ANCHOR SLEEP AS A SYNCHRONIZER OF RHYTHMS ON ABNORMAL ROUTINES

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Recent reviews of shift work (Knauth & Rutenfranz, 1976; Rutenfranz & Knauth, 1976; Rutenfranz, Colquhoun, Knauth, & Ghata, 1977; Winget, Hughes, & LaDou, 1978) have emphasized the disadvantages associated with it, whether these are performance decrement, ill-health, job dissatisfaction, increased accidents or social inconvenience. At least in part, these problems seem to arise because the shift worker is required to work, to take his leisure and to sleep at unusual hours. As a result his endogenous circadian rhythms are at variance with the schedule of sleep and wakefulness. With successive days on the same shift these rhythms progressively adapt so that they become more appropriately phased to the cycle of work and sleep, but there is doubt if adaptation is ever complete unless the same shift is worked for a long period of time (Conroy, Elliott, & Mills, 1970; Lobban,1963). Thus it has been shown (Knauth & Rutenfranz, 1976; Knauth, Rutenfranz, Herrmann, & Poeppl, 1978) that rhythms are often flatter when on shift-work than when they are measured in the same subjects on the conventional pattern of diurnal work and nocturnal sleep. The problem is exacerbated by the observation that the rhythms rapidly regain their normal phasing when the worker, generally for reasons of social expedience, reverts to a normal routine during his days off (Åkerstedt & Fröberg, 1975). To avoid this problem of continual adaptation, loss of adaptation and readaptation, rapidly rotating shift systems have been advocated (Knauth & Rutenfranz, 1976; Rutenfranz & Knauth, 1976; Rutenfranz et al., 1977). On such systems, large day-by-day changes of rhythms are not seen but it is possible that in the absence of regular habits the rhythms might free-run with a period in excess of 24 hours and so it would be only by chance that the rhythms of the worker would be appropriate to his schedule, whether this be one of work or leisure.

Clearly it would be an advantage if rhythms could in some way be stabilized to a particular shift, so that after the occasional day off with its associated change in routine the rhythms would still be adapted to the work shift when it was resumed.

There is evidence that sleep directly affects circadian rhythms (Mills, Minors & Waterhouse, 1978a), one result of which is that rhythms are more closely related to midsleep than to clock time (Halberg, Reinhardt, Bartter, Delsea, Gordon, Reinberg, Ghata, Halhuber, Hoffman, Gunther, Knapp, Pena, & Garcia Sainz, 1969; Mills & Waterhouse, 1973). Therefore a series of experiments has been performed in which an attempt has been made to stabilize the rhythms of subjects by making them take part of their sleep at a regular time each day even though the rest of their sleep-wakefulness routine was irregular. Preliminary accounts of these experiments have appeared (Mills, Minors, & Waterhouse, 1977a; Minors & Waterhouse, 1979).

Methods

The subjects were healthy students aged 18-21. Details are shown in Table 1. The subjects were studied in groups of 2 to 5 in an Isolation Unit,

Table 1

Details of Subjects and Experimental Protocols

Group	Sex	Ages	Length of daily sleep periods during experimental phase (h)	Time of anchor sleep
A	M	19, 20, 18, 18	8	None
B	F	18, 18, 20, 19, 18	2 x 4	None
C	F	18, 21, 20, 18	2 x 4	0000-0400
D	M	19, 20	2 x 4	0000-0400
E	F	19, 19	2 x 4*	0000-0400
F	F	18, 18, 19, 18	2 x 4	0400-0800
G	M	20, 19, 21, 19	2 x 4	0800-1200
H	M	19, 20	2 x 4	1200-1600

* Sequence of irregular sleeps the reverse of groups C, D and F-H.

the ambient air temperature and humidity of which were maintained constant. Further details of this unit have been described elsewhere (Elliott, Mills, Minors, & Waterhouse, 1972). Initially, subjects were studied for a 5-day control period living on a customary nychthemeral routine. During this they slept between midnight and 0800 and ate meals at their customary times. After this control phase subjects were then asked to sleep at irregular times--the experimental phase--according to one of six designs, even though they continued to eat at times as nearly as possible the same as those during the control phase. Lighting was under the control of the subjects; they were instructed to take all sleep periods in the dark.

The different experimental designs are shown in Figures 1 and 2. In the first design, Figure 1A, 4 male subjects (Group A) took a single 8-hour sleep per day, but at a different time each day. The ordering of these times was randomized. In the second experimental design, Figure 1B, 5 female subjects (Group B) took their sleep in two 4-hour periods per day. The time of one of these, labelled with an X in the figure, was such that its mid-point was at the same time as that of the 8-hour sleep on the corresponding day in subjects of Group A. The other 4-hour sleep was always begun 12 hours earlier.

In the remaining experimental designs, Figure 2, the customary 8 hours of sleep per day were again divided into two 4-hour periods. By contrast, how-

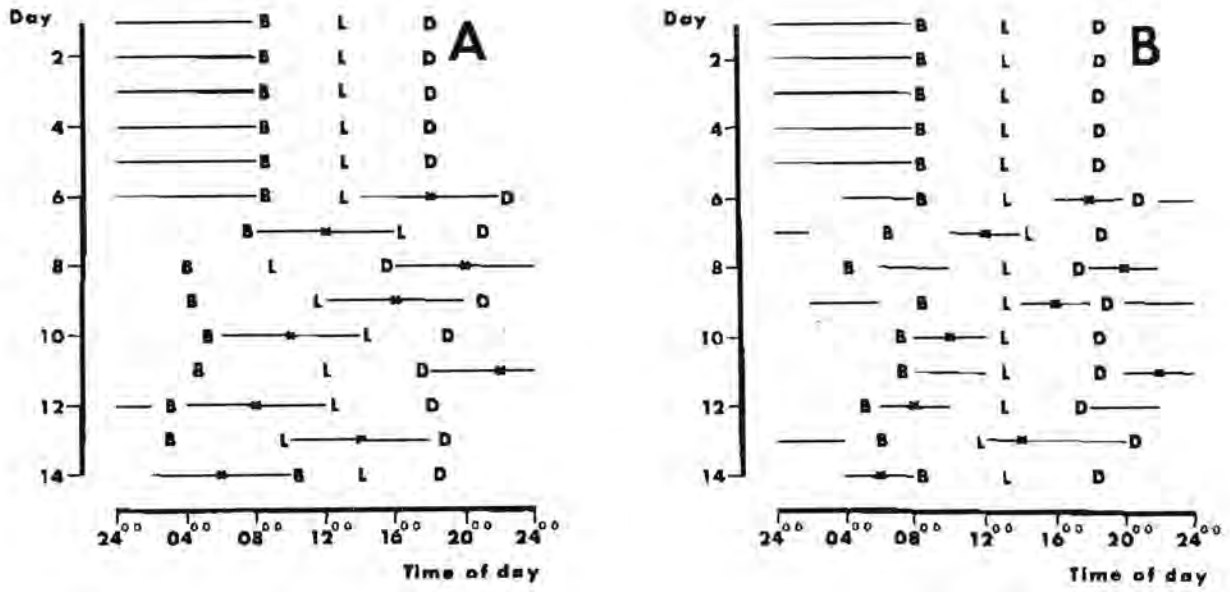

Figure 1. A (left): Experimental protocol for Group A. B (right): Experimental protocol for Group B. Successive days in Isolation Unit from above downwards. Mealtimes indicated as B (breakfast), L (lunch), or D (dinner). Horizontal bars represent times the subjects were in bed. Mid-points of irregularly-timed sleep periods indicated by X.

