CIRCADIAN TEMPERATURE RHYTHM AMPLITUDE AND LONG TERM TOLERANCE OF SHIFTWORKING

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A circadian rhythm may be characterized by its acrophase ϕ (crest time on a 24 h scale, of the best-fitting cosine function to all data), its amplitude $\underline{A}$ (1/2 of the difference between crest and trough) and its mesor M (rhythm adjusted mean) (Halberg & Reinberg, 1967; Halberg, Johnson, Nelson, Runge, & Sothern, 1972).

A phase shift ($\Delta\psi$) of socio-ecological synchronizers (ψs) is followed by an acrophase shift ($\Delta\phi$) of the rhythm which is in the same direction and of the same magnitude as $\Delta\psi$. Practical examples of $\Delta\psi$ for mean are:

(a) transmeridian flights across at least 5 time zones ($\Delta\psi > 5$ h);
(b) shiftwork which involves abrupt changes from day work/night sleep to night work/day sleep or vice versa ($\Delta\psi \simeq 8$ h).

A number of studies (Halberg & Reinberg, 1967, 1977; Reinberg, 1970; Aschoff, Hoffmann, Pohl, & Wever, 1975) have shown that the time needed for a rhythm to adjust from the "old" phase to its "new" one after a $\Delta\psi$ varies:

(a) from variable to variable in the same subject (e.g., the body temperature ϕ typically adjusts faster than the urinary 17-OHCS ϕ);
(b) with direction of $\Delta\psi$ (e.g., after a $\Delta\psi$ equivalent to a flight from Paris to New York (phase delay) ϕs adjust faster than after $\Delta\psi$ equivalent ot a flight from New York to Paris (phase advance);
(c) from subject to subject for a given variable.

With Andlauer, Vieux, Ghata and other colleagues, we have used this chronophysiological background (as well as a chronobiological methodology) to try to increase our understanding of individual differences in tolerance of shiftwork (Reinberg, Vieux, Ghata, Chaumont, & Laporte, 1978a, 1978b; Andlauer & Reinberg, 1979).

From clinical evidence, it appears that in a population of healthy human adults, only a limited proportion (the exact value has not yet been ascertained) are able to sustain shiftwork (Akerstedt, 1976; Landier & Vieux, 1976; Andlauer, Carpentier, & Cazamian, 1977). Many people, even after only a few months of shiftwork, suffer from fatigue and sleep disturbances, as well as from other symptoms. Clinical symptoms of intolerance may be seen in some people after several years of shiftwork and/or when they reach 40 or 50 years of age. However, other people are able to do shiftwork for all of their active life span without exhibiting medical problems or complaints. Unfortunately, at the present time, it is not possible to predict whether or not an individual will tolerate shiftwork easily for many years. It is only by on-the-job experience that it is possible to evaluate this capability.

Since the number of persons involved in shiftwork and transmeridian flights is large (almost one million people are employed on shiftwork in France), and since it is of interest, both to the employer and employee to know the likelihood of being able to continue in shiftwork, it is of practical concern to evaluate data from chronobiological studies with the particular aim of identifying possible indices for predicting successful long-term tolerance of shiftwork schedules. The amplitude of the circadian rhythm of body temperature (among other variables) was considered as a candidate for such an index, and was tested in relation to two complementary hypotheses.

The first of these hypotheses (advanced by Aschoff, 1978) is that the circadian amplitude of certain variables, such as oral temperature, is a chronobiological index indicative of the ability to phase shift circadian rhythms. Put as a question, this hypothesis asks: Is a rapid adjustment of ϕ to a phase shift of the ψs associated with a small circadian amplitude?

The question posed by the second hypothesis (advanced by Andlauer, 1971) is: Is a good clinical tolerance of shiftwork related to a large amplitude of the oral temperature circadian rhythm?

Data gathered from previous studies on oil refinery shiftworkers (Reinberg et al., 1973, 1975, 1976a, 1976b) were complemented and reanalyzed to test whether or not $\underline{A}$s and $\Delta\phi$s (resulting from $\Delta\psi$s) are correlated for variables such as oral temperature, peak expiratory flow, urinary 17-OHCS, etc.(Study 1).

The possible relationship between the circadian amplitude of the oral temperature rhythm and tolerance of shiftwork was merely suggested by inspection of the raw data from 25 subjects. The hypothesis of Andlauer (1971) referred to above was therefore, in fact, a proposal for further studies. These have since been carried out (Andlauer & Reinberg, 1979) and involved shiftworkers from two different industries (Study 2).

The experimental protocol of Study 3 was designed to test both the hypotheses together, i.e., that the cirdadian rhythm amplitude of oral temperature is related either to speed of rhythm adjustment and/or to tolerance of shiftwork. In testing these hypotheses, the problem of their compatibility (and even that of their complementarity) was taken into account (Reinberg, Vieux, Andlauer, Guillet, Laporte, & Nicolai, 1979). From a practical point of view, complementarity would mean that the circadian temperature rhythm in a tolerant subject (resistant to the long-term effects of shiftwork) would have a large amplitude, and would phase adjust slowly to a $\Delta\psi$. In a non-tolerant subject (with medical complaints that indicated some degree of health loss),the rhythm would have a small amplitude, and would adjust rapidly. At the same time, it had to be borne in mind that someone with an excellent history of tolerance of shiftworking for many years might begin to have problems on reaching his fifties or even his forties. Thus, the subjects' ages and their known tolerance of shiftwork were taken into consideration when forming the groups of Study 3, in which rhythm parameters such as $\underline{A}$, ϕ and $\Delta\phi$ were estimated from individual time series.

