Desynchronization and Resynchronization of Human Circadian Rhythms

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Circadian rhythms of activity, of body temperature and of urine excretion have been measured in human subjects, kept in isolation in an underground bunker, either in constant conditions or exposed to artificial light-dark cycles as Zeitgebers. In constant conditions, free-running rhythms synchronous in all functions have been demonstrated as well as cases with internal desynchronization. Entrainment to an artificial 26.7-hour day resulted in changes of phase-angle differences as to be predicted from oscillation theory, whereas exposure to a 22.7-hour resulted in resynchronization from the Zeitgeber. A group of four subjects showed, in constant conditions, synchronous circadian rhythms during the first 10 days, thereafter desynchronization between one subject and the rest of the group. Shifts of the artificial light-dark cycle by 6 hours were followed by the activity-cycles of the subjects rather immediately; the rhythms of body temperature, however, did not regain their normal phases until several days had elapsed.

IN BIOLOGY as well as in medicine increasing attention is being paid to the fact that there is strong temporal order in all living systems.[10,21] The diurnal rhythms provide the most intensively studied examples. They have been described on all levels of organization, from biochemical reactions in the cell up to behavioral patterns of primates. In man, more than 100 functions and structural elements could be named which oscillate between maximal and minimal values once a day. They range from the well known rhythm in deep body temperature to rhythms in mood and in mental performance.[16,20]

As has been shown experimentally, diurnal rhythms are based on endogenous, self-sustained oscillations.[1,7] Under constant conditions, the rhythm continues with its own natural frequency. The period of such a "free running" rhythm deviates more or less from that of the earth's rotation, i. e. from 24 hours. This is indicated by the term "circadian," as introduced by Halberg.[15] Under natural conditions, circadian rhythms are entrained to 24 hours by the synchronizing effects of periodic factors in the environment, called Zeitgebers. Using artificial Zeitgebers, e.g. an artificial light-dark cycle, it is possible to entrain a circadian rhythm to periods other than 24 hours (within some limits). In this case as well as in the case of a constant environment, the circadian system becomes desynchronized from the periodicity of its natural environment: *external desynchronization*. In contrast to this, *internal desynchronization* means that several rhythmic functions within the organism show different periods. Finally, a phase-shift of an artificial Zeitgeber against local time—or a sudden transfer of the organism in westward or eastward direction—may be considered as a type of transient external desynchronization which usually is accompanied by internal desynchronization during a few days. For all three types of desynchronization, experimental evidence is given below.

EXTERNAL DESYNCHRONIZATION

Constant Conditions—In order to demonstrate free running circadian rhythms in man, it is necessary to exclude from the experimental chamber external cues from which a notion of true time could be derived. In this regard, especial care has to be taken about all kinds of noise. At our institute, an underground bunker containing two separate apartments with kitchen and toilet has been in use for several years.[6] When enclosed there in complete isolation and without a time-telling device, a subject continues to show rhythms in wakefulness and sleep as well as in other functions such as urine excretion and body temperature. As can be seen from the black bars on the upper margin of Figure 1, the sleep times drift steadily towards later hours each day (c.f. the change in position with regard to midnight as indicated by the vertical lines). The subject has a clear circadian period of more than 24 hours. Concurrent with each activity-time (white bars on the upper margin), there is a maximum in body temperature and a maximum in urinary excretion of potassium, sodium and water. This means: Although desynchronized from the natural day-night cycle, the organism is internally still synchronized, all functions showing the same circadian