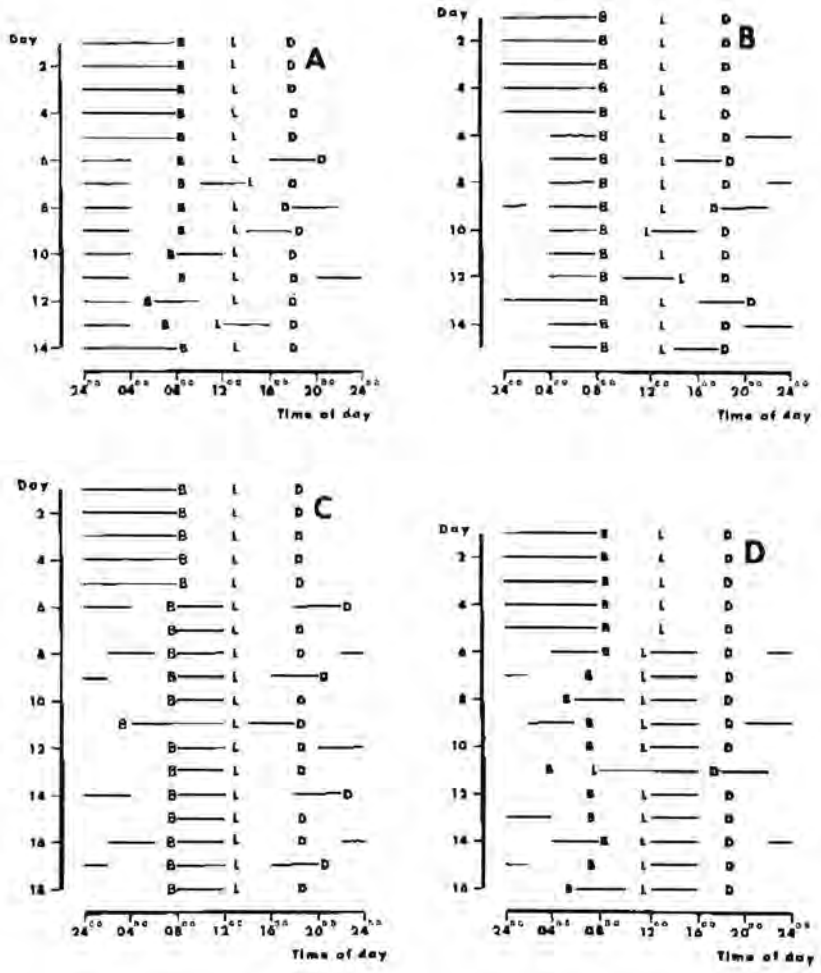

Figure 2. A: Experimental protocol for Groups C and D. B: Experimental protocol for Group F. C: Experimental protocol for Group G. D: Experimental protocol for Group H. Other details as Figure 1.

ever, one of these was taken at a constant time on each day. This constant 4-hour sleep period is referred to by us as 'anchor sleep' and was taken over one of 4 intervals: 0000-0400, Figure 2A; 0400-0800, Figure 2B; 0800-1200, Figure 2C; 1200-1600, Figure 2D. Details of subjects participating in these designs are given in Table 1. The second 4-hour sleep taken in these experiments was at a different time on each successive day. For subjects of Groups C and D, whose anchor sleep was 0000-0400 (Figure 2A) the irregularly-taken 4-hour sleep was at the same time as that taken on the corresponding day by Group B and labelled with an X in Figure 1B. For the other three designs these irregularly-taken sleep periods were 4 hours (anchor sleep 0400-0800, Group F), 8 hours (anchor sleep 0800-1200, Group G) or 12 hours (anchor sleep 1200-1600, Group H) later than on the corresponding day for 0000-0400 anchor sleep experiment. To minimize the effects of sleep deprivation when the anchor sleep was taken at 0800-1200 or at 1200-1600, the irregularly-taken sleep was advanced by one day and so was placed before the anchor sleep rather than after (compare Figures 2B and 2C).

A final group of subjects (Group E) was studied. This group also took an anchor sleep from 0000-0400 but differed from Groups C and D in that it underwent the reverse sequence of irregularly-taken 4-hour sleeps.

Throughout all experiments, subjects micturated on rising from bed and every 2 hours thereafter whilst awake. The volume of all urine passed for each collection period was noted and an aliquot refrigerated for subsequent analysis. Rectal temperature was also measured using a thermistor probe placed 10 cm beyond the anal sphincter. During the hours of wakefulness this temperature was measured by the subjects every hour and during sleep it was telemetered hourly. All urine samples were analyzed by an AutoAnalyzer II, the analyses performed being for sodium, potassium, chloride, creatinine, inorganic phosphate, calcium, and urate. No calcium analysis was performed on the samples produced by Group C due to a technical failure. For each period of collection of urine the flow rate and excretion rates of each of the constituents in urine were determined.

Circadian rhythms were sought by the fitting of cosine curves to the data. For the temperature data the single cosinor method (Halberg, Johnson, Nelson, Runge, & Sothern, 1972) was used and for the urinary data the method of Fort and Mills (1970). For rhythm analyses, experiments were divided into two phases: the control phase, during which the subjects slept at their habitual times; and the experimental phase, during which the schedule of sleeping had been changed as already described. To each phase a spectrum of cosine curves with periods from 22 hours in increments of 0.1 hour to 27 hours were fitted to each variable. The most appropriate period for the rhythm of each variable was assessed as that of the fitted cosine curves which minimized the residual error. The data from the experimental phase were also analyzed by a pergressive serial section analysis (Halberg & Katinas, 1973) in which cosine curves with a period of 24 hours were fitted to 72-hour intervals of data progressively incremented by 24 hours. Other statistical analyses will be described as they arise in the following section.

