Reprint from:

WAKING AND SLEEPING

International Journal for Wakefulness, Fatigue, Sleep and Dreams

ORIGINAL CONTRIBUTIONS

Waking and Sleeping (1977), 1:259–279

Chronobiologic Serial Sections Gauge Circadian Rhythm Adjustments following Transmeridian Flight and Life in Novel Environment

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Key words: *Circadian rhythms — Adjustment — Transmeridian Flight — Pollution — Peak Expiratory Flow.*

Abstract. Circadian rhythms were examined by chronobiologic serial sections applied to self-measurements of oral temperature, peak expiratory flow, vital capacity, eye-hand skill and heart rate, as well as urinary volume, sodium and potassium, by a presumably healthy young woman before and after 2 transmeridian flights across 6 time zones. Polarity characterized the adjustments of these circadian rhythms in that the rhythms' timing changed faster following the flight from east to west (even though this flight takes place in a direction away from home) as compared to the adjustment rate after the homeward flight (from west to east). Adjustment rates differ among variables and the variables themselves differ in the prominence of their circadian rhythmicity. Noisiness notwithstanding, chronobiologic serial sections represent useful tools in the hands of a physiologist interested in the extent of coupling among circadian rhythms, in the hands of an ecologist wishing to exploit predictable physiologic variability for environmental monitoring or in the hands of the physician assessing the shift-behavior of pathologic as well as physiologic rhythms (metarhythmometry) for diagnosis and therapy.

Ajustements de rythmes circadiens mesurés par des sections sérielles chronobiologiques après des vols transméridiens et un séjour dans un environnement nouveau

Résumé. Les rythmes circadiens de plusieurs variables physiologiques (auto-mesures de la température orale, du débit expiratoire de pointe, de la capacité vitale pulmonaire, de la fréquence cardiaque, de la coordination oculo-motrice ainsi que des excrétions urinaires de l'eau, du sodium et du potassium) ont été étudiés chez une jeune femme en bonne santé apparente, avant et après deux vols transméridiens à travers 6 fuseaux horaires. Les sections sérielles chronobiologiques ont été utilisées pour apprécier l'ajustement des rythmes circadiens après ces changements de synchronisation socio-écologique.

Une polarité caractérise les ajustements de ces rythmes circadiens en ce sens que leur déplacement dans l'échelle des 24 heures se fait plus rapidement après le vol d'est en ouest (même si ce vol se fait dans une direction qui éloigne le sujet de son pays) par comparaison à la vitesse de l'ajustement après le vol d'ouest en est (vol de retour au pays d'origine). Les vitesses d'ajustement varient d'une variable à l'autre et ces variables elles-mêmes diffèrent entre elles par la prédominance de leur rythmicité circadienne. Malgré le «bruit» que comportent les séries expérimentales, les sections sérielles chronobiologiques représentent des instruments utiles: dans les mains du physiologiste qui s'intéresse à l'étendue de couplage entre rythmes circadiens; dans les mains de l'écologiste qui souhaite exploiter la variabilité physiologique prévisible en vue du contrôle de l'environnement; ou dans les mains du médecin utilisant le comportement de rythmes physiologiques ou pathologiques, après un changement de phase des synchroniseurs dans le cycle de 24 heures (ce qu'on appelle la métarythmométrie) en vue du diagnostic ou de la thérapeutique.

Introduction

In one and the same organism various circadian rhythmic functions can reveal differences in their adjustment to a new schedule instituted, for instance, in the habitual environment or after geographic transposition into a new environment (Halberg, 1969; Halberg and Reinberg, 1967). Chronobiologic serial sections (Halberg et al., 1964) here serve to examine the speed, the extent and the direction as well as the regularity of adjustments in the case of a presumably healthy young woman who carried out self-mea-

Supported by U.S. Public Health Service (5-K06-GM-13981-14), National Cancer Institute (1R01-CA-14445-01) and the Environmental Protection Agency (R804512-01-1) and by the "Fondation de l'Industrie Pharmaceutique pour la Recherche" Contract n° 20