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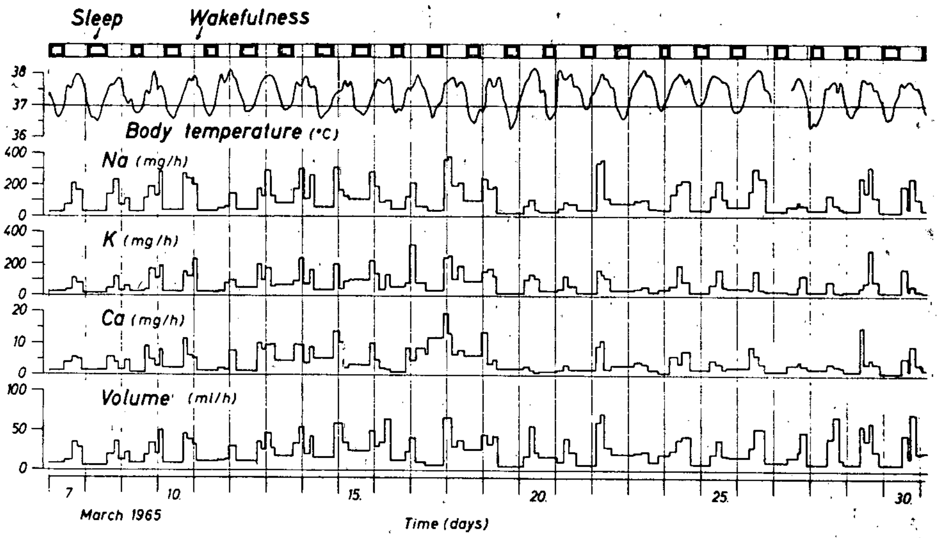

Fig. 1. Free-running circadian rhythms in a human subject, enclosed for 24 days in an underground bunker without time cues. The four curves from below give the urinary excretion of water, calcium, potassium and sodium respectively. Vertical lines drawn at midnight (From 11).

period of about 24.9 hours.[11]

The deviation of the circadian period from 24 hours becomes more conspicuous in Figure 2 where data of a second experiment are presented in another manner. The horizontal continuous lines represent the time spans when the subject is out of bed (activity-time), the dotted lines the following time spans in bed (rest- or sleep-times). Open circles indicate the minima of rectal temperature. The first 6 days show the behavior under normal conditions outside the bunker. The subject is enclosed into the bunker at the 7th day at 16:00. For the first few days in isolation, the period is still close to 24 hours. However, after 8 days of bunker life, the activity- and sleep-times as well as the minima of body temperature drift towards later hours each day. At the 17th day of isolation, the subject awakes at 2:00 in the morning, having "lost" nearly one day. When he then is released from the bunker, he is out of phase with local time by about 6 hours. This difference is nearly fully corrected already the following day with regard to the activity cycle. Body temperature, however, regains its normal phase (i.e. minimum at about 5:00) not until the 8th day after the subject has left the bunker.

The continuation of internal synchronization during a state of external desynchronization does not imply that the "phase-map" describing the phase-relationship between different rhythmic functions,[2] remains unchanged. On the contrary, both Figure 1 and Figure 2 indicate that the free running circadian system is characterized by a minimum of body temperature which coincides with the beginning of sleep-time whereas in the entrained organism the minimum of body temperature occurs rather towards the end of sleep-time. Systematic changes in the internal phase-relationship of this kind have been observed in more than 50 subjects studied so far; they already suggest that the rhythms of body temperature and of activity may be looked upon as separate oscillators.[12]

Entrainment to Odd Days—By using artificial light-dark cycles (including dawn and dusk twilights), it is possible to entrain subjects in the bunker to non-24-hour periods.[13] An example is given in Figure 3. For the first 8 days, the subject is exposed to a 24-hour day with 15 hours of light and 9 hours of darkness. Obviously, the subject belongs to the group of "late risers," showing a large negative phase-angle difference between his awakening time (onset of horizontal continuous lines) and light-on. The minimum of body temperature (open circles) occurs after the middle of sleep-time (dotted lines). From the 9th day on, the light is turned on and off each day 2.7 hours later; the Zeitgeber period therefore is now 26.7 hours. As a response, the subject reduces his negative phase-angle difference to the Zeitgeber continuously until