Results

Sleep Taken at Irregular Times (Groups A and B)

Examples of the behaviour of the acrohpases of 24-hour cosine curves fitted pergressively to data from subjects of Groups A and B are shown in Figures 3 and 4. In both cases it can be seen that during the experimental phase, when the subjects slept at irregular times, the acrophase was initially similar to that determined by fitting a 24-hour cosine curve to the entire control phase. Thereafter the acrophase became progressively later, a finding in accord with the view that the rhythm was free-running with a period of greater than 24 hours. This conclusion has been confirmed for the group as a whole by determining the mean period of rhythms (derived from all variables and all subjects) during both the control and the experimental phases. For Group A the mean period of rhythms during the control phase was 24.160 $\pm$ 0.103 hours and for Group B the corresponding mean was 24.195 $\pm$ 0.106 hours; in neither case was this significantly different from 24 hours at the 5% level. By contrast, the mean period of rhythms for both these groups during the experimental phase was significantly ($p < .05$) greater than 24 hours (24.516 $\pm$ 0.191 hours, Group A; 24.683 $\pm$ 0.159 hours, Group B). Further, in both groups, paired t-tests showed that the period determined during the experimental phase was significantly greater ($p < .05$ by one-tailed test) than that determined during the control phase (mean difference: 0.360 $\pm$ 0.205 hours, Group A; 0.486 $\pm$ 0.198 hours, Group B).

It, thus, appeared in both these groups that, despite the fact that meals were taken at regular times throughout, stable 24-hour rhythms were not obtained; rather, rhythms appeared to free-run with a period greater than 24-hours.

Anchor Sleep 0000-0400 (Groups C, D, and E)

Pergressive serial section analysis of the data from Groups C and D showed that the acrophases of the cosine curves fitted to the experimental phase remained at a fairly constant time throughout. An example is shown in Figure 5. It can be seen in this Figure that the acrophase occurs at a time which is also similar to that determined during the control phase. It, thus, appears that rhythms retained a 24-hour period and a phase similar to that determined whilst subjects lived on their customary nychthemeral routine. The results from subjects of Group E, for whom the ordering of the irregularly taken sleeps over successive days was the reverse of that for Groups C and D, were very similar. An example is shown in Figure 6. Therefore, for statistical analysis, the three groups have been considered together.

In these groups, then, it appears that taking a 4-hour sleep at a regular time was associated with stable 24-hour rhythms. This has been confirmed by fitting a spectrum of cosine curves, as described previously, and by determining the period of the rhythms during all but the first 4 days of the experimental phase. [The reason for omitting the first 4 days of the experimental phase was to remove the effects of any transient changes which might occur immediately after subjects started sleeping at irregular times--for further comments, see later.] The mean period of all rhythms from subjects of Groups C-E was not significantly different from 24 hours as shown in Table 2, column A.

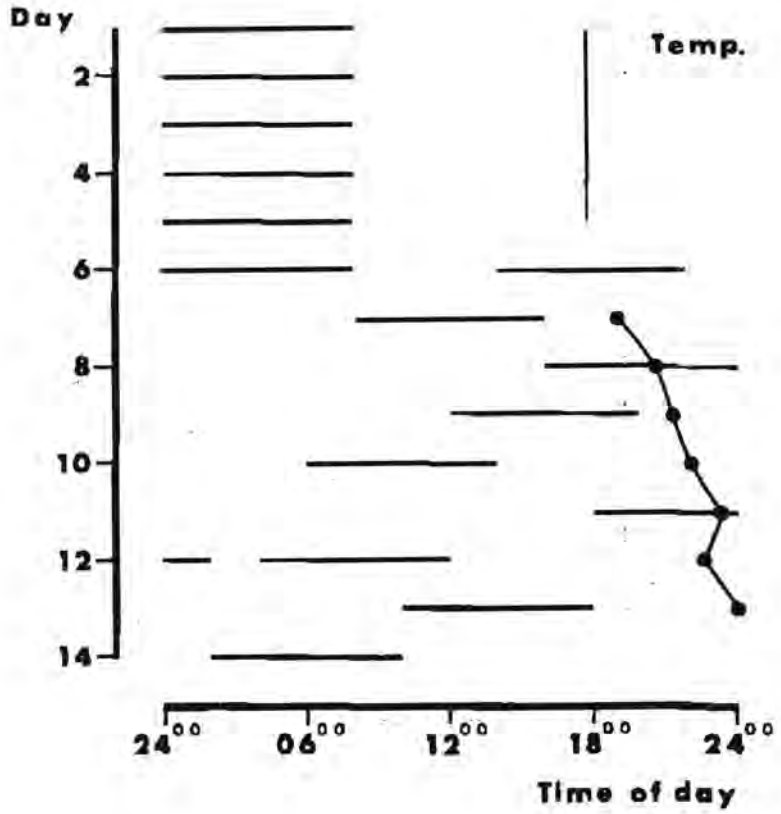

Figure 3. Rectal temperature rhythm in a subject of Group A. Acrophases of 24-h cosine curves fitted to 72 hours of data pergressively incremented by 24 hours. Acrophase of 24-h cosine curve fitted to all control phase as shown in vertical line.

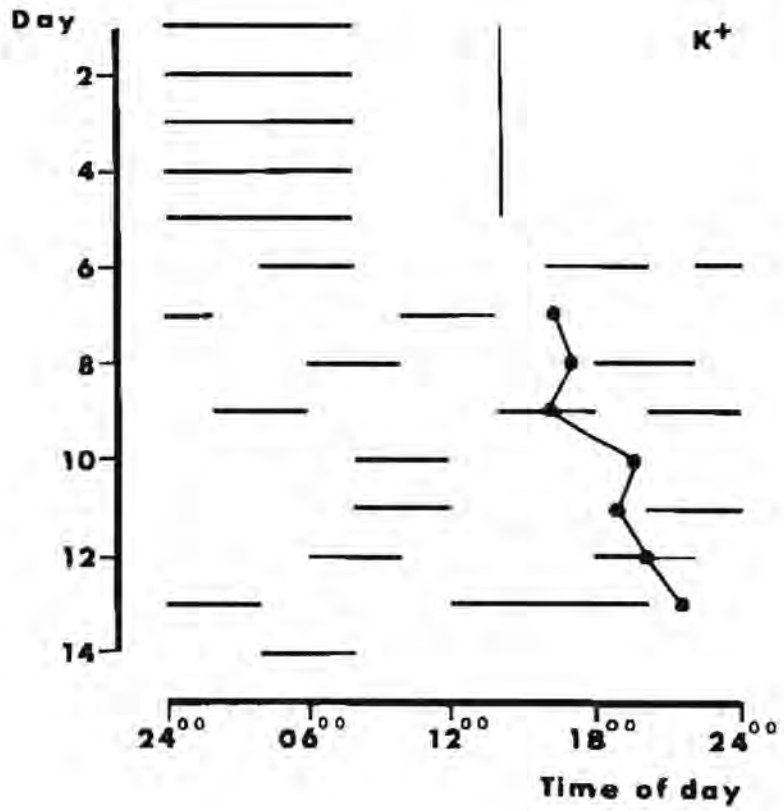

Figure 4. Urinary potassium rhythm in a subject of Group B. Data plotted as in Figure 3.