Table 1. Events during study

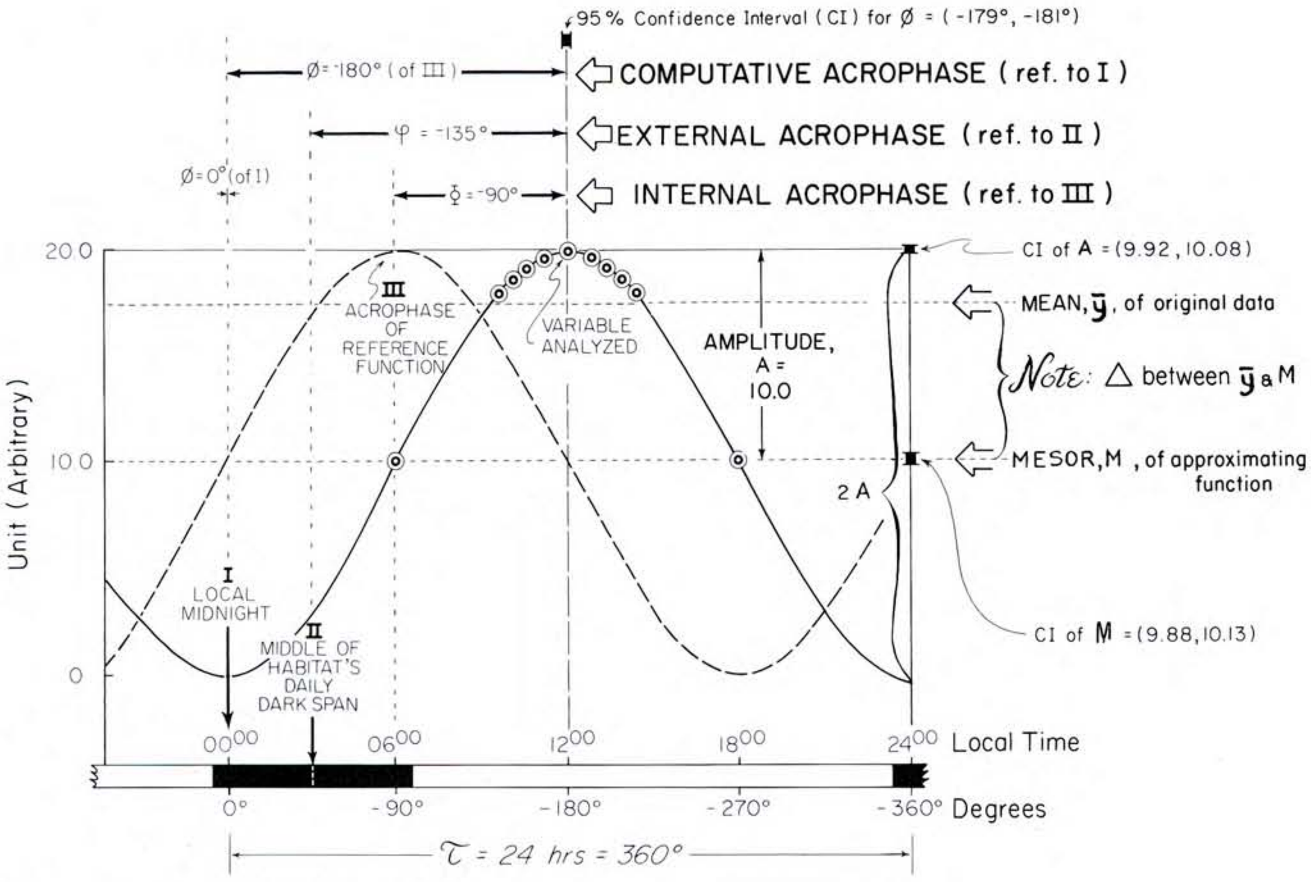
Study stage	SS event No.	Symbols		
I		S	– July 30	Start self-measurements in France (Paris-Toulon)
	1	↓	Sept. 1	Transmeridian flight across 6 time zones (Paris-New York-Minneapolis)
II		A	b – Sept. 28	U.S. domestic flights bridging 1 time zone (Minneapolis-Denver)
		A	c –Oct. 2	(Denver-San Francisco)
		A	d –Oct. 7	(San Francisco-Denver)
		A	e –Oct. 8	(Denver-Minneapolis)
		†	f –Oct. 15	Death of a beloved grandmother
		A	g –Nov. 3	U.S. domestic flight bridging 1 time zone (Minneapolis-New York)
	2	↑	Nov. 11	Transmeridian flight across 6 time zones (New York-Paris)
III		E	–Dec. 27	End of self-measurements

First days of consecutive menstruations recorded in relation to study: July 30, August 27, September 22, October 18, November 12, December 7. The mean menstrual period was 25.8 days between January and June and 25.6 days during the sojourn in the U.S.A.

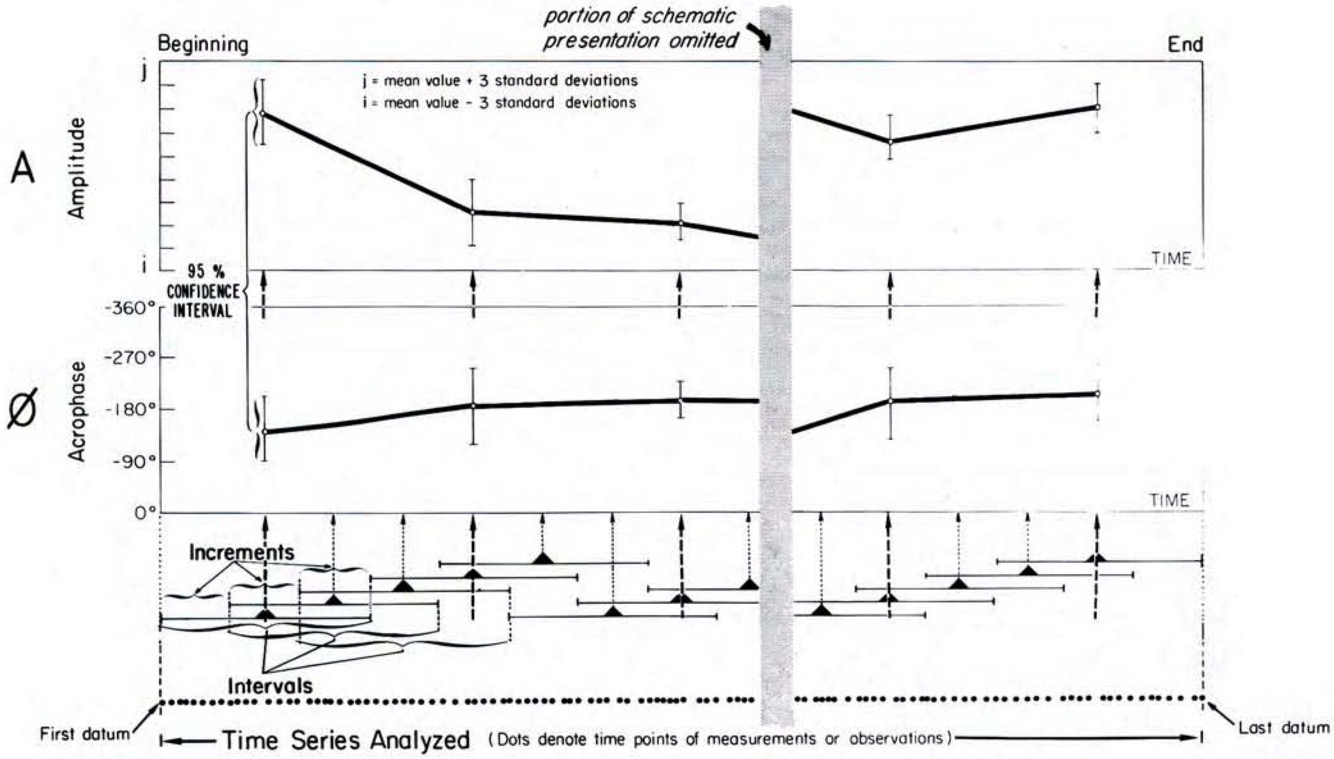
surements in France, during a stay of several months in the U.S.A., and upon her return to France. *Differences in speed of adjustment and perhaps even in direction* thus are discerned among physiologic circadian rhythms. These findings in themselves are of interest to those transferred to new environments and/or subjected to new schedules of activity, with or without geographic displacement. Self-measurement (for data collection) combined with chronobiologic serial sections (for data analysis) has broader applicability in physiology for exploring (by the extent of stationarity) the stability or lability of biologic rhythm characteristics as a function of time and for gauging the time course of changes in such rhythm characteristics following environmental and/or organismic manipulation. The extent to which the transient changes in the time relations among rhythms alter the organism's immediate psychophysiologic performance and long-term fate, including the lifespan, constitutes a related problem beyond our scope herein.