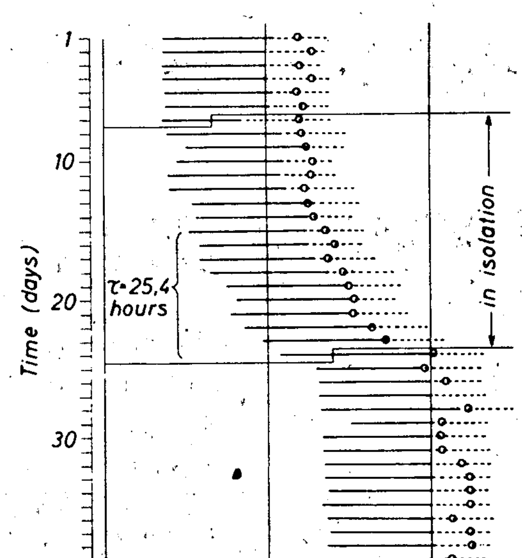

Fig. 2. Circadian rhythms in a subject living, first, under natural conditions, then for 17 days in isolation underground, and finally again under natural conditions. Subsequent days drawn underneath each other. Horizontal continuous lines: wakefulness. Dotted lines: sleep. Open circles: minima of body temperature. τ = circadian period.

he eventually awakes at or even before the time of light-on. The diagram also demonstrates that the minima of body temperature become advanced relative to the activity-cycle, eventually coinciding with the end of activity-time rather than with the end of sleep-time. In other words: Both the external as well as the internal phase-relationships are influenced by a change of the Zeitgeber period.

At day 23, the Zeitgeber with a normal period of 24 hours is re-introduced. In contrast to the first change from a 24-hour to a 26.7-hour period which has not been perceived by the subject, this return to a normal period gives the subject the sensation of a change in conditions. Nevertheless, he does not readjust himself immediately. As can be seen from the minima of body temperature, a normal phase-relationship is not regained even after 11 days.

The experiment is concluded with the introduction of a light-dark cycle the period of which is 22.7 hours.

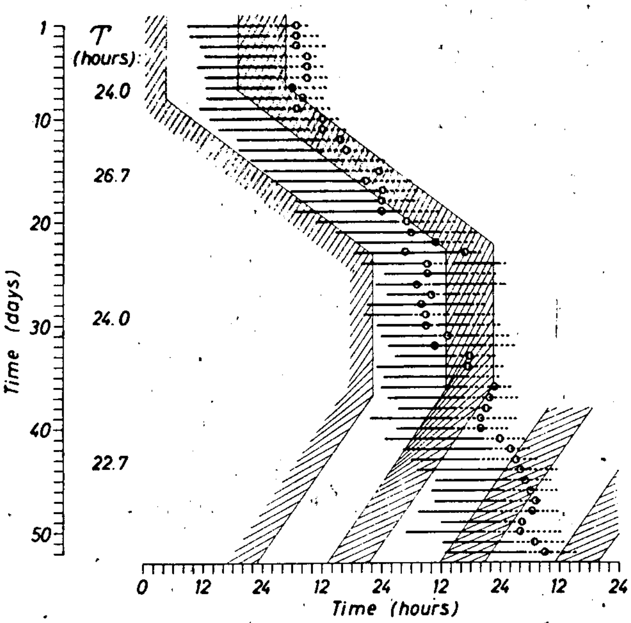

Fig. 3. Circadian rhythms in a subject, kept in isolation and exposed to an artificial light-dark cycle. T = Zeitgeber period. Shaded area: darkness. Horizontal continuous lines: wakefulness. Dotted lines: sleep. Open circles: minima of body temperature (From 13).

The diagram clearly shows that the subject does not follow this short day. He drifts away with a circadian period which, in average, is longer than 24 hours. Therefore, he is "crossing" through the Zeitgeber several times. During this part of the experiment, the remarkable point is the appearance of "relative coordination." By this term, as first used by v. Holst,[17] it is meant that there is still an influence of the Zeitgeber on the circadian system, however, the influence is not strong enough to produce entrainment. The circadian rhythm, therefore, crosses through the Zeitgeber with a varying speed. Twice, there is an obvious tendency of the rhythm to lock on to the Zeitgeber, but each time the rhythm again drifts away after a few periods.