Is a Large Amplitude Related to a Slow Phase-Shift in the Circadian Rhythms of Shiftworkers? (Study 1)

Subjects. Twenty-five male shiftworkers in two French oil refineries (Reichstett & Petit-Couronne) who had been on shiftwork (shiftwork duration for from 1-16 years) were used as subjects. At Reichstett there were 20 subjects, ranging in age from 24-48, whose shift length was 7 days (weekly rotation); at Petit-Couronne there were 5 subjects, ranging in age from 21-28, whose shift length was 3-4 days (rapid rotation).

Methods

Self-measurements of oral temperature, grip strength and peak expiratory flow were performed every 4 hours (except during sleep) at the same clock time on Day 1 (among others) of each shift ($\Delta\psi$). Total urine voidings (for determination of urinary 17-OHCS, K^+, Na^+, etc.) were collected simultaneously. The data gathering covered a 6-8 week span.

The single cosinor method (Halberg et al., 1972) was used to quantify the amplitude ($\bar{A}$) and the acrophase (ϕ) of the rhythm of each variable for each subject on each shift.

For each variable and each of the 25 subjects, we derived:

(1) the mean amplitude $\bar{A}$, computed from all available time series (in so doing, the total variance of this parameter was taken into consideration):

(2) the magnitude (or the speed) of the acrophase shift $\Delta\phi$. $\Delta\phi$ was defined as the difference (in hours) between ϕ on control days (diurnal work and activity/nocturnal sleep) and ϕ on the first night shift day (the 24 h span following the first session of nocturnal work/diurnal rest and sleep). The estimated $\Delta\phi$s correspond to a phase delay ($\Delta\psi$) of approximately 7.5 h.

Correlation coefficients were calculated between $\bar{A}$ and $\Delta\phi$ for each variable, and also between the $\Delta\phi$s of the different variables.

Results

Figure 1 shows the negative correlation obtained between $\bar{A}$ and $\Delta\phi$ for oral temperature ($r = -.63$; $p < .01$); the lower the amplitude, the greater the $\Delta\phi$.

Table 1 shows similar significant negative correlations between $\bar{A}$ and $\Delta\phi$ for peak expiratory flow (PEF) and urinary excretion of 17-OHCS. However, the correlations between $\bar{A}$ and $\Delta\phi$ were not statistically significant for grip strength, or for urinary excretion of K^+ and Na^+.

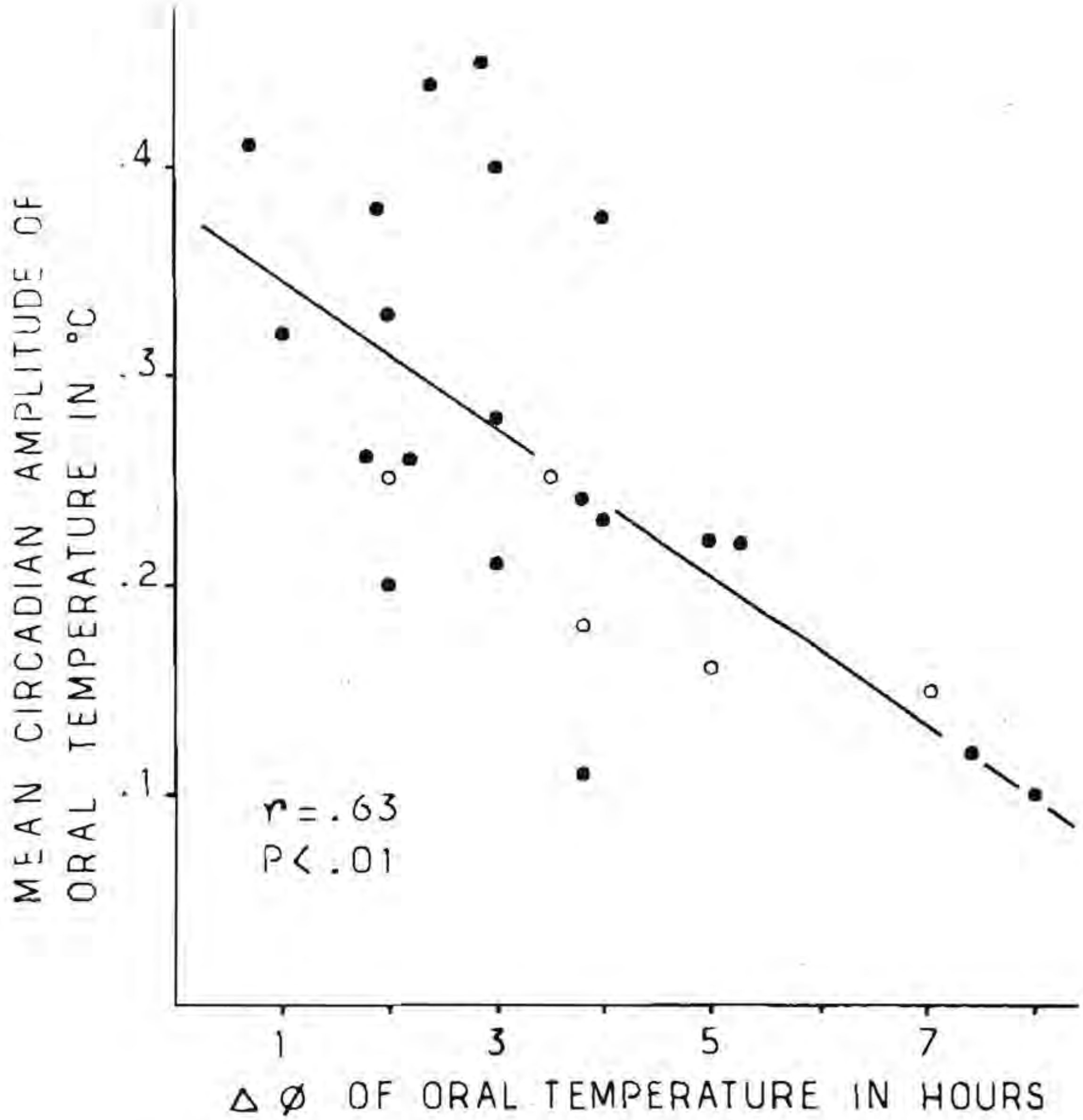

Figure 1. Correlation between individual mean amplitude (A) and acrophase shift (Δϕ) of the oral temperature circadian rhythm (Study 1): subjects from the Reichstett study (O); subjects from the Petit-Couronne study (O).

