Introduction

by O. Benoit

Laboratoire de Physiologie, U3 INSERM, 91, Boulevard de l'Hôpital, F-75634 Paris Cedex 13, France

The influence of the environment on sleep is a vast area for study. The study comprises both the phylogenetic and ontogenetic disciplines and is concerned not only with the alteration of sleep patterns as a function of upbringing and maturation, but also with the effects of geographic and ecological conditions on sleep and their resulting interplay with psychosocial factors.

This review deals only with human sleep. It is necessarily limited to the influence on sleep of the few environmental factors which have been studied, such as noise and temperature. We know practically nothing about the influence of living conditions (urban vs country living, a nomadic vs sedentary existence, etc.) or the influence of climate and latitude on the endogenous sleep-wake process.

As life styles change, the question of the endogenous flexibility of the sleep-wake process becomes more and more important. It is critical to know how sleep-wake cycles can be adapted to modern living which often forces people to work at varying times or stay up for prolonged periods, as for example during transoceanic flights. This question is particularly critical in today's world where greater numbers of people are forced to extend or radically alter their sleep-wake cycles.

As if this were not enough, modern day sleep-wake problems are further exacerbated by factors such as noise, pollution and stress associated with work and crowded living conditions, all of which must be better understood.

Man has no doubt always adapted his sleep-wake cycle to environmental conditions. Among them, the search for a safe place to sleep was of particular importance. Later, the discovery of fire and the development of clothing and housing freed man from the pressures of the external environment. It became possible to take pleasure in sleeping.

Ironically, today we are again confronted by environmental problems, although, as we have noted, they are of an entirely different sort. But in addition, the internalization of existing, environmentally produced daily stress may add another dimension to problems with our sleep-wake cycles.

The first paper by D.S. Minors and J.M. Waterhouse introduces the problem. They describe the exogenous and endogenous components of the human sleep-wake cycle, and stress the characteristics and the limits of the entrainment by Zeitgebers of the sleep-wake circadian oscillator.

T. Åkerstedt presents the latest data on the influence of work schedules on sleep. He clearly shows that work schedules interfering with normal hours for sleeping generally induce fatigue and subjective/objective sleep disturbances, which are indicative of the limits of adaptability of the biological sleep-wake process to abnormal routines.

J. Foret analyzes the relationships between daytime activity (physical and mental) and subsequent sleep. This article suggests that diurnal activity is able to modulate sleep need and sleep patterns either on a short term or on a long term basis by modifying the internal environment of sleep.

The next two papers deal with the problem of interactions between external conditions (temperature and noise) and sleep. The first paper, by A. Muzet, J.-P. Libert and V. Candas, shows that ambient temperature affects sleep in different ways depending on the balance between thermoregulation control and sleep needs. The results strongly suggest a coupling between the thermoregulatory system and the sleep mechanisms. The second paper by M. Vallet and J. Mouret makes clear that a typical nuisance such as noise is disruptive of sleep and there is little habituation, at least for cardiovascular responses. Unfortunately, we do not yet know if noise experienced during the waking state (for example, on the job or in the everyday surroundings) has a similar disruptive effect.

In the final paper, I present a tentative view of the homeostatic and adaptative role of sleep.

It became strikingly evident, in the course or writing this chapter, how immense the need is for research which will improve our understanding of the roles of genetic and environmental factors involved in a given sleep-wake behavior and the possibilities of different biological sleep-wake processes to adjust to a particular environment.

0014-4754/84/050410-01$1.50 + 0.20/0

The sleep-wakefulness rhythm, exogenous and endogenous factors (in man)

by D.S. Minors and J.M. Waterhouse

Department of Physiology, University of Manchester, Manchester M13 9PT (England)

Introduction

Man is a rhythmic creature living in a rhythmic world. Even though the external peridicities to which he is exposed range from years (e.g. sunspot cycle) through annual, monthly (tidal) and daily rhythms, the dominant one shows a period of 24 h in attune with the solar day. Rhythms which follow this period are termed *circadian*. The movements (tropisms) of leaves are in phase with

that of the sun as too are the habits of many animals that either hunt by day or avoid capture by being active at night. As far as man is concerned, in a hunter-gatherer society an adherence to the light-dark cycle imposed by the sun is marked; in an industrialized society, a 24-h or nychthemeral pattern is observed also, but the factors which are responsible for this are different. Thus, the advent of artificial lighting and methods of storing food have freed man from a subservience to the light-dark cycle. Nevertheless, the 24-h rhythms persist, now due to the impositions of a social structure which determines when we should sleep, eat and arrange work and leisure.

The problem we shall be concerned with in this paper is the extent to which the sleep-wakefulness or activity cycle is determined by such external or exogenous factors rather than be some internal or endogenous «clock-like» mechanism. Recent general accounts of the field have appeared and act as broad introductions to it[22,29,44].