The whole experiment shown in Figure 3 demonstrates, first, desynchronization from the natural 24-hour-period by means of an artificial Zeitgeber, and, second, desynchronization from the Zeitgeber itself. The results could partly have been predicted. The changes in phase-angle difference during entrainment to a 26.7-hour period are to be expected from oscillation theory.[3,8] The failure of entrainment to a 22.7-hour period is not too surprising in the light of the long circadian periods usually shown by human subjects when kept in constant conditions. The results are also in accordance with the findings of Lewis and Lobban[19] who, in their Spitzbergen experiment, observed that adjustment to a 27-hour day was easier and more complete than adjustment to a 21-hour day. Whether or not a subject becomes entrained by a short Zeitgeber period, depends on many factors, including the great interindividual variability of natural circadian periods. That synchronization with a 22-hour day is possible in a bunker-type experiment, has recently been demonstrated by Jenner.[18]

INTERNAL DESYNCHRONIZATION

More Than One Oscillator?—In man, when his circadian oscillator is free running under constant conditions, the phase-map does not necessarily remain synchronized. It may happen that the rhythm of body temperature and the rhythm of activity and rest have different, non-integral frequencies. An example is given in Figure 4. During the first 15 days

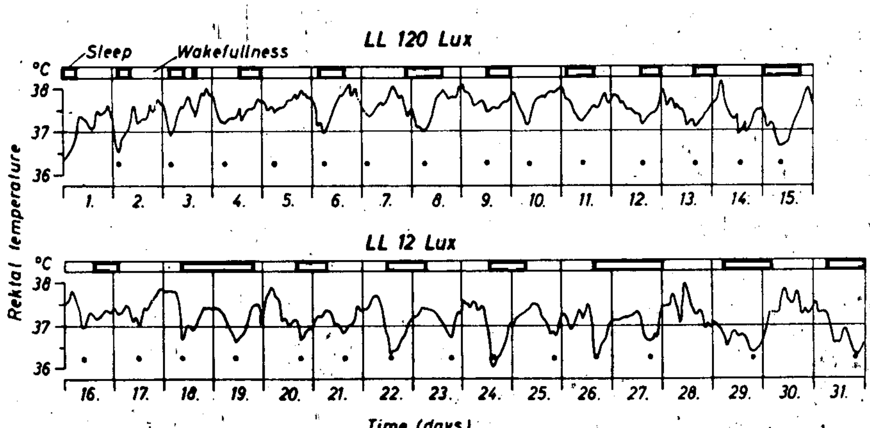

Fig. 4. Circadian rhythms of wakefulness and sleep and of rectal temperature in a subject, enclosed in isolation at two different intensities of constant illumination. Minima of body temperature as used for computations indicated by closed circles. LL: Continuous light (From 11).

of isolation, the subject shows 10 periods in wakefulness and sleep as against 14 periods in body temperature. As a consequence, the minima of body temperature sometimes occur when the subject is asleep, sometimes when the subject is awake. This continuous change in the phase-relationship between the two rhythms results in a periodic change of the temperature's amplitude, being large when the maximum coincides with activity, and being small when the maximum coincides with sleep.[11]

After 15 days of isolation, the period of the activity-cycle becomes extremely long, with sleep times up to 24 hours and more (c.f. 18./19. and 26./27. day in Figure 4). During this time, the rhythm of body temperature has still a circadian-like period which is half that of the activity cycle. This results in synchronization between the two rhythms in a 1:2-ratio: There are two minima of body temperature for one cycle in activity and rest (c.f. days 21 to 25). Such "circa-bidian" periods of activity and rest with synchronized circadian rhythms of body temperature have been observed in about 10 percent of all subjects studied so far.[24] In a few cases, those rhythms have lasted over the full course of an experiment, i.e., up to 28 days. The subjects do not realize the unusual long activity-times which can come close to 30 hours. Since they keep their normal habits with only three meals per "day," they lose weight by the pounds.