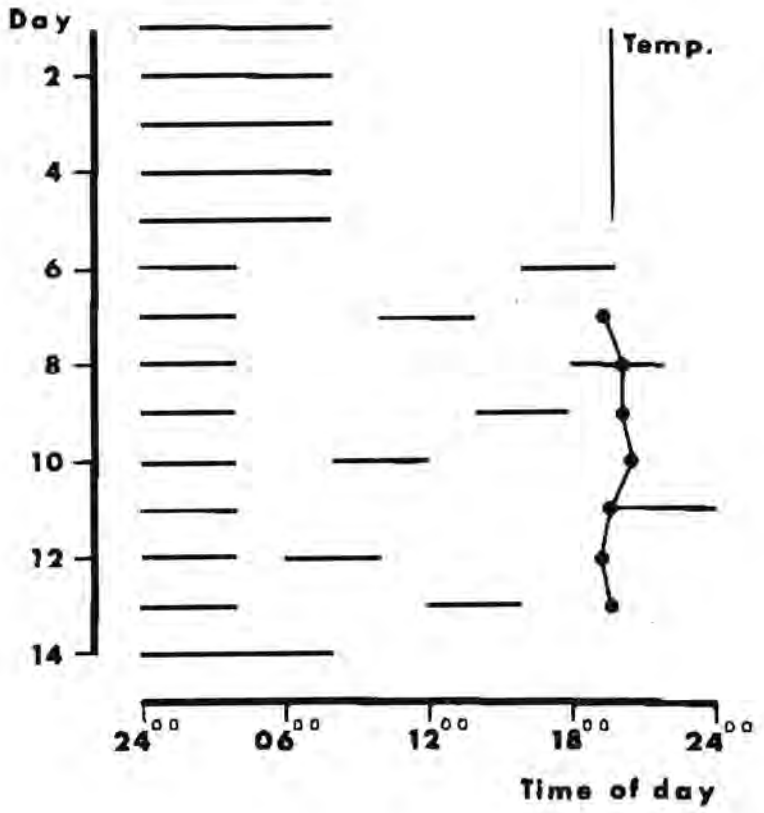

Figure 5. Rectal temperature rhythm in a subject of Group D. Data plotted as in Figure 3.

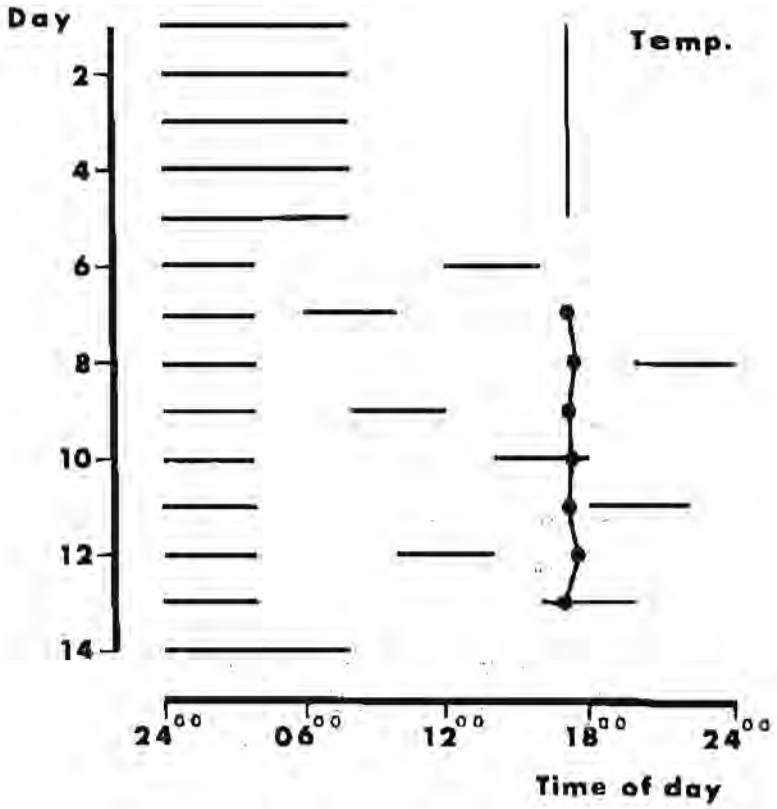

Figure 6. Rectal temperature rhythm in a subject of Group E. Data plotted as in Figure 3.

Anchor Sleep at Other Times (Groups F, G, and H)

The results from the previous section lead one to speculate if taking an anchor sleep at times other than 0000-0400 would also result in stable 24-hour rhythms. An example of the behaviour of the acrophases of cosine curves progressively fitted to the data of Group F, whose anchor sleep was 0400-0800, is shown in Figure 7. As for Groups C, D, and E the acrophases were stable during the experimental phase. However, as the example shows, the acrophase was sometimes a few hours later during the experimental phase than in the control phase, though in other cases its timing in the two phases was indistinguishable. As previously, the mean period of the rhythms for all variables was determined over all but the first 4 days of the experimental phase and is shown in Table 2, column A. This mean was not significantly different from 24 hours.

Table 2

Mean Periods of Rhythms During the Experimental Phase for the Different Groups

	A		B	
	Period during experimental phase. Mean ± 1 S.E. (hours)	p*	Difference in period between initial and later part of experimental phase. Mean ± 1 S.E. (hours)	p**
Groups C, D, and E	24.166 ± 0.164 (n=47)	ns	-0.295 ± 0.227 (n=38)	ns
Group F	24.191 ± 0.137 (n=34)	ns	+0.303 ± 0.175 (n=29)	ns
Group G	23.977 ± 0.081 (n=35)	ns	+0.667 ± 0.150 (n=33)	0.001
Group H	24.213 ± 0.168 (n=15)	ns	+0.686 ± 0.264 (n=14)	0.021

Column A: Mean period derived from all but the first 4 days (Group H, 6 days) of the experimental phase.
Column B: Mean difference in period of rhythms between the initial 4 days (Group H, 6 days) of the experimental phase and the remainder of the experimental phase (+ indicates period longer during the initial days).
p* probability that the difference is significantly different from 24 (unpaired t-test, two-tailed).
p** probability that difference is significantly different from zero (paired t-test, two-tailed).
ns $p > .05$.