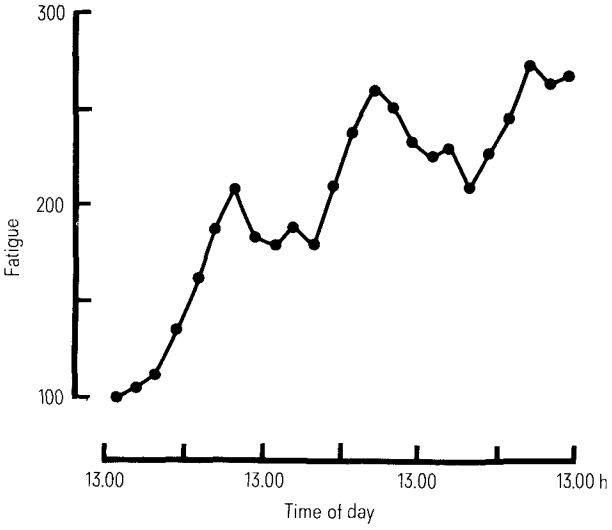

Figure 1. Mean self-rating of fatigue, measured every 3 h in 63 subjects over 72 h during which no sleep was allowed. Note that, despite the overall gradual increase in fatigue, circadian changes can also be seen. (Data of Fröberg et al.[9]).

Endogenous component to the activity cycle

Personal experience suggests that factors exist other than external ones, since we feel we are becoming drowsy in the evening and that, for some time after getting out of bed in the morning, we are in the process of 'waking up'. This is particularly noticeable if we stay up all night: until about 04.00 h we feel progressively more fatigued, but thereafter we begin to improve, even though our sleep deprivation has increased.

More formally, the presence of an endogenous component to the activity rhythm can be established by a number of protocols, as below.

1. The constant routine and related protocols

In the constant routine, rhythmicities in the external environment are minimized as much as possible[9,19]. In its most refined form, the experiment is performed in constant lighting, humidity and temperature, and subjects are required to remain awake and to show equal activity and social interaction throughout the experimental period. In addition, food intake is by regular and equal snacks, the composition of which is regulated so that the total 24-h intake is approximately normal.

Clearly, sleep and wakefulness cannot be measured under these circumstances. However, it is possible to assess fatigue and the assumption is that fatigue assesses the requirement of the body for sleep and the ease of falling asleep. One study which fulfilled many of these requirements lasted just under 3 days and used army personnel[9]. The results are shown in figure 1. Not surprizingly, although the general trend was for fatigue to increase throughout, in addition there was a superimposed rhythmicity which peaked during the night and was at a minimum during the day.

2. Sleep at abnormal times

Several groups have investigated the ability of subjects to sleep at abnormal times[1,2,11,39]. There are the general findings that to fall asleep in the hours immediately before noon (07.00–11.00 h) is difficult and that sleeps started then tend to be short. Also, sleep onset is easiest at about 04.00 and sleep duration is longest when started at about 19.00 h. Note that this last finding argues against the effect being wholly due to prior wakefulness since, in that case, the best time would have been after 19.00 h. It has also been found that if people are woken from their sleep for 15 min, then the time taken to get back to sleep is not constant at different times of the nychthemeron[35]. In these experiments, rhythmicity is not due to external factors, noise etc., since these were controlled.

After a time-zone transition there is a sudden change in the external environment as the traveller is exposed to the new local time. For some days after the flight, often in spite of having lost sleep, the traveller has difficulty in sleeping at the new local night-time. In addition, at certain times of the day (late afternoon after a westward flight, morning after one to the east), fatigue is marked. The explanation is that the internal clock is still 'registering' the old time so that fatigue is expressed during the old night-time and there is difficulty in sleeping at the former day-time[14].

3. Sleep under free-running conditions

Subjects can be placed in environments in which there are no cues as to real time. Environments that have been used are caves and specially-constructed isolation units[10,18,41,44]. In such circumstances, subjects do not become arrythmic; instead they continue to show a rhythmic pattern of sleeping, waking, mealtimes, as well as of body temperature, urinary excretion, etc. all of which 'run slow' with a period in excess of 24 h. This, of course, was the classical way of demonstrating an endogenous clock with a circadian (circa – about: diem – day) period. More recently a major study upon over 150 subjects has enabled many properties of the rest-activity cycle to be determined[44].

A major factor is its reliability with a period of 25.0 ± 0.5 h (mean $\pm$ SD). However, the major labora-

tory studies have all found various irregularities in a proportion of subjects: on occasion these develop after some days in isolation, but at other times they are observed at the onset of the experiment[12,18,41,44].

4. *Sleep on non-24-h schedules*

When pilots are involved in long-haul flights around the globe their duty schedules can become irregular[30,33,34]. In some cases, sleep times do not become equally irregular (fig. 2). Part of the sleep is taken as a nap before or after a flight, but there is also a tendency for sleep to be taken progressively later (free-running rhythm?) even though this might not coincide with local night. In cases where performance decrement due to sleep fatigue is to be avoided, hypnotics have been recommended as a counter-measure[31,32].

A schedule which, though often difficult to carry out, gives valuable information is that involving subjects living on days of abnormal length. In this, subjects shielded from real time cues are required to follow watches that run at the wrong speed, so that real and local days do not coincide. In the experiment shown in figure 3, a 21-h clock was stopped after 4 whole days by local time but, in reality, only 3½ days – that is when local and real time were 12 h out of phase. At this point the subject was asked to continue the experiment by estimating time 'as well as you can'. For some days after the clock was stopped, the activity cycle continued to advance with a period close to 21-h as though some internal clock or oscillator (that had previously adjusted by the experimental clock) was continuing to run[24].