In the experiment shown in Figure 4, internal desynchronization takes place immediately after the beginning of isolation. In other cases, the subjects start to become desynchronized much later. In the example given in Figure 5, the circadian system remains internally synchronized for the first 8 days of isolation; only the phase-relationship between body temperature and activity becomes more positive as to be expected. The mean circadian period during this time is 24.9 hours, as indicated by the dashed line. Thereafter, the picture changes suddenly and without any obvious reason. The 9. activity-cycle starts with a delay, the 10. is extremely long, and the following periods are of average 33.2 hours long. The rhythm of body temperature does not follow this extreme lengthening of the activity cycle. As can be seen from the closed circles, the minima of body temperature become advanced relative to the activity-time already at day 9 and 10, and they keep thereafter a circadian Period of about 24.9 hours (The dotted circles indicate the continuous change in phase-relationship between body temperature and activity).

From these and similar results, several conclusions may be drawn: (1) The rhythm of body temperature is not a mere consequence of the rhythm in activity and rest; (2) both rhythms possibly have to be looked upon as separate oscillators; (3) the two oscillators are normally synchronized with each other in a 1:1-ratio, the phase-angle difference between them depending on the circadian period; (4) the two oscillators may also be entrained with each other in a 1:2-ratio (entrainment by demultiplication) and (5) the two oscillators may even free run with different frequencies.

It is fair to assume that temporal order as it has been developed by evolution, is a prerequisite for health and efficiency.[4] Since internal desynchronization (disorder) seems to occur in cases of external desynchronization, an environment without Zeitgebers or with improper Zeitgebers may be a hazardous one. There is also evidence that for free running circadian rhythms in man the appearance or non-appearance of desynchronization depends on several circumstances. Among these, electromagnetic fields seem to be important. As has been shown recently by Wever[24] shielding against nat-

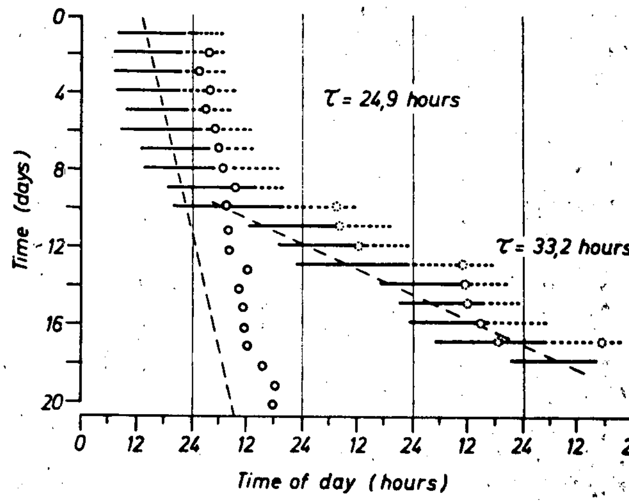

Fig. 5. Free running circadian rhythm in a human subject, enclosed in an underground bunker without time cues. Solid lines: Activity-time; dotted lines: Rest-time. Circles: Minima of body temperature, drawn twice from day 10 on in order to indicate the true circadian period (closed circles) as well as the changes in phase-relationship to the activity cycle (dotted circles).