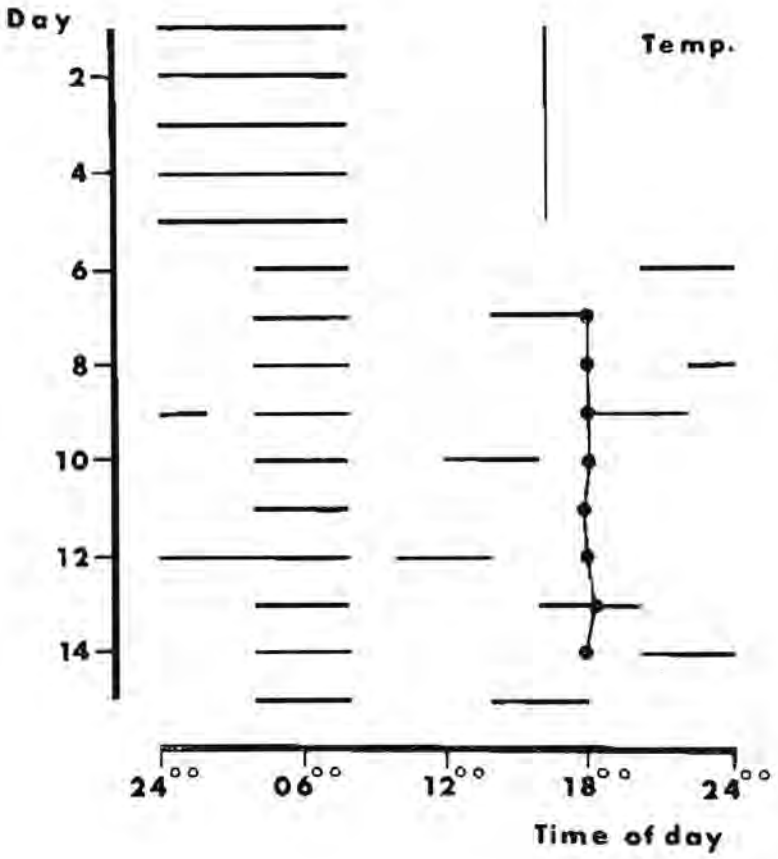

Figure 7. Rectal temperature rhythm in a subject of Group F. Data plotted as in Figure 3.

The results from Groups G and H differed slightly from those of other groups. Figures 8 and 9 show examples of the behaviour of the acrophases derived from cosine curves fitted pergressively to data from these two groups. In both cases it can be seen that, during the latter part of the experimental phase, the acrophase was constant but that this stability was not gained immediately. In the initial part of the experimental phase the acrophase became progressively later such that, once stability was attained, the acrophase of the rhythm was later than that determined during the initial control phase. In addition, the time required to attain stability was different in the two groups; inspection of all the data indicate it took about 4 days in Group G but about 6 days in Group H (see examples in Figures 8 and 9). Therefore, to confirm stability during the latter part of the experimental phase, the mean periods of rhythms of all variables have been determined as previously but for Group H the first 6, rather than 4, days have been omitted. The mean periods so determined are shown in Table 2, column A; in neither case was this mean significantly different from 24 hours.

How Was Stability Attained?

From the preceding sections it is evident that in all groups who took an anchor sleep, stable 24-hour rhythms were obtained at least towards the end of the experimental phase. For Groups C, D, E, and F (Figures 5, 6, and 7) this stability appeared almost immediately, whilst for Groups G and H stable 24-hour rhythms appeared only after an initial period during which the acrophase of the rhythms became progressively later. It, thus, appears that for these last two groups the period of rhythms initially changed during the experimental phase; during the early stages of the experimental phase the period was greater than that during the remainder of the experiment. Evidence in favour of this has been obtained in two ways.

Firstly, by fitting a spectrum of cosine curves we have compared, by paired t-test, the period of the rhythm during the initial 4 days of the experimental phase (for Group H the initial 6 days) with the period determined during the remainder of the experimental phase; the mean differences for all variables for the different groups are shown in Table 2, column B. For Groups C, D, E, and F the mean difference was not significantly different from zero indicating that the period did not change significantly during the two parts of the experimental phase. By contrast, for Groups G and H, the period of rhythms was longer in the initial phase of the experiment and this difference was statistically significant.

The second way in which a change in period of rhythms has been confirmed is by a pergressive serial section analysis in which, for each variable, a spectrum of cosine curves with different periods has been fitted to sections of data from the experimental phase. The sections chosen were the first 24 hours of the experimental phase and then sections obtained by progressively incrementing by 24 hours the amount of data analyzed until the entire experiment.. phase was covered. This analysis was continued by progressively decrementing the data to which the spectrum of cosine curves was fitted by omitting the first 24 hours of data, then the second 24 hours and so on, until only the last day's data were included. In all cases the best fit period was that of the cosine curve which minimized the residual error. Such an analysis would indicate whether the dominant periodicity changed during the course of a

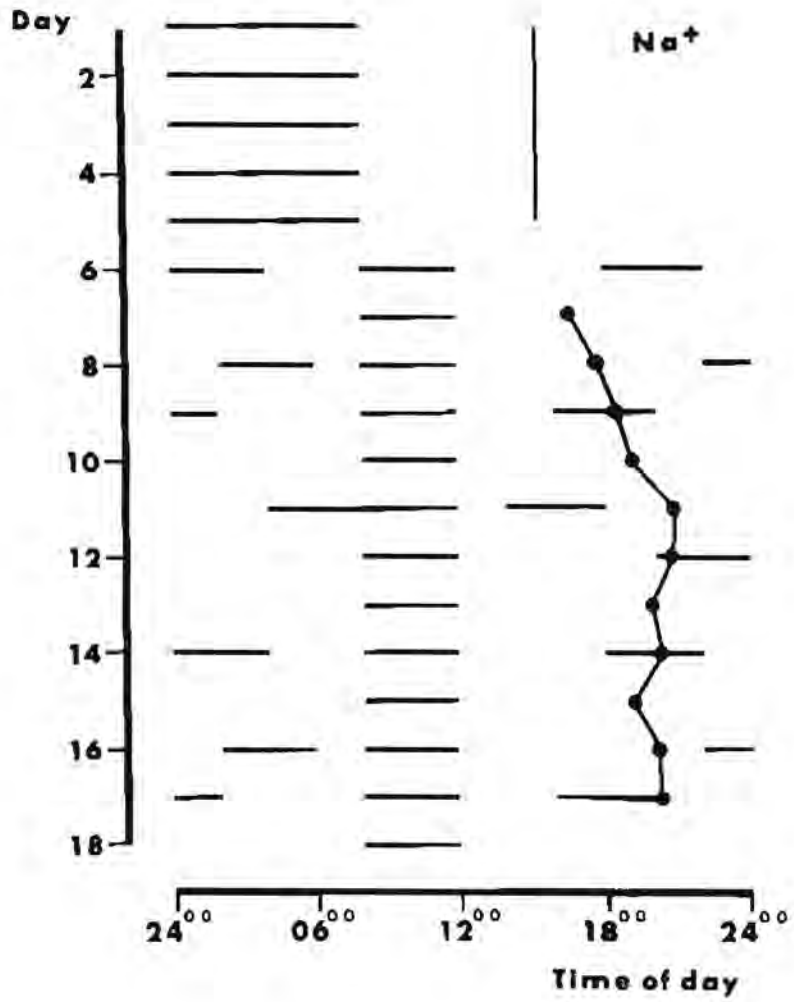

Figure 8. Urinary sodium rhythm in a subject of Group G. Data plotted as in Figure 3.

