is ignored, the results can be misleading.

Some illnesses show considerable daily variation, either in incidence or the severity of

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symptoms. Cerebral strokes and heart attacks occur more frequently between 6 am and noon than any other six-hour period, and the incidence of asthma attacks is greatest in the evening and at night. People with rheumatoid arthritis tend to experience their worst symptoms on waking in the morning.

These variations can be understood in terms of normal circadian rhythms in physiology and biochemistry. Thus, the increased incidence of cardiovascular morbidity in the morning can be explained as due to a combination of cyclic changes that occur normally. In the mornings, cardiac activity rises, there is an increase in sympathetic muscle tone and systemic blood pressure rises (all of which place greater demands on the heart), while blood platelets show a greater propensity to stick together, and the mechanisms for breaking down clots are less active. In susceptible individuals, these combined factors might combine to tilt the balance towards a cardiovascular crisis.

Similarly, the evening peak in asthmatic symptoms coincides with falling levels of both adrenaline, a bronchodilator, and cortisol, a natural immuno-suppressant hormone. Everyone experiences some constriction of the airways in the evening, but in asthmatics who have hypersensitive airways, the constriction is exaggerated and can lead to the discomfort or even a major asthmatic attack. With rheumatoid arthritis, the low evening plasma levels of cortisol lead, after a delay of some hours, to increased pain in the joints.

With disorders that show a circadian rhythm in terms of risk or severity, the timing of the treatment should reflect this. The standard treatment for patients with hypertension or rheumatoid arthritis used to be a once daily dosage of a drug (beta-blockers, for the former and non-steroidal immunosuppressive drugs for the latter). Morning was often chosen in order to reduce the chance of the patient forgetting to take the medication! This regimen is unsatisfactory since the effect of the drug has worn off by the time it is most needed, about 18 hours after dosage. More recently, therefore, clinicians have started to prescribe these therapeutics in divided doses, to be taken morning and evening or slow-release formulations so that the drug can be present throughout the 24 hours. However, there is no firm evidence yet of the superiority of divided-dose regimens over the conventional morning-only dosing regimen. A different problem is encountered in replacement hormone to patients with a pituitary malfunction, which can lead to delayed puberty or stunted growth. If hormone levels are maintained at a constant high level by frequent, regular injections, the target organs become refractory to the effects of treatment. Duplicating the normal rhythm of hormone concentration in the plasma by administering it once per day before retiring, so that the overnight values are high but daytime values are low, overcomes this problem. It is not only more effective in advancing puberty or producing a growth spurt but it is also cheaper, since less hormone needs to be given.

This growing awareness of the relationship between circadian rhythms, illness and therapy has led to the development of the field of chronopharmacology, which is a systematic study of how the body clock affects the treatment and efficacy of drugs. The same dose of a drug may show different kinetics of uptake, metabolism and excretion according to the time of the day when it is taken. The uptake of a drug from the gut depends upon the circadian rhythm of blood flow to this organ, the rate of its metabolism depends upon the rhythms of hepatic detoxification enzymes. The excretion of the drug in the urine depends upon circadian changes in renal haemodynamics, in tubular function and in passive reabsorption. Furthermore, the sensitivity of a tissue to a drug can also show time-dependence, probably due to circadian rhythms in receptor numbers and properties.

The implications of these factors may be significant for patients with chronic conditions (who have to take a particular medicine indefinitely), or if the amount of drug administered is the maximum tolerated. For example, in the treatment of cancers, work is currently establishing modes and times of drug administration that offer the greatest efficacy in killing the cancerous cells with the least toxicity. Many of the drugs used in cancer chemotherapy prevent cell division. In the healthy tissue there is a circadian rhythm of cell division, whereas these rhythms are absent from cancerous tissue, where the cells tend to divide continuously. The efficacy of the drug is increased and potential toxicity decreased, therefore, if it is given at a time when healthy cells are less likely to be dividing (and are less sensitive to the drug). Results so far indicate that the careful timing of drug administration – often using a series of programmable pumps, each with its own circadian profile of delivery – enables higher doses of a drug to be given with less toxic side effects and with a better prognosis for the cancer patient.

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