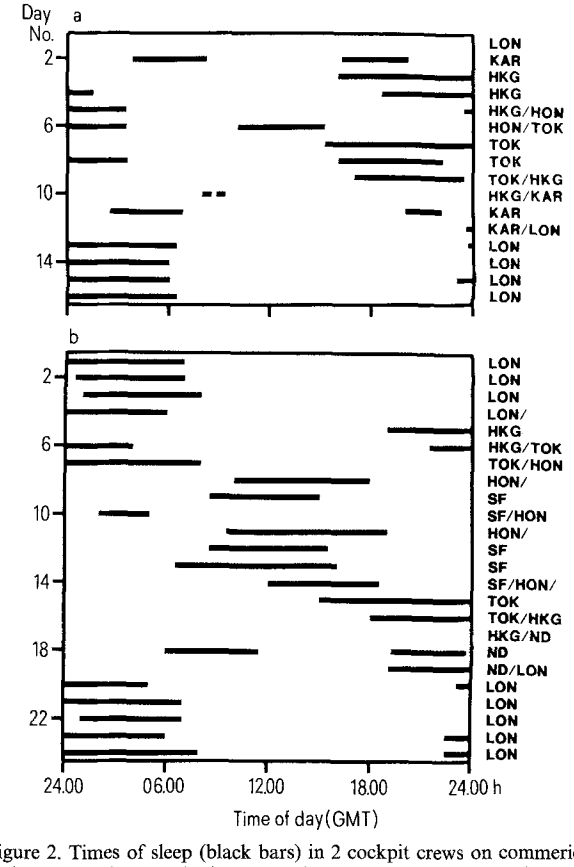

Figure 2. Times of sleep (black bars) in 2 cockpit crews on commerical flights. The right of each plot shows the city of residence on each day. A slash indicates days on which flights were made. (LON, London; KAR, Karachi; HKG, Hong Kong; HON, Honolulu; TOK, Tokyo; SF, San Francisco; ND, New Delhi). *a* Pilot on a 12-day tour from London/Honolulu/London; *b* Pilot on Far East tour, London/San Francisco/London. Note that in *b* on the westbound flight (day 13 on) the times of sleep become progressively later. (Data of Preston[33,34]).

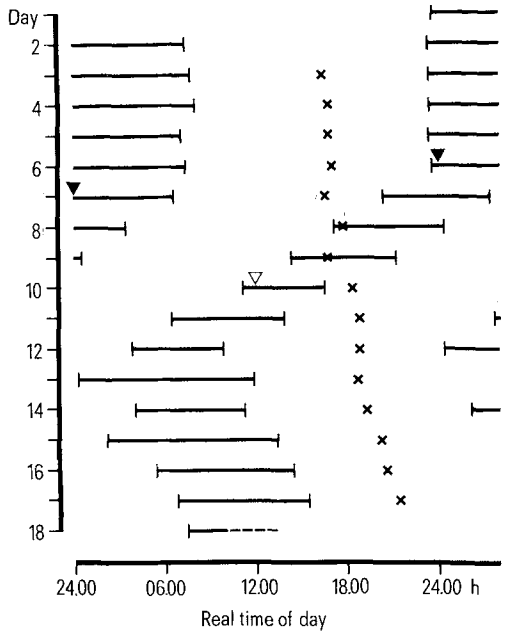

Figure 3. The sleep-wakefulness rhythm (black bars indicate time in bed) and rhythm of rectal temperature (× indicates daily acrophase) in a single female subject studied in an isolation unit. Initially, the subject lived on 24-h time but at the point marked ▼ the clock in the unit was adjusted to run fast so that when it indicated the passage of 24 h, only 21 h had actually elapsed. At the point marked ▽ the clock was stopped and the subject allowed to free-run. For clarity, the time scale represents over 24 h. (From Minors and Waterhouse[24]).

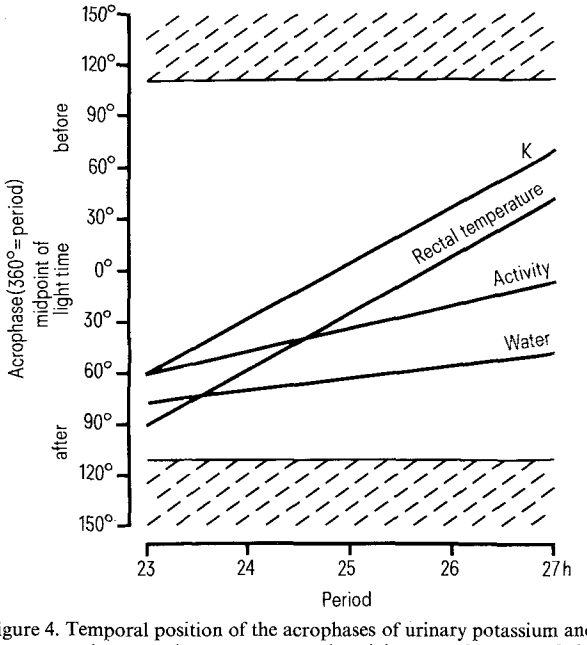

Figure 4. Temporal position of the acrophases of urinary potassium and water excretion, rectal temperature and activity as a function of the period of the light-dark cycle. Acrophases expressed relative to the middle of the light time. Data from 6 subjects with 13 light-dark cycle periods. Hatched area represents dark time. (From Wever[42], fig. 5).