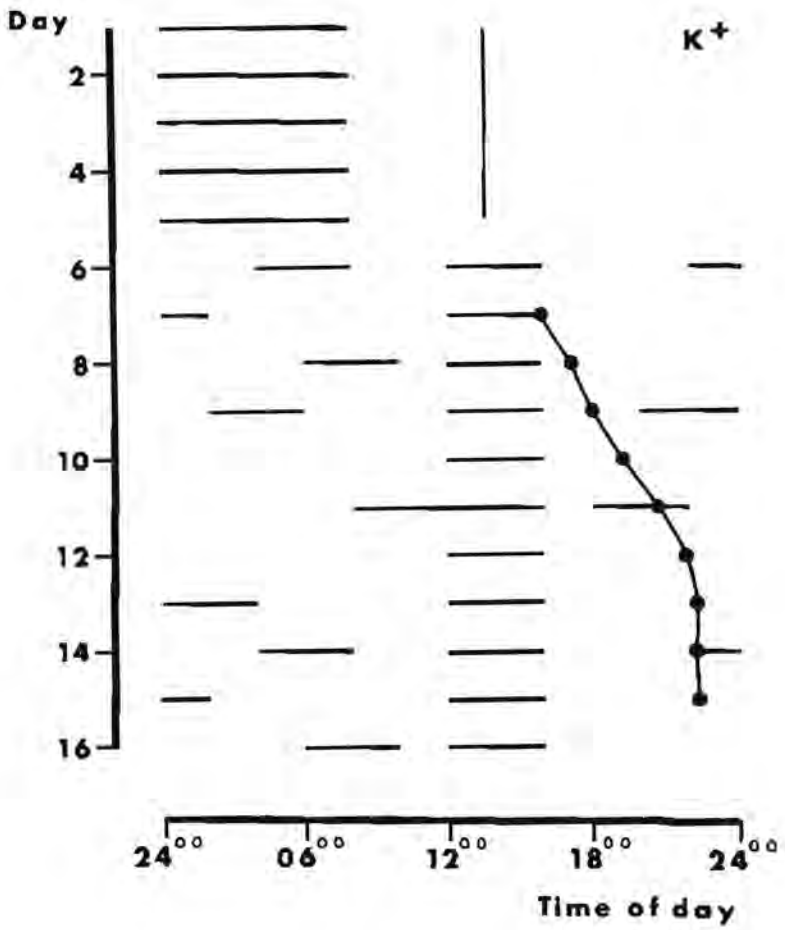

Figure 9. Urinary potassium rhythm in a subject of Group H. Data plotted as in Figure 3.

long stretch of data. For example, if the period changed from a longer to a shorter value, the period of the best-fitting cosine curves should be longer during the initial sections (when the amount of data was being increased) than during the later sections (when the amount of data was being decreased). Examples of this analysis applied to the potassium excretory data for subjects from the different groups are shown in Figure 10. For subjects of Groups G and H the period was initially in excess of 24 hours but by the latter stages, during which data from the latter days only was being considered, the period was close to 24 hours. For the subjects of Group G this 24-hour period was attained sooner than for the subjects of Group H whose rhythm showed a 24-hour rhythm only by the end of the experiment. By contrast, for the subjects of Group B the period remained fairly constant and greater than 24 hours throughout, confirming our earlier conclusion that the rhythm was free-running. Finally, the subjects representative of Groups C and F also showed a constant period throughout, but, in both cases the period was very close to 24 hours. With temperature, chloride, and sodium, similar conclusions could be drawn; with the other urinary constituents the rather greater amount of noise associated with the data precluded such firm inferences.

In conclusion, these analyses suggest that when the anchor sleep was either 0000-0400 or 0400-0800, stable 24-hour rhythms were rapidly obtained and maintained thereafter. When the anchor sleep was taken from 0800-1200 or 1200-1600, however, rhythms oscillated initially with a period greater than 24 hours, as might occur if they were free-running, but then were stabilized to a 24-hour period.

Sleep or Meals Producing Stability?

In all the experimental designs, meals were eaten at times as near as possible to those during the control phase. The possibility exists, therefore, that the regular mealtimes were responsible for the stable 24-hour rhythms in Groups C-H. There is evidence against such a view. First, stable 24-hour rhythms were not obtained in subjects of Groups A and B who also ate meals at the same time as during the control phase. Second, the acrophase of the 24-hour rhythms should not have been different from that determined during the initial control days if mealtimes were a controlling influence. However, when the difference in acrophase between the control phase and the latter part of the experimental phase was calculated, a large difference was found for Groups G and H. The mean difference in acrophase is shown for three variables in Figure 11. The upper, middle, and lower dashed lines in this Figure represent the changes in the times of retiring, mid-sleep, and rising respectively for the different anchor sleep times. It can be seen that, for each anchor sleep time, the change of acrophase from that during the control phase was closely parallel to the changes in sleep time, though it is not possible to ascribe this change to any particular aspect of sleep. Certainly the observed changes do not follow the horizontal full lines as would be the case if mealtimes rather than sleep were and important determinant of phase. Similar results were obtained with the other urinary constituents, but, for calcium, phosphate, and creatinine there was considerable variation.

In conclusion, the phase of the stable 24-hour rhythms obtained during our anchor sleep experiments depends on the time of the anchor sleep, the phase-shift being approximately equal to the time by which the mid-sleep is shifted.