Table 1

Correlation Between the Circadian Rhythm Amplitude A and the Acrophase Shift After the First Night Shift for Six Variables

Variables	r	p
Oral temperature	−0.63	< 0.01
Peak expiratory flow	−0.53	< 0.01
Grip Strength	−0.20	> 0.05
Urinary 17-OHCS	−0.60	< 0.01
Urinary potassium	−0.15	> 0.05
Urinary sodium	−0.18	> 0.05

It was of interest to examine whether or not the amplitudes of different variables were correlated. It appeared that the _A_ of oral temperature was correlated with the _A_ of PEF ($r = .48$; $p < .05$) but not with the _A_ of urinary 17-OHCS ($r = .07$; $p > .05$). A (positive) correlation between subjects' age and circadian rhythm _A_ was found only for PEF: the older the subject, the larger the _A_ ($r = .57$; $p < .01$).

Is a Large Circadian Rhythm Amplitude in Oral Temperature Related to Good Clinical Tolerance of Shiftwork? (Study 2)

Subjects. Forty-eight shiftworkers volunteered for the study. Twenty-three were employed in a plant of the Steel Industry (SI) near the city of Saint-Etienne; the other 25 were employed in a plant of the Chemical Industry (CI) near the city of Grenoble. Age distribution was quite similar within groups (industry) and subgroups (tolerance of shiftwork). However, a large number of non-tolerant subjects had been employed as shiftworkers for at least 10 years. This unequal distribution was not surprising, since intolerance to shiftwork tends to increase with age (Akerstedt, 1976; Landier & Vieux, 1976). The steel workers had a seven-day shift (weekly rotation). The chemical workers worked a rapidly rotating system with a shift duration of two days.

Criteria for assessing tolerance of shiftwork. Clinical tolerance was assessed conventionally by considering both the existence and the intensity of 3 types of shiftwork-associated problems. These can be classified as _digestive_, _neurological_ and _sleep disturbing_. With respect to digestive problems, the common complaints were: dyspepsia, gastritis, colitis, and peptic ulcer. Neurological problems were mainly unusual irritability and persistent fatigue. The latter differed from the physiological fatigue resulting from physical and/or mental effort since it did not disappear after rest. Sleep disturbances included poor subjective quality of sleep, insomnia and frequent awakening. In some individuals, two or three types of problems were sometimes found together.

It must be emphasised that a person who has been shiftworking for many years is well able to recognize changes both in his capacity to carry out work and in his physical vigor following nocturnal sleep when off duty. Thus, it was possible in this study to use a subject's own reports, as well as clinical observations, to judge the degree to which he was tolerating (or not tolerating) his shiftwork schedule.

Methods

Normal large-scaled calibrated clinical thermometers (accurate to 1/20° C) were used for oral temperature measurements. Data were collected over a 4-week span on the last day (i.e., either the second or seventh) of each of the shifts, at 2 h intervals and fixed clock hours.

Both conventional (t-tests of differences between means; Chi Square tests of group distributions, etc.) and cosinor (Halberg et al., 1972) methods were used for statistical analyses.

Results

The differences between the maximum and the minimum (Max-min Diff) were pooled over shifts for group and subgroup analyses. Table 2 indicates a highly statistically significant difference in the Max-min Diff between subjects tolerating and not tolerating shiftwork. This is true for both SI and CI shiftworkers.

Table 2

Mean Difference Between Circadian Maxima and Minima in Oral Temperature (°C) in Shiftworkers Showing Good and Poor Tolerance of Shiftwork

Group (Shift-duration)		Tolerance of Shiftwork Good	Poor	p
Steel Industry [SI] (7 days)	X	1.42	1.06	<.005
	SE	0.13	0.09	
	N	9	14	
Chemical Industry [CI] (2 days)	X	1.16	0.77	<.005
	SE	0.06	0.08	
	N	11	14	
SI + CI Combined	X	1.28	0.92	<.005
	SE	0.08	0.07	
	N	20	28	

Cosinor analysis detected statistically significant circadian rhythms in both tolerant and intolerant subgroups of subjects working in both the steel and chemical industries. The Mesor values of these rhythms were not statistically different in the different groups, or in tolerant and intolerant subjects. The acrophase locations were very similar (around 1600) in all cases.

Statistically significant differences were found only in amplitude: a small circadian $\underline{A}$ was associated with poor shiftwork tolerance, while good tolerance to shiftwork was associated with a relatively large $\underline{A}$ (see Table 3).

Table 3

Summary of Single Cosinor Analysis of the Cirdadian Rhythms in Oral Temperature (°C) of Subjects with Good or Poor Tolerance of Shiftwork

Group (Shift Duration)	Tolerance of Shiftwork	Rhythm Detection $P(\underline{A}=0)$	Mesor ISE (°C)	Amplitude (°C) (95% limits)	Acrophase (hr min) (95% limits)
Steel Industry	Good (N=9)	<.005	36.66±.17	.49(.41-.56)	16.41(16.07-17.)
[SI] (7 days)	Poor (N=14)	<.005	36.62±.10	.32(.26-.38)	15.34(14.55-16.)
Chemical Industry	Good (N=11)	<.005	36.85±.08	.35(.30-.40)	15.52(15.19-16.)
[CI] (2 days)	Poor (N=14)	<.005	36.86±.06	.25(.21-.29)	16.24(15.44-17.)
[SI + CI]	Good (N=20)	<.005	36.77±.06	.40(.36-.44)	16.21(15.57-16.)
Combined	Poor (N=28)	<.005	36.76±.04	.27(.24-.31)	16.02(15.33-16.)