In other experiments (fig. 4) the phasing of the rhythm relative to imposed light-dark cycles of different lengths was investigated[42]. If the rhythm were determined wholly by the external cycles, then its phasing would not change relative to it, for example, always at 'lights-on' or in the middle of the light time. The results indicate that relative phasing of activity varies with the imposed period.

5. *The development of rhythms during infancy*

Data from studies investigating the development of rhythmicity during infancy imply the presence of an internal oscillator controlling the activity cycle[23]. Figure 5 shows the development of the rhythm of sleep and wakefulness over the course of the first 6 months of life[15]. The child was demand-fed and lived in an environment in which there was an alternation of light and dark. The observations, that sleeps were 'appropriately' phased during the night by about the 17th week of life and that they were distributed randomly up to week 10, do not enable a decision to be made as to whether the circadian rhythmicity was due to an internal oscillator or external factors. However, the observation that activity rhythms with a period in excess of 24 h were present from weeks 10–17 does suggest than an internal component, not yet entrained to the nychthemeron, was present.

6. *An oscillator model of activity*

All these results can be explained more easily if it is postulated that the alternation between sleep and wakefulness depends partly upon some internal oscillator.

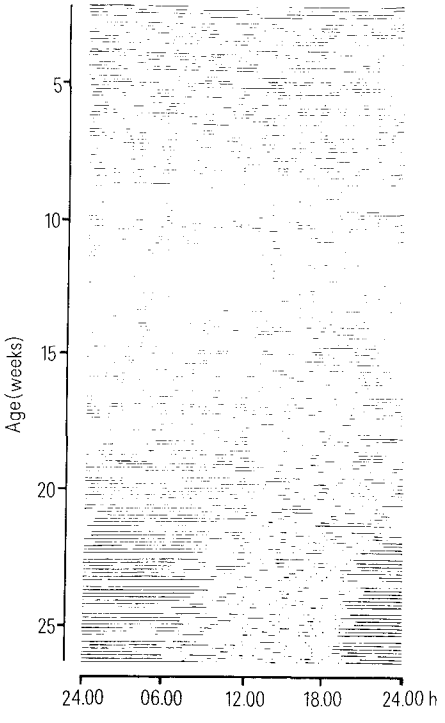

Figure 5. The distribution of sleep (black bars) and wakefulness in an infant from the 4th to 182nd day of life. Dots indicate feeds. (From Kleitman and Engelmann[15], fig. 3).

This idea has been developed by Aschoff and his colleagues[5,42,45]. They investigated the relationship between sleep length and prior wakefulness in a number of species, including man. The intuitive result – that long periods of wakefulness would be succeeded by long periods of sleep – was not borne out by their data. Instead, an inverse relationship was found. This fits in better with the view that the alternation between sleep and wakefulness is determined by an oscillator. Thus, if the oscillator were responsible for causing waking to occur at a certain time each day, then a late night would be followed by a short sleep and an early sleep onset would be followed by a sleep that was longer than average. Even though data in favor of this view were found by Aschoff et al. from their own studies, data from a more recent study upon free-running subjects did not support it[8,41].

Are the activity and body temperature rhythms independent?

So far we have described the experimental protocols and some of the data that suggest that sleep and wakefulness are determined by an internal oscillator. Such an approach has been used to indicate that almost any biological variable had some degree of endogenous rhythmicity! Now a basic knowledge of human physiology suggests that many variables influence each other. Thus, it would not be surprising to learn that the circadian rhythms of excretion of sodium and chloride are closely linked[17]. Other links are, perhaps, not as obvious. Thus, a relationship between the timing of rhythms or airway resistance and blood eosinophil counts might exist since both are influenced to some extent by plasma cortisol levels. However, the phase-locking between the two rhythms need not be strong since each is affected by other factors.

This concept of a nexus between different rhythms has been discussed elsewhere in more detail[22,27,29]. The circadian rhythm of body temperature, in particular, effects many other circadian rhythmicities including that in activity as will be considered later. An implication of this is that many of the observations already cited in favor of sleep and wakefulness being due to an oscillator would occur also if sleep and wakefulness were a consequence of the temperature rhythm. In order to establish that activity is produced by an oscillator different from that for body temperature, it becomes necessary to investigate if there is any independence between the two rhythms.

This can be approached in a number of ways: what these ways have in common is that each is an attempt to change the timing of the two rhythms by different amounts, thereby showing that neither can be wholly responsible for the other.

After shifts in external rhythms (as after time-zone transition when all shift by the same amount, or during shiftwork when only some change), it is possible to investigate whether the rhythms adjust at different rates. This has proved useful for many cases (e.g. urinary functions, plasma cortisol, deep body temperature) but is far less so for the sleep-wakefulness rhythm[6,7,40]. This is because most subjects consciously change their

activity pattern to accord with new local time or a new shift, thereby over-riding any effect that an oscillator controlling this variable might have.

In the time-free environments of caves and isolation units, it has often been found that various anomalies of the sleep-wakefulness cycle occur. Figure 6 shows data from Chabert, a volunteer who spent 4 months in isolation in a cave[12]. The periods marked i and ii in this figure show anomalies of the sleep-wakefulness cycle and similar anomalies have been observed in isolation unit experiments also[8, 18, 41, 44]. What many of these anomalies share is that activity continues to behave rhythmically, but no longer with a circadian period. Thus, rhythmicity can be an alternation of long and short sleeps 180° out of phase (i in fig. 6) or a period of about 50 h (ii in fig. 6). Importantly, at the same time, the temperature rhythm continues to show circadian rhythmicity.