Subject and Methods

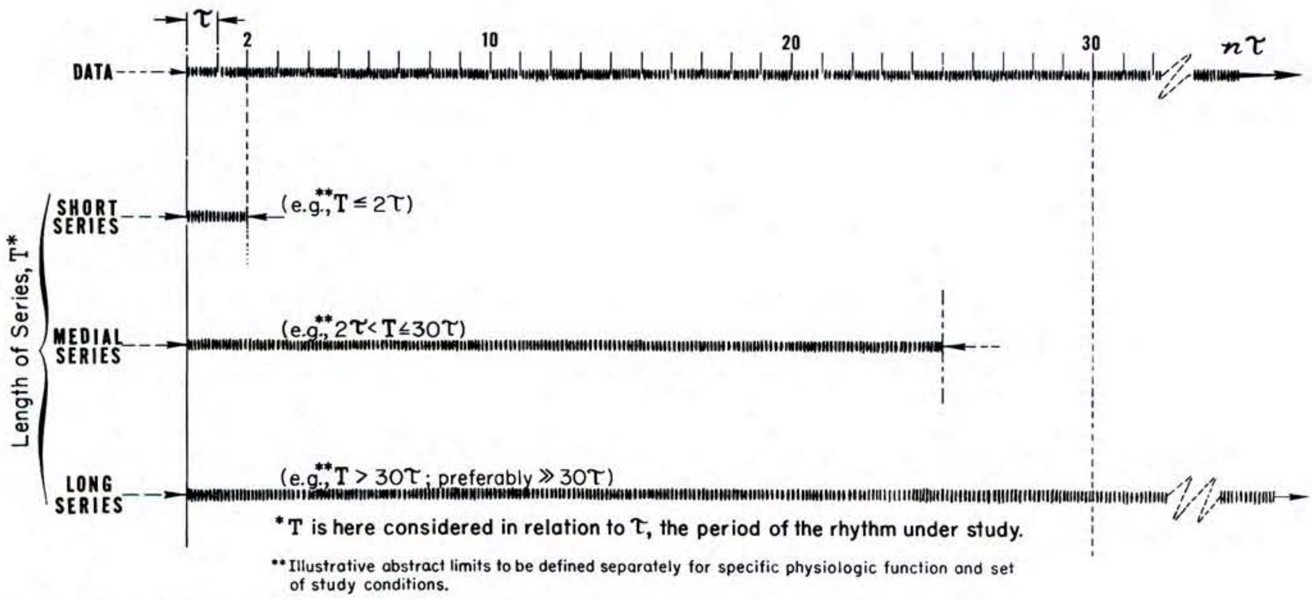
A presumably healthy woman, 17 years of age, was the subject of this study covering a span of several months during which she experienced the events shown in Table 1. The times of several transmeridian



Scheme 1. Scheme of quantitative rhythm characteristics



Scheme 2. Part of chronobiologic serial section. Pergressive amplitude and acrophase displacement by a fixed increment of a fixed interval analyzed for transforming a time series into diagrams of acrophase and amplitude



Scheme 3. Arbitrary period-criteria for classifying length of time series*

flights, including two intercontinental ones, indicate also the start of changes in both her physical and social environments. Several (at least 4) times a day throughout this study she self-measured her oral temperature with a "basal" thermometer, her full-minute pulse using a stop-watch, her peak expiratory flow (PEF) with a Wright Peak Flow Meter, her vital capacity (VC) with a Wright Respirometer and tested her eye-hand skill by a coordinometer (Halberg et al., 1972; Runge et al., 1974). She also recorded the total volume of urine at each voiding and froze a 25 ml aliquot for subsequent determination of Na^+ and K^+ by flame photometry (and eventually of other constituents).