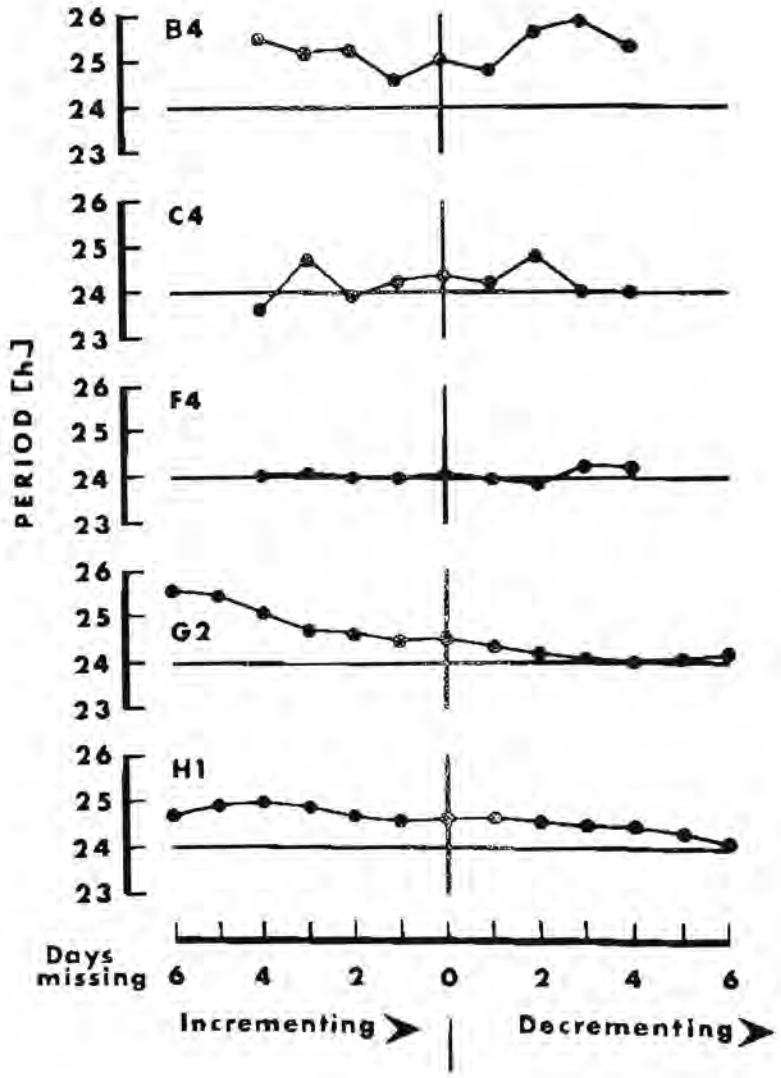

Figure 10. Urinary potassium rhythm, selected subjects from different groups as labelled. Period of best-fitting cosine curve applied to different amounts of data from experimental phase. Vertical line indicated the section when all data were considered. For other details, see text.

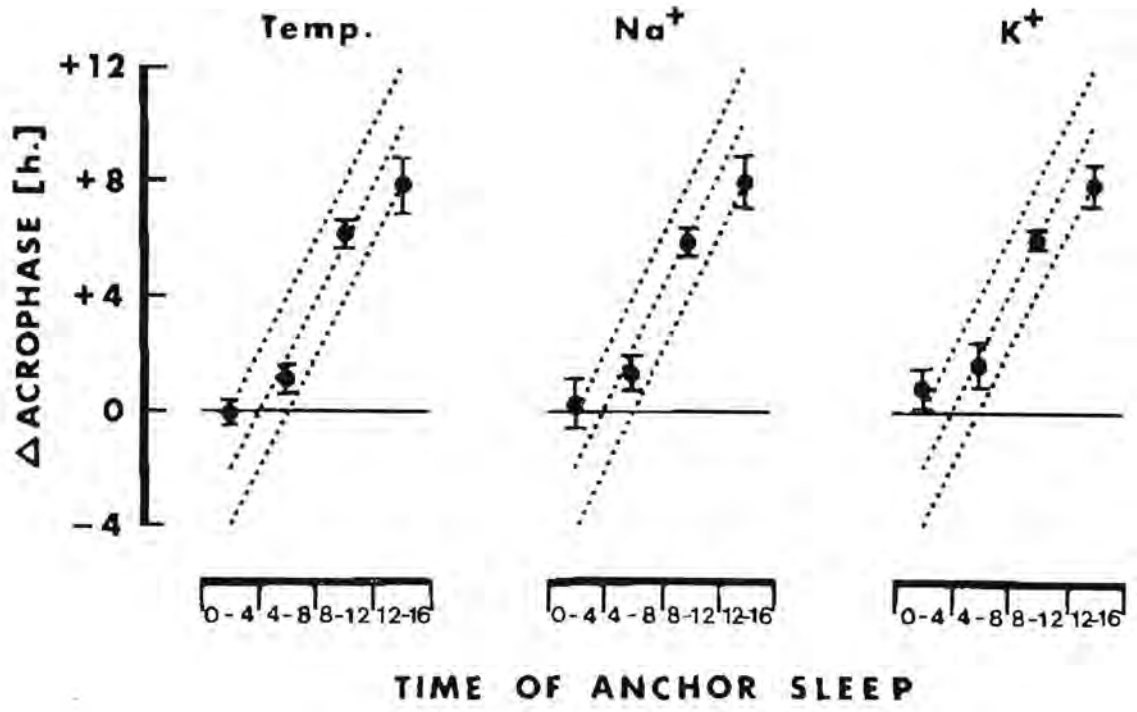

Figure 11. Change in acrophase, as compared with control phase value, when anchor sleep taken at different times for rectal temperature, sodium and potassium. + indicates phase delay. Dotted lines indicate result predicted if change in acrophase due solely to time of retiring (top), mid-sleep (middle), or time of rising (bottom). Horizontal unbroken line indicates result predicted if change in acrophase due solely to mealtimes. Results expressed as mean ± 1 S.E.

Discussion

Our results indicate that the rhythms of subjects undergoing irregular routines free-run but that, in the presence of an anchor sleep, the rhythms are stabilized with a period indistinguishable from 24 hours (see Table 2).

That people on irregular routines have free-running rhythms has been found occasionally by others, for example by Colquhoun and his colleagues in their experiments upon submariner watchkeepers (1978, 1979). Studies performed upon workers involving rapidly-rotating shift systems have been interpreted to show an absence of marked changes in rhythms on different days (Rutenfranz et al., 1977). However, these data have not been analyzed in a way that would enable a decision to be made as to whether or not the rhythms were free-running in these circumstances. In previous work, we have found rhythms with a period in excess of 24 hours in a single subject who underwent a series of simulated time-zone transitions (Mills et al., 1978c) and similarities would seem to exist between changes in routine associated with continual time-zone displacement and the effect of rapidly-rotating shifts.

Free-running rhythms are also found when subjects are isolated from external time clues, whether they are placed in a bunker (Wever, 1975a), an Isolation Unit (Mills et al., 1974), or a cave (Mills, 1964). What all these people might have in common, together with our Groups A and B, are external conditions that fail to provide sufficient temporal stability so that the endogenous rhythms cannot be synchronized to the external environment and so they free-run.

There does not seem to be much precedent for our demonstration that an anchor sleep can stabilize rhythms in subjects on an otherwise irregular routine. Colquhoun et al. (1978) have pointed out that there seemed to be a greater stability of temperature rhythm in submariner watchkeepers who took sleep at as regular hours as their shift system would allow.

The implication of our finding is that the rhythms of shift-workers might be stabilized if they took at least some of their sleep during their days off at the same time as when working. For this reason, our anchor sleep at 0800-1200 (Group G) is particularly significant since this is at a time that is both appropriate for workers after a night shift and socially acceptable during days off.