An even more convincing independence between the two rhythms can be seen in cases of spontaneous internal desynchronization (fig. 7, days 16 onwards)[43]. In this the sleep-wake and temperature rhythms take up different periods. This phenomenon is generally believed to provide same of the strongest evidence that more than one endogenous rhythmic influence can affect the body. Normally, the two oscillators controlling activity and temperature are coupled but uncouple spontaneously in about one-third of cases[44]. When this has happened, the sleep-wakefulness rhythm shows a period of about 33 h, and that of deep body temperature decreases by about 0.5 h when compared with the value when the rhythms were synchronized (fig. 7). (Sometimes the activity period shortens to about 16 h: in these cases the temperature rhythm lengthens by about 0.5 h). These results are interpreted to mean that the free-running period observed in subjects with internally synchronized rhythms is a compromise between the different periods of two oscillators: it is a period far closer to that of the temperature oscillator since the former is considerably (about 9 times) stronger than the latter.

Recently, attempts have been made to model the human circadian system[13, 16]. In these models, two or more oscillators (with properties believed to mimic those of the temperature and activity oscillators in man) are coupled and the output from such a system is computed after it has been exposed to simulated time-zone shifts, non-24-h days etc. Certainly, the results are impressively similar to those from real studies upon humans: the problem is to know how closely the components of the model, and their interaction, mimic the situation in vivo.

The concept that different oscillators have different strengths, implies that they might be differently affected by rhythmic external influences (zeitgebers). Thus, the

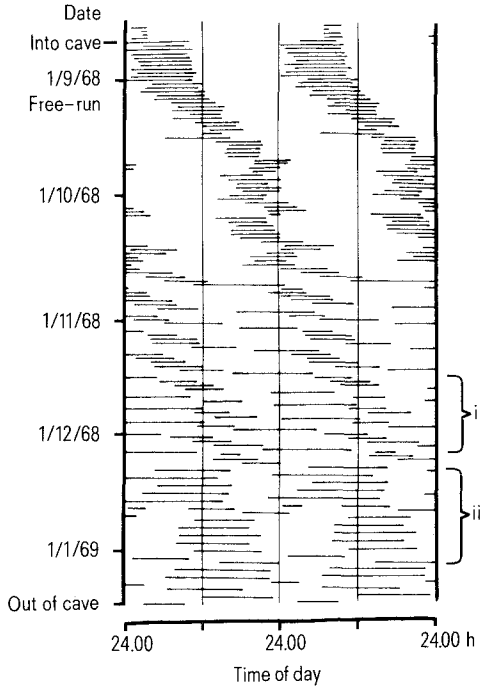

Figure 6. The rhythm of sleep (black) and activity (white) in Chabert during 4 months' temporal isolation in a cave. The periods marked i and ii correspond to the anomalies described in the text. See text for further details. (Data of Jouvet et al.[12]).

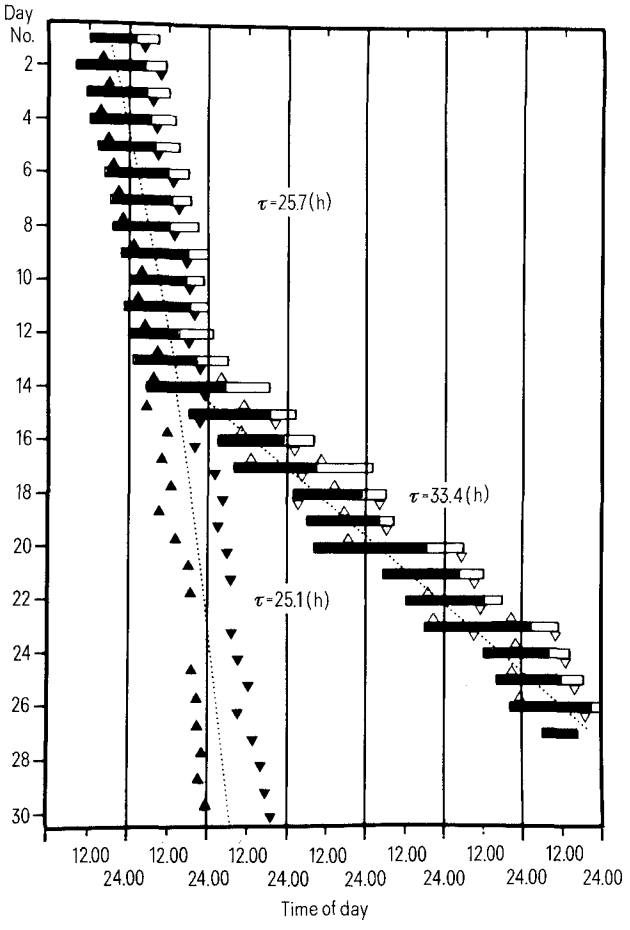

Figure 7. Circadian rhythms of wakefulness and sleep (black and white bars respectively) and of rectal temperature (▲ maxima, ▼ minima) in a subject who lived alone in an isolation unit without indication of the time of day. Successive days are plotted from above downwards. From days 1 through to 14 the subject is internally synchronized with the two rhythms showing similar periods (25.7 h). At day 15 spontaneous desynchronization takes place so that hereafter the two rhythms show different periods (rectal temperature 25.1 h: sleep-wakefulness 33.4 h). Open triangles show temporally corrected positions of temperature, maxima and minima represented by corresponding black triangles. (From Wever[43], fig. 7).