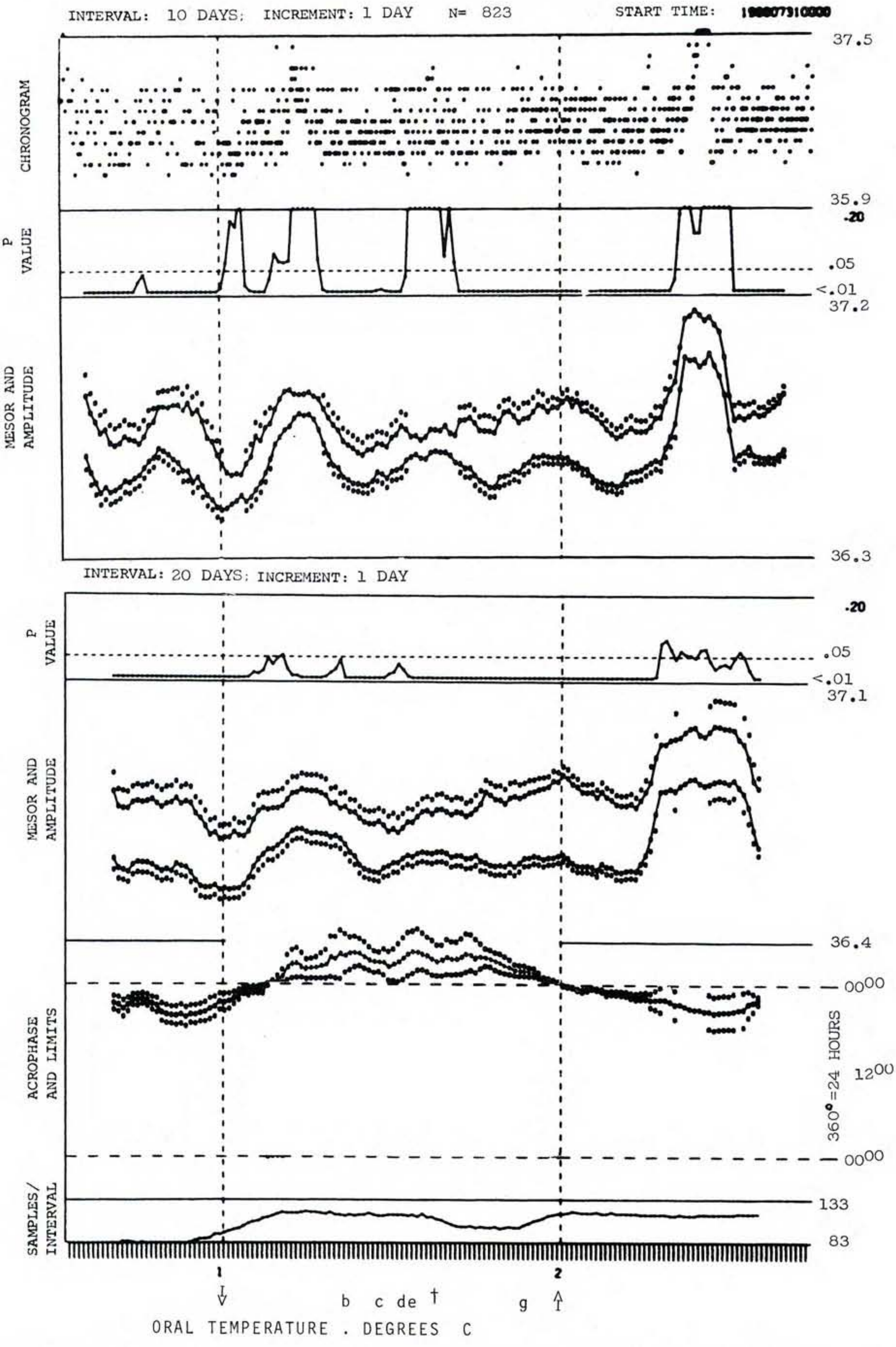


Fig. 1. Circadian rhythm in body temperature of a presumably healthy young woman before and after westward (1) and eastward (2) flights across 6 time zones