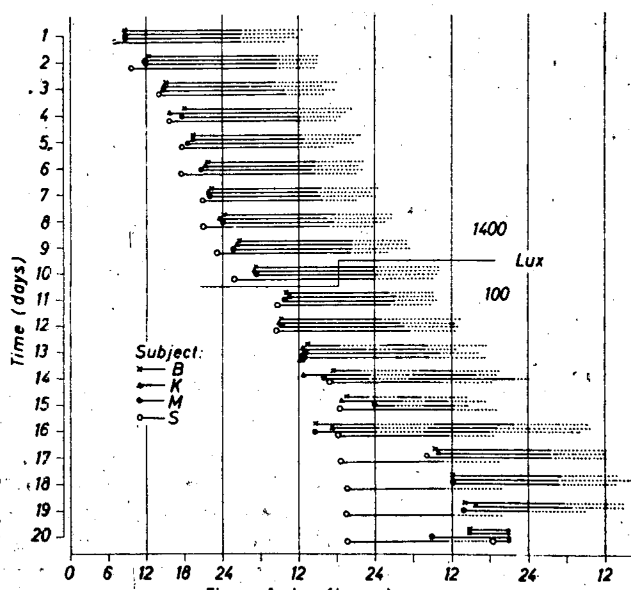

Fig. 6. Circadian rhythms in a group of four subjects, kept underground in isolation at two different intensities of illumination. Horizontal continuous lines: wakefulness. Dotted lines: sleep. (From 22).

ural electric and magnetic fields (as done in one of the two bunker apartments), presumably facilitates internal desynchronization.

Group Effects—If several subjects are enclosed in the bunker at the same time, they usually all try to keep the same circadian period. In case of two subjects, the compromise is rather easily achieved. In the case of four subjects, the situation becomes more complex. The diagram in Figure 6 gives the results of such an experiment.[22] During the first 10 days of isolation, the average circadian period of the whole group is 26.2 hours. Three members of the group are also close to each other in their times of getting up. Subject S, however, wakes up about 2 hours earlier than the rest of the group. He has, in technical terms, a leading phase or a positive phase-angle difference to the three other subjects. According to oscillation theory, this indicates that subject S may have a higher natural frequency than the rest of the group.

Two pieces of evidence support the hypothesis that subject S has a rather short natural circadian period. (a) During the first 10 days, the rhythm in urine excretion of subject S nearly disappears towards day 5, and it reappears towards day 10. A likely explanation for this phenomenon is that subject S has a rhythm of urine excretion the period of which is shorter than that of the activity-cycle and which has not become entrained to the rather long period of the group's activity-cycle. The rhythm of urine excretion, therefore, shows a beat-phenomenon, being first in phase, then out of phase and finally again in phase with the activity-cycle.[17] (b) When, at day 10, the intensity of illumination in the room is reduced from 1400 to 100 lux, the three "slow" members of the group lengthen their circadian periods by roughly 1 hour. This, obviously, is too much for subject S. After a few days of compromise, he drifts away from the rest of the group with a period which is now close to 24 hours.

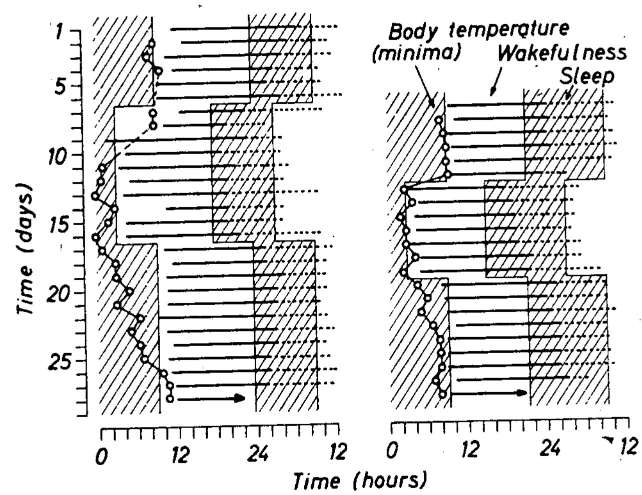

Fig. 7. Effects of phase-shifts of the Zeitgeber on the circadian rhythms in two subjects, kept separately in isolation and exposed to artificial light-dark cycles. Simulation of 'flights' by, first, shortening the light-dark cycle once by 6 hours ('eastward') and, second, by lengthening the light-dark cycle once by 6 hours ('westward'). Shaded area: darkness. Horizontal continuous lines: wakefulness. Dotted lines: sleep. Open circles: Minima of body temperature.