stronger the oscillator the less will it be adjusted by the zeitgeber and the smaller will be its range of entrainment. These are implications that can be tested. Thus, first, figure 4 shows that changed zeitgeber periods have a marked effect upon the activity rhythm (whose phase therefore changes little) and a much lesser effect upon the temperature rhythm (whose phase changes much more). This result confirms that the two oscillators are of different strengths. (Strictly, the same result could be obtained if the two rhythms were influenced to different extents by a single oscillator, but the present result is to be interpreted against the background provided by the spontaneous internal desynchronization result, already described).

Secondly, one can attempt to adjust the different rhythms to zeitgeber periods deviating progressively more from 24 h. The work so far reported[44] indicates that the temperature oscillator cannot adjust to zeitgeber periods in excess of about 27.5 h and that the oscillator concerned with activity cannot adjust to a period above about 35 h. Figure 3 shows results from an experiment in which a zeitgeber of 21 h was used (beyond the range of entrainment of the temperature oscillator). Until day 10, the sleep-wakefulness rhythm was imposed upon the subject by the experimental protocol but thereafter the subject was free to choose her habits. It will be noted that, from days 10–13, the activity rhythm continued with a 21-h period independent of the temperature rhythm. This not only implies the presence of more than one oscillator but also that the activity oscillator alone had been entrained to the 21 h day. By day 14, the two rhythms were again in phase, and thereafter the activity rhythm followed that in temperature; this last result suggests again that the temperature oscillator is stronger than that causing the rhythm in activity[24].

Finally, if more than one oscillator exists, it might be possible by manipulation of some of the zeitgebers to affect the different oscillators differentially. Much work along these lines has been performed upon the squirrel monkey by Moore-Ede and his colleagues[28, 29, 36, 38]. However, the work on humans is extremely scarce. An experiment which demonstrates this technique has been reported by Wever[44]. A subject was given a 24-h light: dark zeitgeber and he showed internal desynchronization with an activity period of 33 h and a temperature period of 24 h. This was interpreted to indicate that the temperature oscillator was entrained at a time when the activity rhythm was not. Note that the reciprocal result – that the activity but not the temperature rhythm had been entrained – would not provide such strong evidence for the presence of separate activity and temperature oscillators. In such a case, the activity might have been imposed by the light-dark schedule rather than result from an entrained oscillator controlling activity.

Interaction between activity and temperature

Even though the circadian rhythms of activity and temperature can be separated, they are normally coupled to each other; recent interest has been shown in attempts to assess the extent to which the temperature rhythm influences that of activity. As has already been mentioned, it has been found that not only the time it takes to fall asleep, but also the duration of sleep, depends upon the temperature cycle[46, 47, 48]. Thus, to get to sleep when body temperature is rising or high is difficult and sleep duration is longest when sleep onset coincides with a falling deep body temperature. These points will be discussed further in a later paper in this volume.

Such results cannot be interpreted only as a direct effect of temperature upon activity since they might be due instead to an effect upon the activity oscillator. The normal 'trapping' of this oscillator by temperature has already been discussed and can be seen on days 13+ in figure 3. However, a direct effect of temperature can be inferred from free-running experiments showing spontaneous internal dissociation (fig. 7) or other irregularities (fig. 6). In these, a component of activity shows a period equal to that of the temperature rhythm and is appropriately phased: that is, activity decreases and 'naps' are most likely to take place whenever the temperature rhythm is at its nadir[44].

The interaction between activity and temperature rhythm is a two-way process; activity has a direct effect upon the body temperature and there is also some evidence that the activity rhythm can entrain that of temperature.

Sleep directly depresses body temperature by about 0.2 °C and this effect has been called 'masking'[3, 4, 20, 41]. An implication of masking (which is by no means confined to the temperature rhythm) is that when rhythms are measured nychthemerally, that is when sleep is allowed, they might not reflect accurately the internal oscillator. Thus, after time-zone transition experiments, the rates of adaptation often reported might be over-estimates[6]. More accurate estimates of the rate of adaptation can be obtained by removing masking effects by placing subjects on a constant routine. Results indicate not only that rates of adjustment might be slower than once thought but also that adjustment to an eastward shift (when local time is advanced) takes place by a delay of the internal clock more often than was once supposed[19]. So far, adjustment to shift work has been studied under nychthemeral conditions only.

Finally, there is some evidence that regular sleep patterns can entrain a free-running temperature rhythm. When subjects were placed on irregular sleep-wakefulness schedules, their urinary and deep body temperature rhythms demonstrated a period greater than 24 h[21, 25]. When measured under nychthemeral conditions, rhythms could be stabilized to a 24-h period by taking 4-h sleeps ('anchor' sleeps) at the same time each day despite a second 4-h sleep being taken at an irregular time. Measured this way, the stability could have been an artefact due to the masking produced by the regular anchor sleep. That is, regular sleeps would produce regular falls in a variable and this would produce what appeared to be a stable circadian rhythm independent of what was happening to the internal oscillators. These internal oscillators were assessed more directly by measuring the circadian rhythms under constant routine conditions. When this was done, two endogenous components to the temperature rhythm were found; one of these had been stabilized by the anchor sleeps[26].