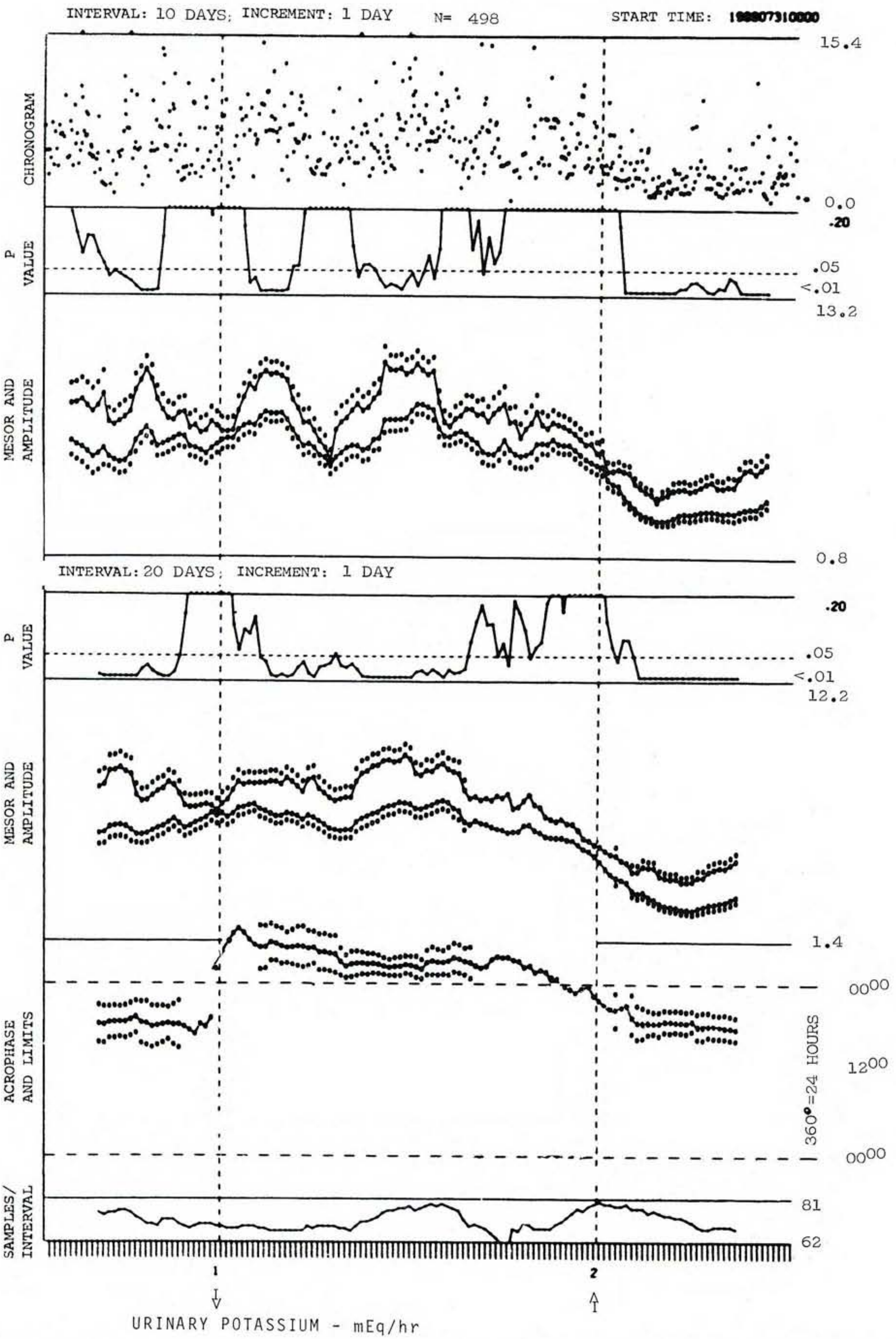


Fig. 2. Circadian rhythm in urinary potassium of a presumably healthy young woman before and after westward (1) and eastward (2) flights across 6 time zones