Individual differences. The Chi Square test was used to examine the association between tolerance of shiftwork and the Max-min Diff in oral temperature rhythm in the different groups. The association was not statistically significant for the SI subjects, but it was for the CI subjects: in this group, of the 11 subjects who tolerated shiftwork, 9 had an average Max-min Diff greater than 0.94°C, while of the 14 subjects who did not tolerate shiftwork, 9 had a Max-min Diff less than 0.94°C (Chi Square = 5.31; $p < .025$). When the data was pooled across industries, of the 20 subjects who tolerated shiftwork, 16 had a Max-min Diff greater than 1.07°C, while of the 28 subjects who did not tolerate shiftwork, 18 had a Max-min Diff less than 1.07°C (Chi Square = 9.22; $p < .005$).

Circadian Rhythm Amplitude, Tolerance to Shiftwork, and Age (Study 3)

Subjects

Twenty-nine oil refinery operators on a rapidly rotating shift system (3-4 days) volunteered for this study. Four groups of subjects were formed:

- Group I: 6 young operators with no previous complaints. Mean age = 25.3 years (range 21 to 35 years). Mean shiftworking duration = 2.3 years (range 1 to 4 years);
- Group II: 10 senior operators with no history of shiftwork-related problems. Mean age = 50 years (range 44 to 57 years). Mean shiftworking duration = 25.1 years (range 15 to 32 years);
- Group III: 6 senior operators with minor complaints such as feeling tired after the night shift, and poor sleep quality. Mean age = 50.2

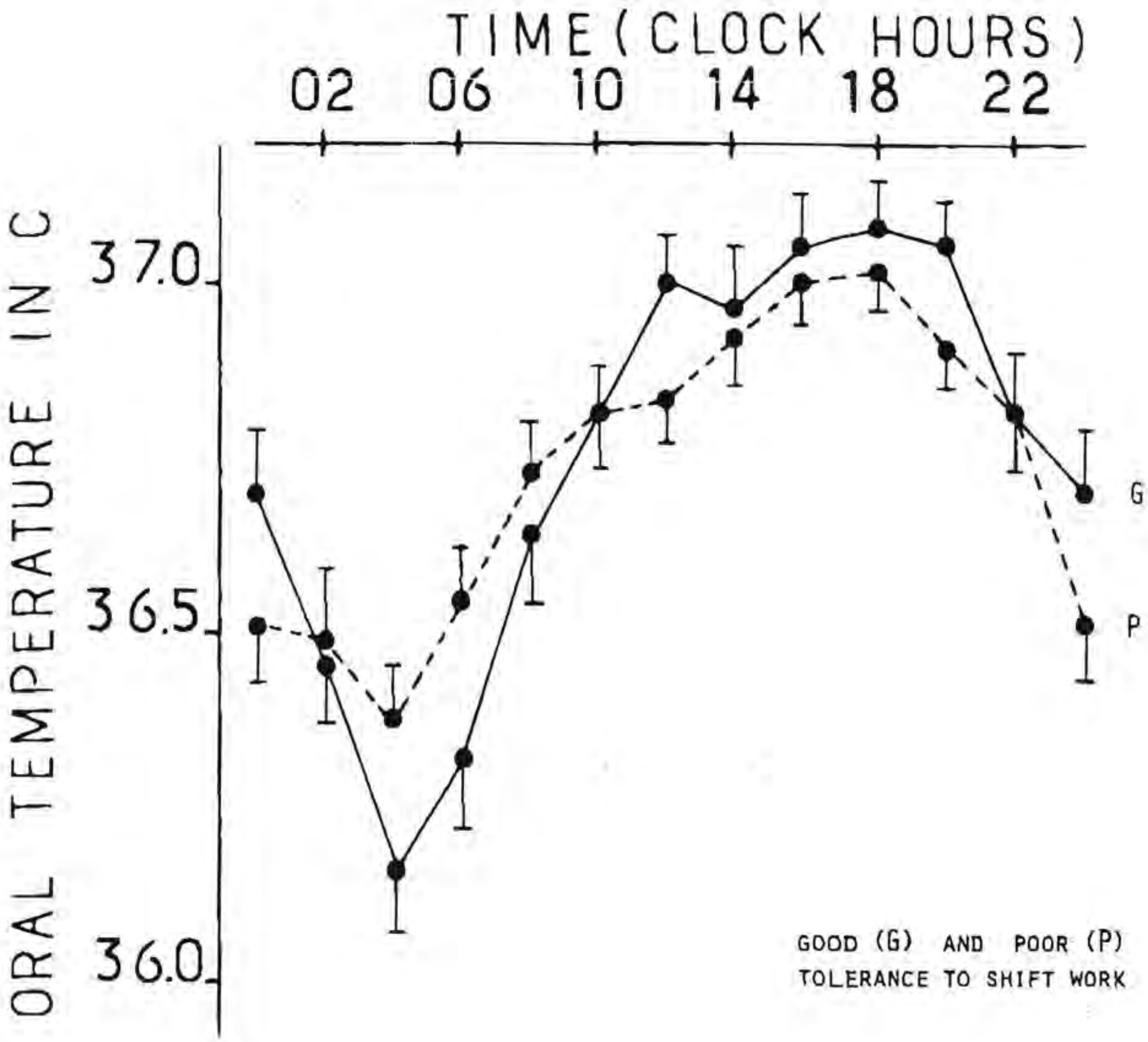

Figure 2. Circadian oral temperature rhythms of subjects with Good (G) or Poor (P) tolerance of shiftwork (Study 2): Means ± ISE.