1 Åkerstedt, T., and Gillberg, M., The circadian variation of experimentally displaced sleep. Sleep *4* (1981) 159–169.
2 Åkerstedt, T., and Gillberg, M., The circadian pattern of unrestricted sleep and its relation to body temperature, hormones and alertness, in: Biological Rhythms, Sleep and Shift Work, pp. 481–498. Eds L.C. Johnson, D.I. Tepas, W.P. Colquhoun and M.J. Colligan. MTP, Lancaster 1981.
3 Aschoff, J., Features of circadian rhythms relevant for the design of shift schedules. Ergonomics *21* (1978) 739–754.
4 Aschoff, J., Circadian rhythms: interference with and dependence on work-rest schedules, in: Biological Rhythms, Sleep and Shift Work, pp. 11–34. Eds L.C. Johnson, D.T. Tepas, W.P. Colquhoun and M.J. Colligan. MTP, Lancaster 1981.
5 Aschoff, J., Gerecke, U., Kureck, A., Pohl, H., Rieger, P., v Saint Paul, U., and Wever, R., Independent parameters of circadian activity rhythms in birds and man, in: Biochronometry, pp. 3–27. Ed. M. Menaker. Natl Acad. Sci., Washington D.C. 1971.
6 Aschoff, J., Hoffman, K., Pohl, H., and Wever, R., Re-entrainment of circadian rhythms after phase-shifts of the zeitgeber. Chronobiologia *2* (1975) 23–78.
7 Chaumont, A.-J., Laporte, A., Nicolai, A., and Reinberg, A., Adjustment of shift workers to a weekly rotation (Study 1). Chronobiologia, suppl. 1 (1979) 27–34.
8 Czeisler, C.A., Weitzman, E.D., Moore-Ede, M.C., Zimmerman, J.C., and Knauer, R.S., Human sleep: its duration and organization depend on its circadian phase. Science *210* (1980) 1264–1267.
9 Fröberg, J., Karlsson, C.-G., Levi, L., and Lidbeg, L., Circadian variations in performance, psychological ratings, catecholamine excretion and diuresis during prolonged sleep deprivation. Int. J. Psychobiol. *2* (1972) 23–36.
10 Halberg, F., Reinberg, A., Haus, E., Ghata, J., and Siffre, M., Human biological rhythms during and after several months of isolation underground in natural caves. Bull. nat. speleological Soc. *32* (1970) 89–115.
11 Johnson, L.C., On varying work/sleep schedules: issues and perspectives as seen by a sleep researcher, in: Biological Rhythms, Sleep and Shift Work, pp. 335–346. Eds L.C. Johnson, D.I. Tepas, W.P. Colquhoun and M.J. Colligan. MTP, Lancaster 1981.
12 Jouvet, M., Mouret, J., Chouvet, G., and Siffre, M., Towards a 48-hour day: experimental bicircadian rhythm in man, in: Circadian Oscillators and Organisation in Nervous Systems, pp. 491–497. Ed. C.S. Pittendrigh. MIT, Cambridge, Massachussetts 1975.
13 Kawato, M., Fujita, K., Suzuki, R., and Winfree, A.T., A three-oscillator model of the human circadian system controlling the core temperature rhythms and the sleep-wake cycle. J. theor. Biol. *98* (1982) 369–392.
14 Klein, K.E., and Wegmann, H.-M., Circadian rhythms in air operations, in: Sleep, Wakefulness and Circadian Rhythm, AGARD Lecture series No. 105, chapt. 10. AGARD 1979.
15 Kleitman, N., and Engelmann, T.G., Sleep characteristics of infants. J. appl. Physiol. *6* (1953) 269–282.
16 Kronauer, R.E., Czeisler, C.A., Pilato, S.F., Moore-Ede, M.C., and Weitzman, E.D., Mathematical model of the human circadian system with two interacting oscillators. Am. J. Physiol. *242* (1982) R3-R17.
17 Mills, J.N., Phase relations between components of human circadian rhythms, in: Chronobiology, pp. 560–563. Eds E. Scheving, F. Halberg and J.E. Pauly. Igaku Shoin, Tokyo 1974.
18 Mills, J.N., Minors, D.S., and Waterhouse, J.M., The circadian rhythms of human subjects without timepieces or indication of the alternation of day and night. J. Physiol. *240* (1974) 567–594.
19 Mills, J.N., Minors, D.S., and Waterhouse, J.M., Adaptation to abrupt time shifts of the oscillator(s) controlling human circadian rhythms. J. Physiol. *285* (1978) 455–470.
20 Mills, J.N., Minors, D.S., and Waterhouse, J.M., The effect of sleep upon human circadian rhythms. Chronobiologia *5* (1978) 14–27.
21 Minors, D.S., and Waterhouse, J.M., Anchor sleep as a synchronizer of rhythms on abnormal schedules. Int. J. Chronobiol. *7* (1980) 165–188.
22 Minors, D.S., and Waterhouse, J.M., Circadian Rhythms and the Human. Wright. P.S.G., Bristol 1981.
23 Minors, D.S., and Waterhouse, J.M., Development of circadian rhythms in infancy, in: Scientific Foundations of Paediatrics, 2nd edn. Eds J.A. Davis and J. Dobbing. Heinemann, London 1981.