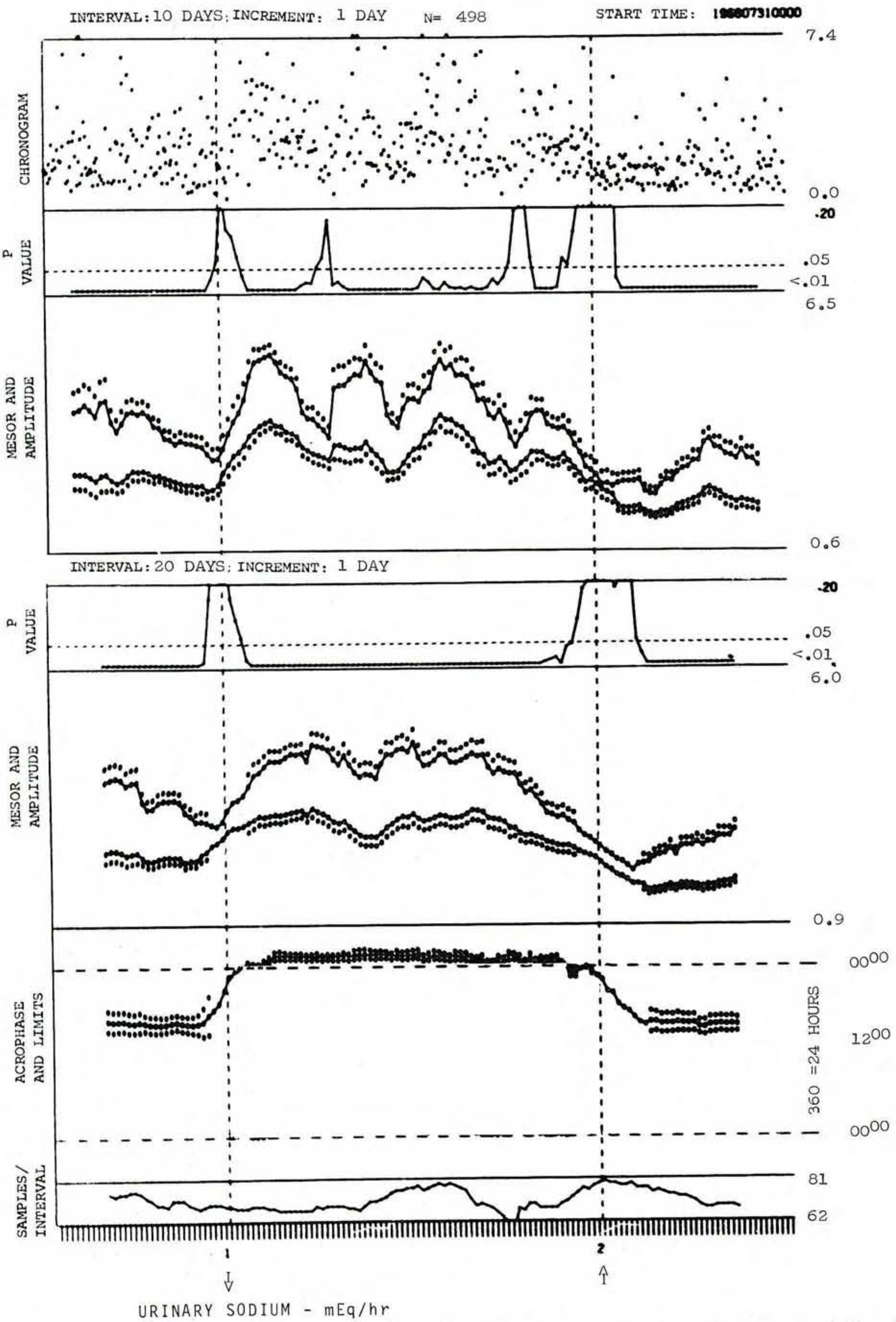


Fig. 3. Circadian rhythm in urinary sodium of a presumably healthy young woman before and after westward (1) and eastward (2) flights across 6 time zones

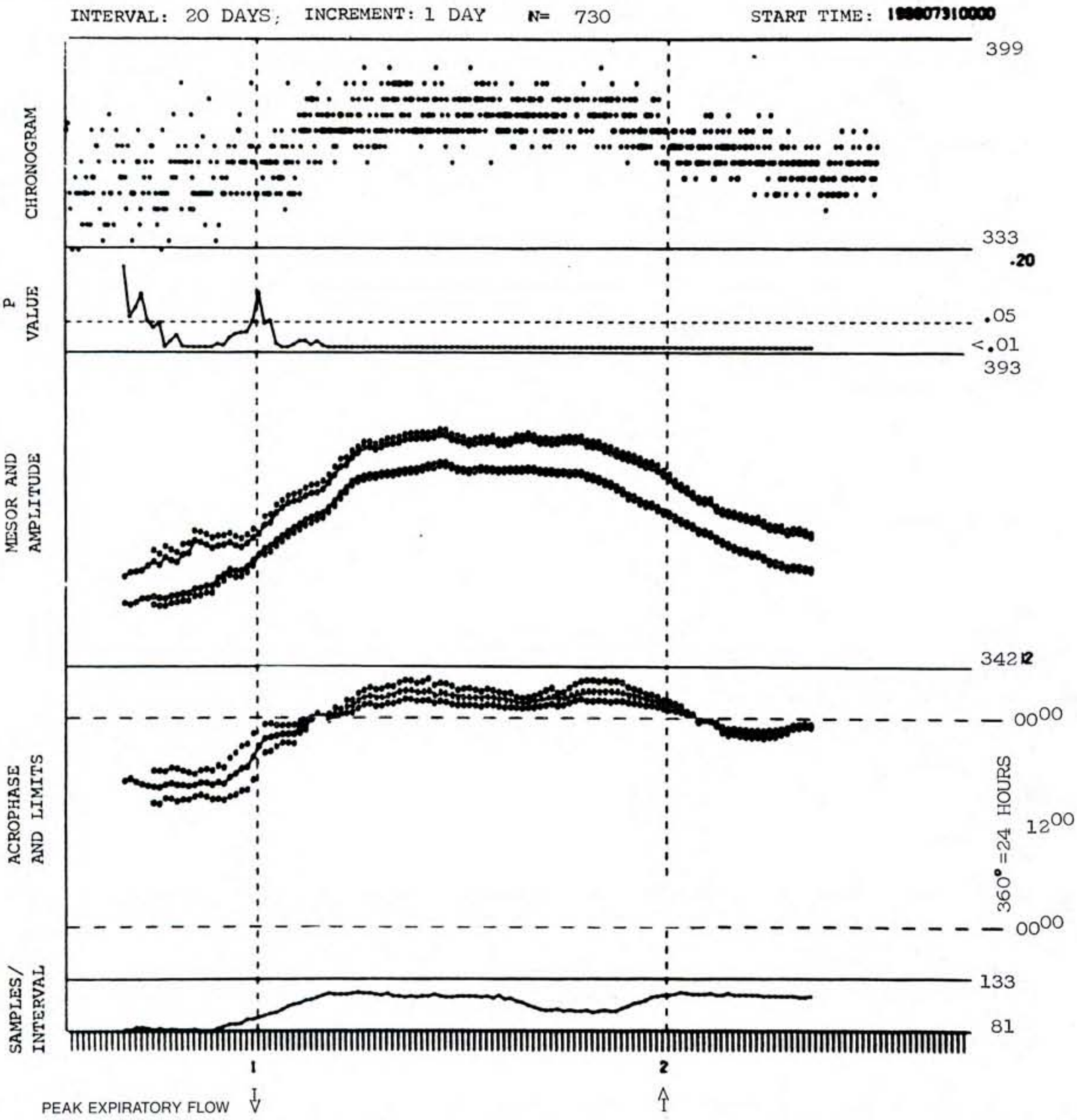


Fig. 4. Circadian rhythm in peak flow (L/min) of a presumably healthy young woman before and after westward (1) and eastward (2) flights across 6 time zones

Data were transferred to punchcards and analyzed by the least squares fitting of a 24-hour cosine curve to derive so-called chronobiologic serial sections (CSS) (Halberg et al., 1965, 1972). Scheme 1 documents the rhythm characteristics investigated and Scheme 2 illustrates the pergressive analysis of a chronobiologic serial section.