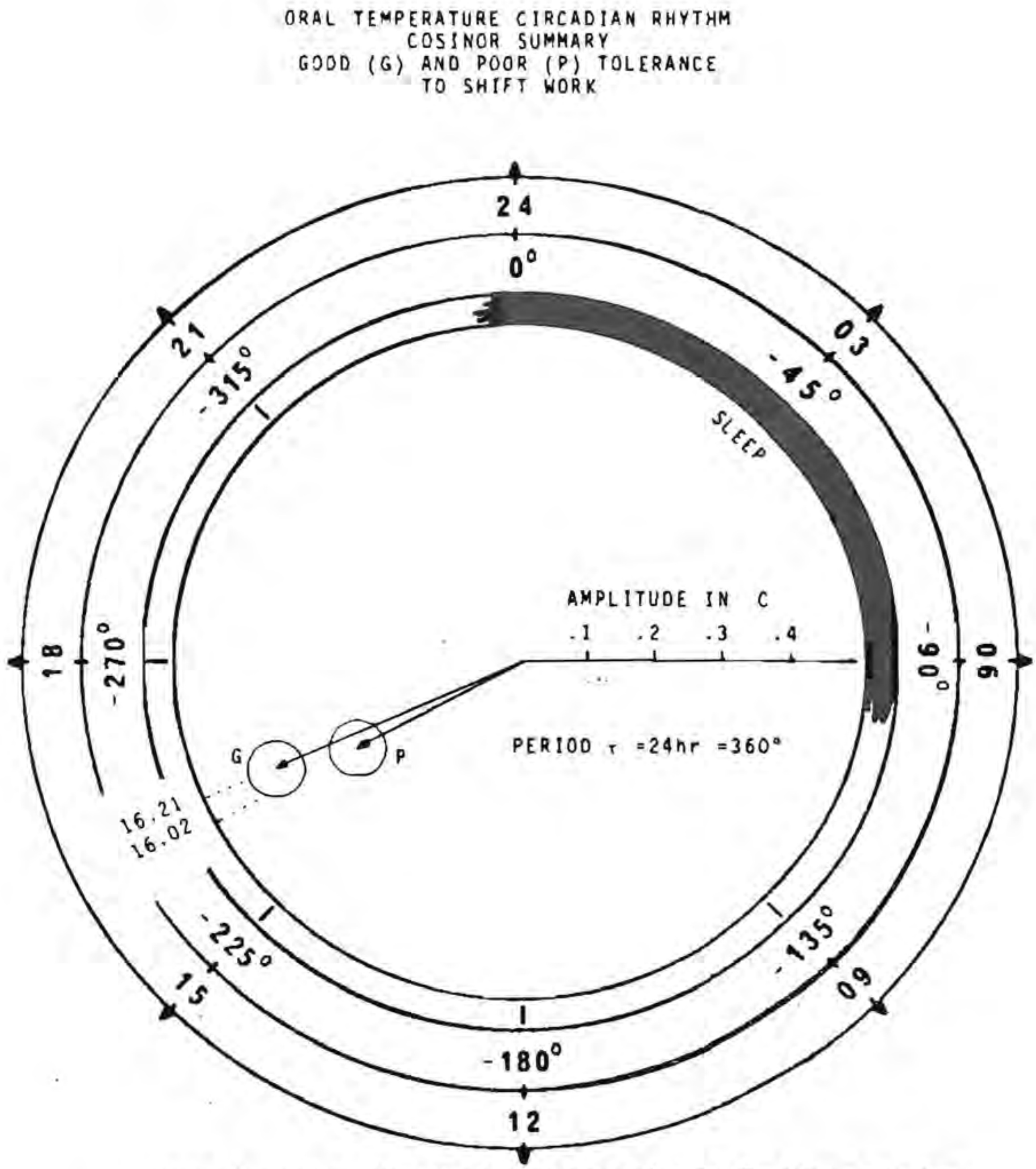

Figure 3. Cosinor plot of oral temperature rhythms of subjects with Good (G) or Poor (P) tolerance of shiftwork (Study 2): Circadian rhythms are detectable in both groups. Acrophases are similar, but amplitudes differ significantly ($p < .001$), confirming the impression gained from inspection of the curves in Figure 2.

years (range 46 to 56 years). Mean shiftworking duration = 26 years (range 22 to 31 years);

Group IV: 7 senior operators with major complaints such as persistent fatigue, large subjective deterioration in sleep quality, use of sleeping pills. Mean age = 47.4 years (range 30 to 56 years). Mean shiftworking duration = 22.9 years (range 9 to 29 years).

Senior operators' opinions and actions were a major determinant of their allocation to Group II, III, or IV. Those constituting Group III considered themselves capable of continuing shiftwork while those constituting Group IV had, in fact, already requested or agreed to be taken off shiftwork. [The salary of a shiftworker in this refinery was not reduced on resumption of regular day work; thus, there were no financial considerations in this decision.]

Methods

Oral temperature was measured every four hours at fixed clock times (except during sleep). Large clinical mercury thermometers (as in Study 2) were used.

For each of the 29 individuals, a longitudinal time series over 3 weeks (approximately 100 data points) was obtained, from which the oral temperature rhythm was assessed. As for Studies 1 and 2, various statistical methods were used to analyze the data.

Results

Hypothesis I. The relationship between A and $\Delta\phi$ for all the subjects in Study 3 is shown in Figure 4. As in Study 1, there was a significant negative correlation between the two variables, of a magnitude comparable to the one observed in that study. Hypothesis I is, thus, reconfirmed by the results.

Hypothesis II. Max-min Diff gives some idea of the differences in rhythm amplitude between the groups. The Max-min Diff was 0.80°C ± 0.04 (1 SE) for Group I; 0.76 = 0.03 for Group II; 0.70 = 0.05 for Group III; and only 0.48 ± 0.04 for Group IV. The difference between Group IV and Groups I and II combined was highly statistically significant ($p < .0005$). The mean rhythms for Group II and IV are shown in Figure 5.