24 Minors, D.S., and Waterhouse, J.M., Endogenous and exogenous components of circadian rhythms when living on a 21-h day. Int. J. Chronobiol. *8* (1981) 31–48.
25 Minors, D.S., and Waterhouse, J.M., Anchor sleep as a synchronizer on abnormal routines, in: Biological Rhythms, Sleep and Shift Work, pp. 399–414. Eds L.C. Johnson, D.I. Tepas, W.P. Colquhoun and M.J. Colligan. MTP, Lancaster 1981.
26 Minors, D.S., and Waterhouse, J.M., Does 'anchor sleep' entrain the internal clock(s)? Evidence from constant routine studies. J. Physiol. *345* (1983) 451–467.
27 Moore-Ede, M.C., Schmelzer, W.S., Kass, D.A., and Herd, J.A., Internal organization of the circadian timing system in multicellular animals. Fedn Proc. *35* (1976) 2333–2338.
28 Moore-Ede, M.C., and Sulzman, F.M:, Internal Temporal Order, in: Handbook of Behavioural Neurobiology, vol. 4, pp. 215–241. Ed. J. Aschoff. Plenum, New York 1981.
29 Moore-Ede, M.C., Sulzman, F.M., and Fuller, C.A., The clocks that time us. Harvard University, Cambridge, Mass., and London 1982.
30 Nicholson, A.N., Sleep patterns of an airline pilot operating world-wide east-west routes. Aerospace Med. *41* (1970) 626–632.
31 Nicholson, A.N., and Stone, B.M., Hypnotics and shift work, in: Biological Rhythms, Sleep and Shift Work, pp. 383–398. Eds L.C. Johnson, D.I., Tepas, W.P. Colquhoun and M.J. Colligan. MTP, Lancaster 1981.
32 Nicholson, A.N., and Stone, B.M., Sleep and Wakefulness Handbook for Flight Medical Officers, chapt. 8: Hypnotics. AGARD 270 (E). 1982.
33 Preston, F.S., Time zone disruption and sleep patterns in pilots. Trans. Soc. occup. Med. *20* (1970) 77–86.
34 Preston, F.S., Further sleep problems in airline pilots on world-wide schedules. Aerospace Med. *44* (1973) 775–782.
35 Richardson, G.S., Carskadon, A., Orav, E.J., and Dement, W.C., Circadian variation of sleep tendency in elderly and young adult subjects. Sleep *5* (1982) 82–94.
36 Moore-Ede, M., Sulzman, F.M., and Fuller, C.A., Circadian organization in the squirrel monkey: the internal coupling between oscillators, in: Biological Rhythms and their Central Mechanisms, pp. 405–419. Eds M. Suda, O. Hayaishi and H. Nakagawa. Elsevier, Amsterdam 1979.
37 Sulzman, F.M., Fuller, C.A., Hiles, L.G., and Moore-Ede, M.C., Circadian rhythm dissociation in an environment with conflicting temporal information. Am. J. Physiol. *235* (1978) R175–R180.
38 Sulzman, F.M., Fuller, C.A., and Moore-Ede, M.C., Comparison of synchronization of primate circadian rhythms by light and food. Am. J. Physiol. *234* (1978) R130–R135.
39 Taub, J.M., and Berger, R.J., Sleep stage patterns associated with acute shifts in the sleep-wakefulness cycle. Electroenceph. clin. Neurophysiol. *35* (1973) 613–619.
40 Vieux, N., Ghata, J., Laporte, A., Migraine, C., Nicolai, A., and Reinberg, A., Adjustment of shift workers adhering to a three- to four-day rotation (Study 2). Chronobiologia, suppl. 1 (1979) 37–42.
41 Weitzman, E.D., Czeisler, C.A., and Moore-Ede, M.C., Sleep-wake, neuroendocrine and body temperature circadian rhythms under entrained and non-entrained (free-running) conditions in man, in: Biological Rhythms and their Central Mechanism, pp. 199–227. Eds M. Suda, O. Hayaishi and H. Nakagawa. Elsevier, Amsterdam 1979.
42 Wever, R., Mutual relations between different physiological functions in circadian rhythms in man. J. interdisc. Cycle Res. *3* (1972) 253–265.
43 Wever, R., The circadian multi-oscillator system of man. Int. J. Chronobiol. *3* (1975) 19–55.
44 Wever, R.A., The Circadian System of Man. Results of Experiments under Temporal Isolation. Springer, New York/Heidelberg/Berlin 1979.
45 Wever, R.A., On varying work-sleep schedules: the biological rhythm perspective, in: Biological Rhythms, Sleep and Shift Work, pp. 35–60. Eds L.C. Johnson, D.I. Tepas, W.P. Colquhoun and M.J. Colligan. MTP, Lancaster 1981.
46 Winfree, A.T., Human body clocks and the timing of sleep. Nature *297* (1982) 23–27.
47 Winfree, A.T., Circadian timing of sleepiness in man and woman. Am. J. Physiol. *243* (1982) R193–R204.
48 Zulley, J., Wever, R., and Aschoff, J., The dependence of onset and duration of sleep on the circadian rhythm of rectal temperature. Pflügers Arch. *391* (1981) 314–318.

0014-4754/84/050410-07$1.50 + 0.20/0