Just as in the case of histologic serial sections, one must choose a section width beforehand. More specifically, for a CSS, one displaces, by a fixed increment, a fixed time interval for the analysis of data within that interval. Thereby one transforms a time series into serial estimates of a rhythm's characteristics, including its mesor, amplitude and acrophase, among other indices. Increments can be much shorter than the interval analyzed. Moreover, the CSS allows one to vary, in one and the same time series, the interval chosen for analysis, the increment and even the period chosen for the fit, quite apart from permitting the examination of overlapping sections of a given time series. The three constants chosen by the analyst can be modified repeatedly for the case of certain CSS and often must be changed, when the "resolution" of the rhythm characteristics is "fuzzy" because the interval chosen for analysis is too long or too short. One may eventually arrive at the desired interval in an objective fashion by shortening an interval yielding mostly, if not invariably, statistically significant P values (and by lengthening an interval that yields only a few or no statistically significant P-values). The sparseness of measurements/day seriously limits the analyses here presented.

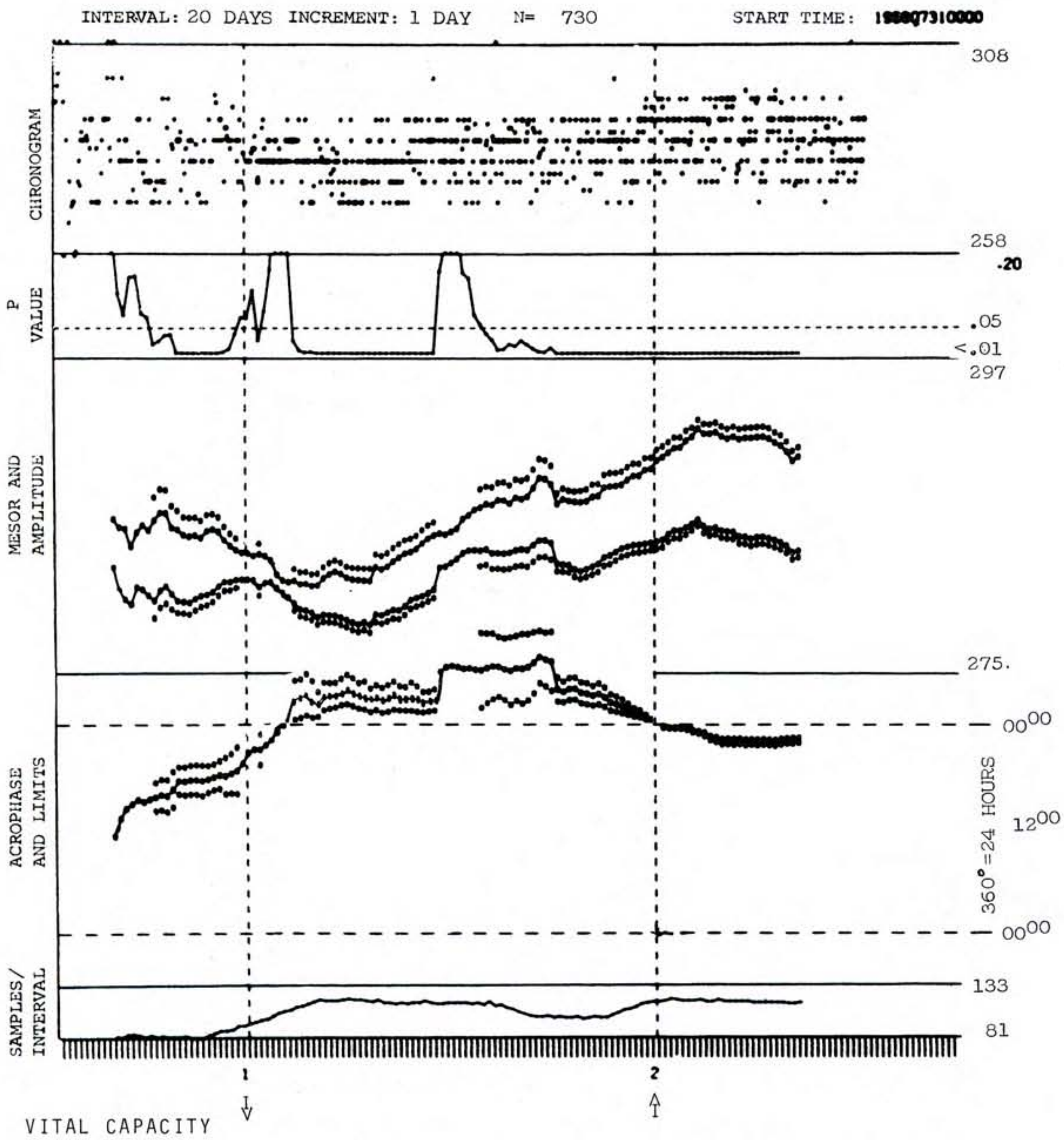


Fig. 5. Circadian rhythm in vital capacity (centiliters) of a presumably healthy young woman before and after westward (1) and eastward (2) flights across 6 time zones

Table 2. Air pollution in Paris at the time of the study

Chemical agent (units)	Vicinity of Home	Vicinity of School	Central lab.	Mean of 6 sites in Paris
CO (PPM)	6.7 from 4 to 10	31.0 from 30 to 40	11.2 from 10 to 20	–
NO_2 (µg/m3)	–	–	30	–
Total dust (g/100 m2/month)	–	–	–	843
Benzo-3,4 pyrène (mg/100 m2/month)	–	–	–	1.0

From data published by the Laboratoire Central de la Préfecture de Police, Paris. Dr P. Chovin.