The results obtained from a cosinor analysis are summarized in Figure 6 and Table 4. A statistically significant circadian rhythm was detectable in each of the four groups. The Mesor did not differ between the groups, being around 36.5°C and the acrophase locations were similar. The amplitude value was also similar in Group I, II, and III, but was significantly reduced in Group IV. Thus, the cosinor analysis shows that the only difference between subjects who are tolerant and intolerant of shiftwork is their temperature circadian A.

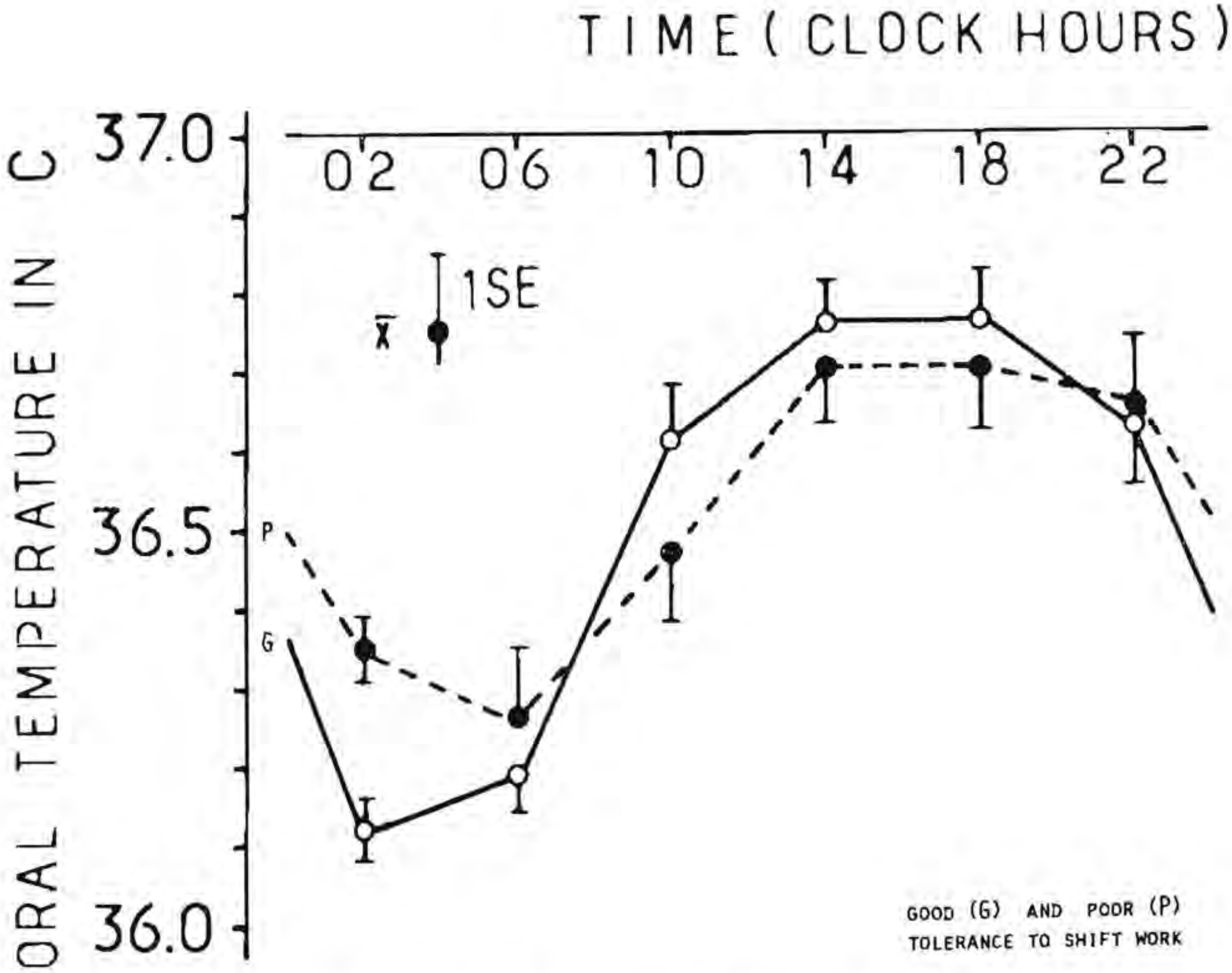

Figure 4. Correlation between individual mean amplitude (A) and acrophase shift (Δφ) of the oral temperature circadian rhythm (Study 3): Pooled data of the four groups.