That the stability we have observed is not a spurious result due to some unknown influence of the irregular components of the routine can be inferred from two sources. First, Group B underwent the same pattern of irregular 4 hour sleeps as Groups C-H but, in the absence of the anchor sleep, showed rhythms with a period in excess of 24 hours. Second, Group E, in whom the sequence of irregular sleeps was reversed in comparison with Groups C and D but who like them had an anchor sleep from 0000-0400, gave results indistinguishable from these two groups.

Even though mealtimes do have some effect upon certain human rhythms (Goetz, Bishop, Halberg, Sothern, Brunning, Senske, Greenberg, Minors, Stoney, Smith, Rosen, Cressley, Haus, & Apfelbaum, 1976), our observation that regular mealtimes alone are not sufficient to stabilize rhythms (Groups A & B) argues

that mealtimes are not a strong zeitgeber in man. In this, humans would seem to differ from monkeys (Sulzman, Fuller, & Moore Ede, 1977) and rats (Krieger & Hauser, 1978), in both of which species mealtimes have been found to act as zeitgeber.

The present observations (Groups C-H) stress the importance of some aspect of sleep as a stabilizing influence. But since sleep is associated with so many changes--in electrophysiology, posture, light, social interaction, etc.--and these cannot be dissociated in our experiments, we are not able to offer evidence for or against specific roles of social interaction (Aschoff, Fatranska, Gerecke, & Giedke, 1974; Wever, 1975b) or light (Mills & Waterhouse, 1973; Lobban, 1967; Miles, Raynal, & Wilson, 1977) as zeitgeber. Certainly our finding that sleep is in some way important accords with the practice of referring acrophases to mid-sleep rather than to clock-time (Halberg et al., 1969; Mills & Waterhouse, 1973).

Even though the different times of anchor sleep in different groups all resulted in stabilized rhythms, there was a shift in acrophase, especially in Groups G and H as shown in Figures 8, 9, and 11. The process by which this shift took place would seem to be similar to changes sometimes seen following time-zone transitions. Thus, a recent report (Aschoff, 1978) has indicated that, when humans undergo a real or simulated time-zone transition in an eastward direction, some subjects adapt to the new time-zones not by progressive advances in their rhythms (even if this would require a shift of acrophase by a smaller number of hours) but instead by delays. Such delays are seen more regularly and clearly when the masking influence of the external environment has been minimized by placing subjects on a 'constant routine' (Mills, Minors, & Waterhouse, 1978b).

In the present study, the rhythms appeared to free-run transiently with a period in excess of 24 hours until they stabilized at their new time, again bearing a relationship between acrophase and mid-sleep that was very similar to that found during the control phase. In Groups C-F, no such free-running phase was observed either because the shift involved was too small or because the rhythm was within the limits of entrainment of an endogenous oscillator by external influences or because the free-running phase was finished in less than 4 days.

Finally, it must be considered whether the observed stability is a true entrainment of the endogenous rhythms or rather the result produced by masking effects of the regular component of the daily routine (Mills et al., 1978a; Mills et al., 1978b). Figure 12 enables a comparison to be made between the daily effect of the random sleeps and the overall trend when data from the whole experimental phase are considered. The period of the cosine curve best fitting all the data was 24.4 hours. However, the decrease in urate excretion associated with sleeps caused the acrophase on successive days to zig-zag between them.

Such an effect will be more obvious in the case of variables with larger exogenous components (for example; urate, Figure 12) than in the case of variables with larger endogenous components (for example; temperature, Figure 3). It is likely that the larger exogenous components in urate, flow, phosphate, calcium, and creatinine rhythms (Mills, Minors, & Waterhouse, 1977b) coupled

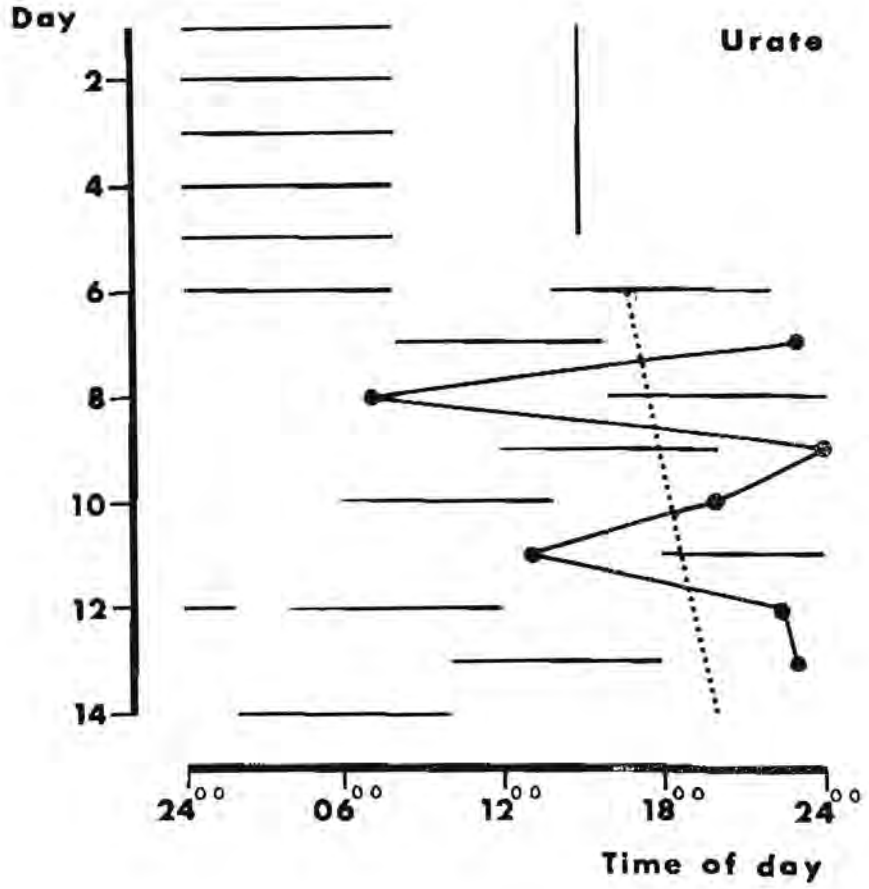

Figure 12. Urinary urate rhythm in a subject of Group A. Data plotted as in Figure 3. Dotted line indicated acrophase and period (24.4 h) of cosine curve best-fitting all data of experimental phase.

with the irregular sleep periods, accounts for the greater variation in these constituents. Further, the result that the stable acrophase bears a consistent relation with mid-sleep would fit with the view that only a direct effect of sleep is being measured. But against this view is the observation that the rhythms seem initially to free-run (Groups G & H). However, a clear distinction between these possibilities can be made only by investigating the rhythms in the absence of external rhythmic factors, that is by the use of a constant routine (Halberg, 1978); experiments to investigate this are being performed.

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July 1981

DHHS (NIOSH) Publication No. 81-127