The experiment demonstrates 'internal' desynchronization if one considers the group a biological unit, built up by four sub-units. It may also be considered as an example for external desynchronization in the case of subject S, the rest of the group being a Zeitgeber for S. The data reported here have some bearing on the results of experiments with crews working on a 4:2-hour work-rest cycle. The continuous changes in phase of the circadian rhythm of the crew, observed in some of these experiments, still need to be explained.[5]

PHASE-SHIFT OF THE ZEITGEBER

It is well known that, after a jet flight in eastward or westward direction, it takes several days to become readjusted to local time. The time necessary for resynchronization depends, first of all, on the amount of phase-shift accomplished by the trip. However, the direction of the trip—whether eastward or westward—also influences the duration of re-entrainment. Experiments demonstrating this effect have been made with birds, kept in artificial light-dark cycles.[14] "Flights" are simulated by shortening or lengthening the Zeitgeber period once for several hours. In average, finches, are resynchronized with the light-dark cycle (as measured by their activity) in about three days when the Zeitgeber has been shortened once by 6 hours; it takes about twice as long when the Zeitgeber has been lengthened once by 6 hours. This 'asymmetry' of the circadian system is in accordance with theoretical considerations, based on a mathematical model.[23]

Similar experiments with human subjects in the bunker have led to similar results.[9] The data presented in Figure 7 show, first, the effects of a "flight" in eastward direction, and, several days later, the effect of a "flight" in westward direction on two male subjects, measured independently. In both subjects, the activity-cycle is adjusted to the shifted Zeitgeber immediately or after a very few days only. The minima of body temperature, however, regain their normal phase (in all but one of the shifts) in a slow gradual manner. And in both subjects, the time for re-entrainment of body temperature is longer after the westward "flight" than it is after the eastward "flight".

The aforementioned rule will, of course, not apply to all individuals and not to other conditions. Whether resynchronization takes longer after a westward or after an eastward flight, depends to a large extent on the natural circadian period of the individual concerned. Even finches become resynchronized quicker after a westward flight if they show especially long periods under constant conditions. Since many human subjects tend to have rather long periods under constant conditions, a large percentage of the population probably may resynchronize easier after a flight in westward direction. The main points of interest are, (1) that there is asymmetry in the circadian system with regard to the speed of resynchronization and (2) that internal desynchroniaztion takes place during re-entrainment after shifts. This means: The many rhythmic functions in an organism differ in the time needed for full resynchronization. Most likely, this transient internal disorder contributes to the loss in efficiency during the first days following a long-distance flight.

CONCLUSIONS

Circadian rhythms are examples of an evolutionary adaptation to time structures in the environment. This process resulted in (a) self-sustained oscillations, the periods of which match approximately that of the environment, (b) species-specific phase-relationships between the circadian oscillations and the environment, warranted by entrainment, and (c) temporal order between a multiplicity of oscillating systems. Maintenance of the temporal order within the organism seems to depend partly on interaction between several oscillators within the organism, and partly on phase-setting effects of the entraining Zeitgeber. Therefore, lack of proper Zeitgebers may have deleterious effects to the organism.[4]

Desynchronization from the natural 24-hour period, whether achieved by artificial Zeitgebers or by isolation from all Zeitgebers, does not necessarily comprise internal disorder. However, it results in changes of the internal phase-relationship the consequences of which are not yet known. It further can result in internal desynchronization which one may expect to be injurious to the organism.

Resynchronization to 24 hours, whether after isolation or after entrainment to odd days, is often accompanied by a transient state of internal desynchronization. The same applies to re-entrainment of an organism after its quick transfer through several time zones. Any attempt to shorten the duration of re-entrainment after shifts or to reduce the loss in efficiency during this time, will depend on a deeper understanding of the underlying circadian mechanism. In several fields of applied physiology, all types of desynchronization mentioned above are of importance. In this regard, especial attention ought to be payed to the interaction between the circadian rhythms of members of a crew as well as to the reaction of a crew to either unusual Zeitgebers or to a shift-work schedule. •

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