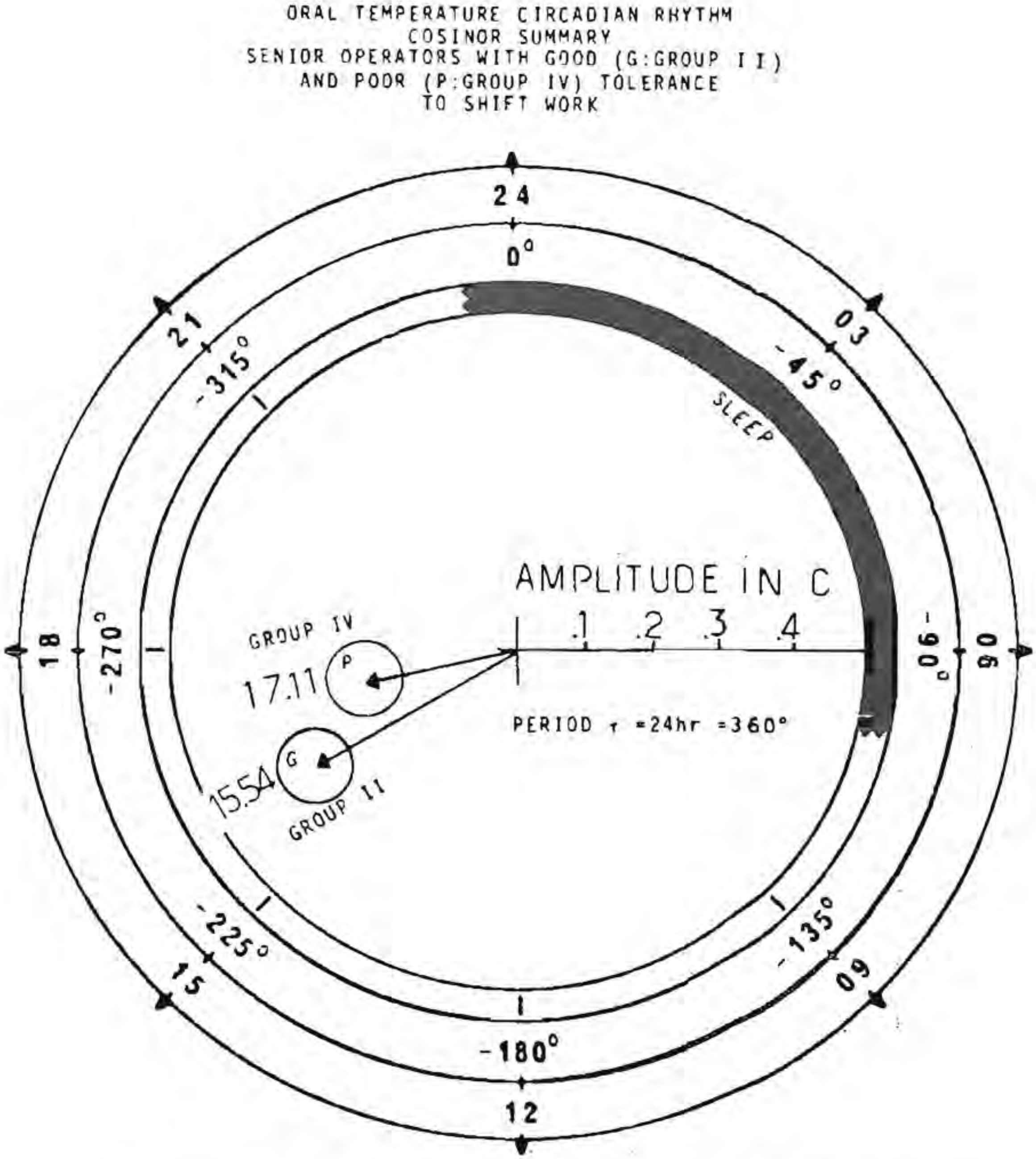

Figure 5. Circadian rhythms of oral temperature (Study 3): Senior operators with Good (G) tolerance of shiftwork (O) [Group II]; Senior operators with Poor (P) tolerance of shiftwork (O) [Group IV].

Table 4

Summary of Cosinor Analysis of the Circadian Rhythms in Oral Temperature of Subjects With Good, Adequate or Poor Tolerance of Shiftwork

Group (Mean age in Years)	Tolerance of Shiftwork	Rhythm Detection P(A=0)	Mesor 1SE (°C)	Amplitude (°C) (95% confidence limits)	Acrophase (hr min) (95% confidence limits)
I (25.3)	Good (N=6)	<.005	36.53±.08	.37 (.29-.45)	15.49 (14.38-17.00)
II (50.0)	Good (N=10)	<.005	36.51±.07	.35 (.30-.40)	15.54 (15.21-16.27)
III (50.2)	Adequate (N=6)	<.005	36.53±.11	.30 (.24-.36)	16.57 (15.41-19.05)
IV (47.4)	Poor (N=7)	<.005	36.52±.12	.23 (.17-.29)	17.11 (16.07-18.14)

Results of Animal Experiments

The results obtained by Yunis, Halberg, McMullen, Roitman, and Frenandes, (1973) and Yunis, Fernandes, Nelson, and Halberg, (1974) with animals may have some bearing on the findings of the present studies. Yunis et al. assessed the circadian rectal temperature parameters A and ϕ in different strains of mice (mainly CBA and NZB) before, during, and after manipulations of the light-dark (LD) synchronizer, in animals of different ages. From their results, it can be deduced that autoimmune resistant mice of strain CBA adjusted slowly after a $\Delta\psi$ resulting from a LD cycle manipulation, and showed a relatively small decrease in the A of the temperature rhythm with age; whereas mice of strain NZB (who develop autoimmune hemolitic anemia, antinuclear antibodies and kidney lesions in their first year of life) adjusted rapidly after the same $\Delta\psi$ of the LD cycle, and showed a relatively large decrease in the circadian A with age. In addition, other results obtained by Yunis et al. suggested that both the speed of adjustment $\Delta\psi$ and the amplitude A of the temperature rhythm, as well as changes in these parameters with age were of genetic orgin.

Comments

The results obtained from the present studies are in good agreement with each other. On the one hand, they show a correlation between A and $\Delta\phi$ of the circadian temperature rhythm, the greater the A, the smaller the $\Delta\phi$. On the other hand, they show that good tolerance of shiftwork is associated with a relatively large A of this rhythm. Both of the hypotheses described in the introduction were thus confirmed.

In order to understand the relationship between the temperature circadian A and tolerance of shiftwork, the possible role played by age (and/or the number of years of shiftwork) must be taken into account. In these experiments,

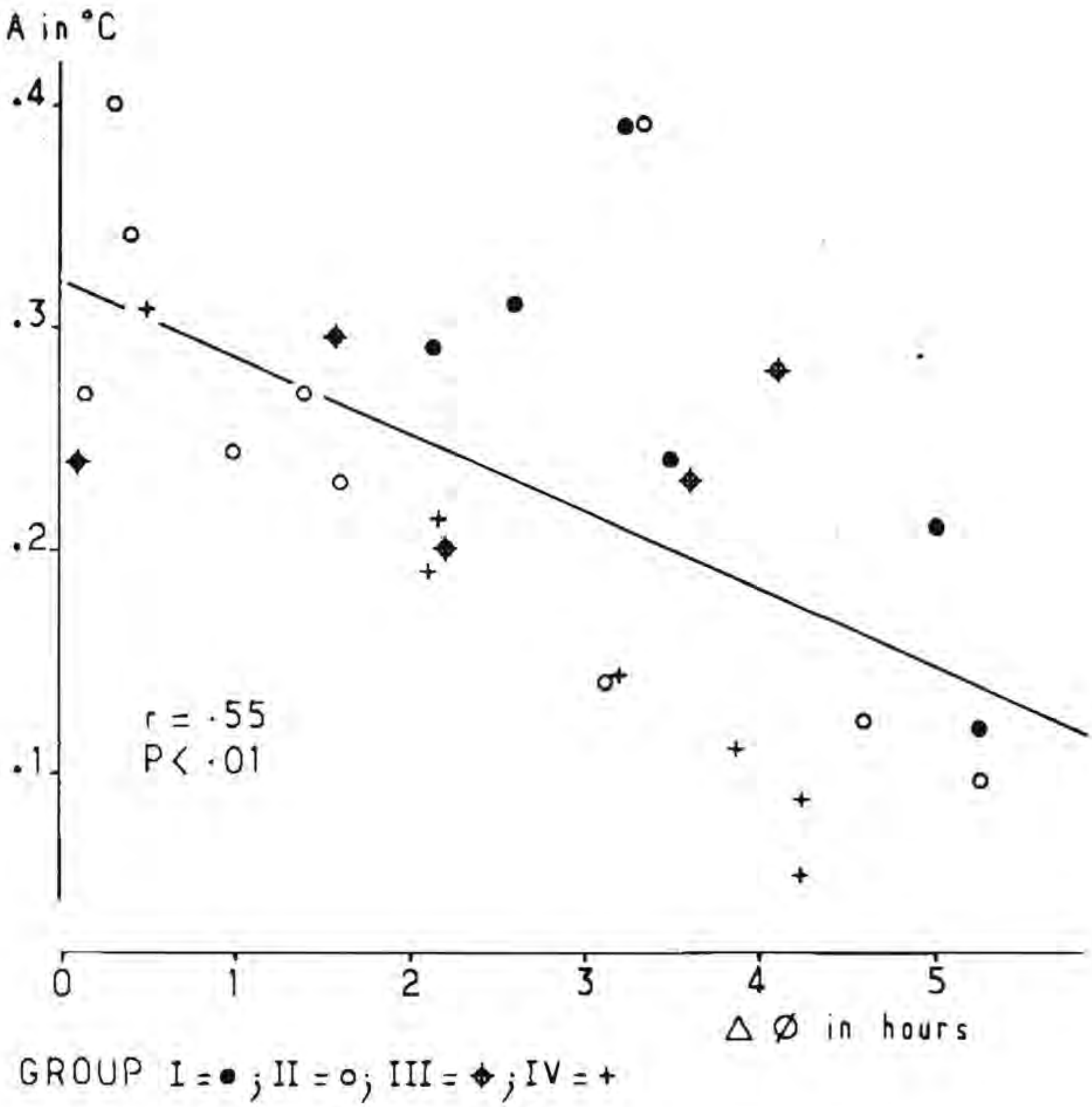

Figure 6. Cosinor plot of oral temperature rhythms of subjects with Good (G) and Poor (P) tolerance of shiftwork (Study 3): Circadian rhythms are detectable in both groups. Acrophases are similar, but amplitudes differ significantly ($p < .01$), confirming the impression gained from inspection of the curves in Figure 4.

we were dealing with subjects of both different ages and tolerance, and not with the effect of age per se. The animal model of Yunis et al. (1973, 1974) suggests that the age-related reduction of the circadian temperature A could be genetically dependent.

Further experiments will be necessary to test the hypothesis that human subjects with a relatively small A (whether resulting from aging or not) actually become intolerant to shiftwork. The possibility that an observed small A could in fact be produced by a history of poor tolerance of shiftwork should also be considered.

Practical Perspectives

If long-term tolerance of shiftwork is associated with a large A and a slow adjustment in the circadian temperature rhythm, shift schedules which do not allow subjects to adjust to a "new" synchronization would seem to be preferable. This means that, for encouraging such tolerance to develop, a rapidly rotating shift system (with shift changes every 2 to 4 days) would be a better choice than the conventional weekly rotating system.

However, it should be kept in mind that in the studies reviewed (Reinberg et al., 1978a, 1978b, in press; Andlauer & Reinberg, in press), the shiftworkers did in fact adjust rapidly, as a group. This ability may be related to the age of the subjects, who in both studies were relatively young (means 34.5 and 24.4 years), and it seems that adjustment is faster in younger than in older shiftworkers. In addition, the samples of subjects were less homogeneous than expected with respect to long-term tolerance of shiftwork. We were, in effect, dealing with an already selected group of "tolerant" shiftworkers (tolerance being defined in this case as having had less than 10 years of this type of work, which was true for 23 of the 26 subjects). Intolerance of shiftwork may only be revealed later (as seen in the subjects of Group IV in Study 3). Thus in considering the findings, the ability to adjust rapidly seems, if anything, to be an advantage in a young subject, but of no help in predicting whether or not he will tolerate shiftwork for 20 years or more. Nonetheless, the amplitude of the circadian temperature rhythm appears to be a good candidate for a chronobiological index of long-term tolerance of shiftwork. Obviously, further studies are needed to assess the practical applicability of these findings.

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THE TWENTY-FOUR HOUR WORKDAY: PROCEEDINGS OF A SYMPOSIUM ON VARIATIONS IN WORK-SLEEP SCHEDULES

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