The pollution has: 1) two daily peaks from 0800 to 0900 and from 1800 to 2000; and 2) an annual rhythm with a peak in November-December and a trough in August.

In the case of long series, Scheme 3, one may start out with an interval equal to the total length of a series; thereafter, one progressively keeps on shortening this interval until either the rhythm is validated for intervals no longer than the period fitted or until the P value obtained in a test for zero amplitude is below 5% for no more than half of the total series analyzed. Too long an interval may obscure a principal aspect of study, e.g., the effect of transmeridian flights. Intervals that are too short will be unstable. It is emphasized that, even for the same subject, different interval lengths may best resolve rhythms, differing in noisiness, in different variables.

Each CSS presents a chronogram, a time plot of original data, in the top row, as in Figure 1. In each chronogram the ordinate scale extends from the overall mean of the time series minus 3 standard deviations (at the bottom) to the mean plus 3 standard deviations (at the top).

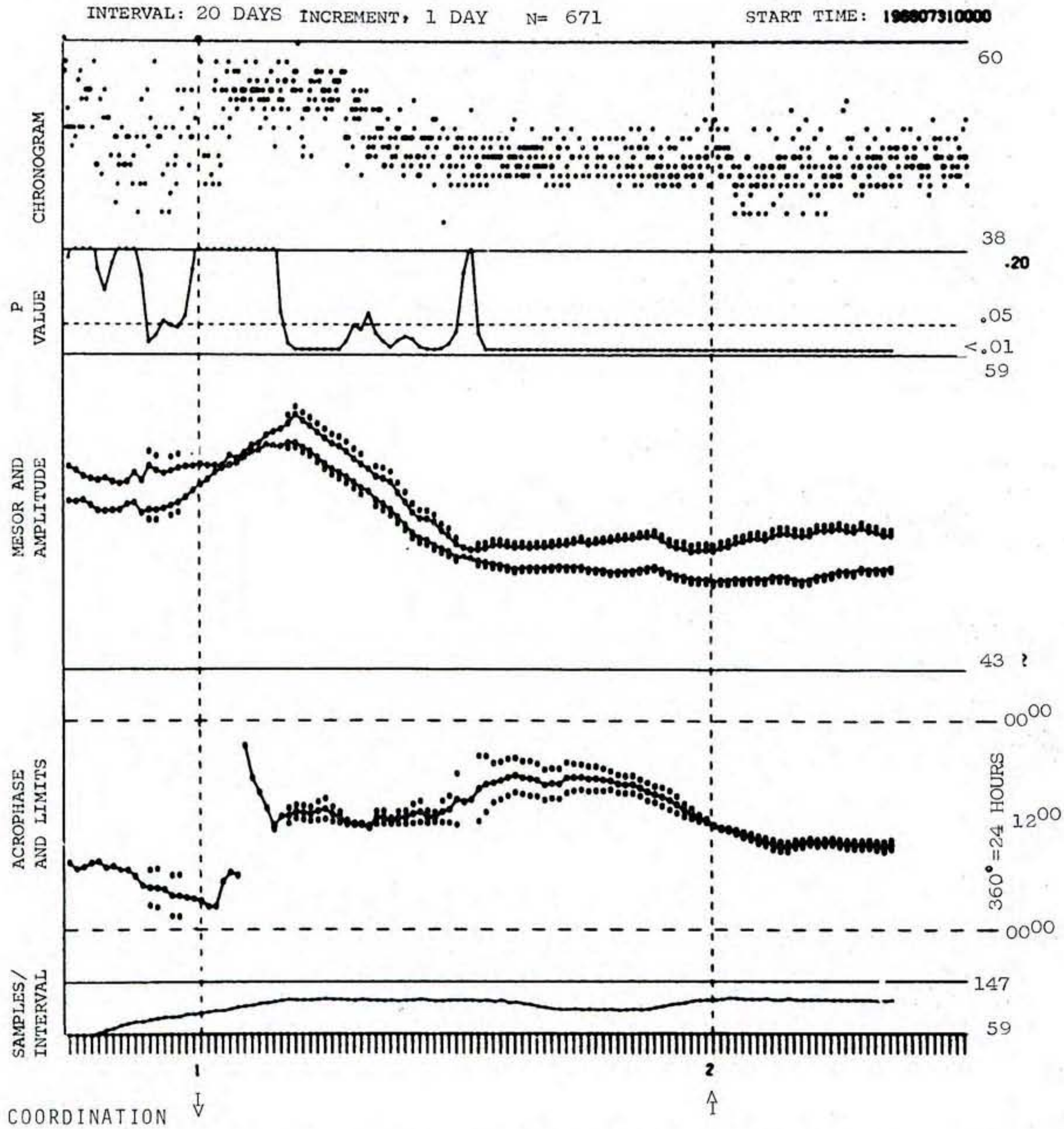


Fig. 6. Circadian rhythm in coordination of a presumably healthy young woman before and after westward (1) and eastward (2) flights across 6 times zones (Units: seconds elapsed while inserting 30 "beads" into a tube according to Runge et al., 1974)

Vertical dashed lines in CSS figure refer to noteworthy events. Thus, in Figure 1 the intercontinental flights (Table 1) are indicated in this way as events 1 and 2. In rows below the chronograms are plotted, on the same time scale, results from fitting a cosine curve to successive data intervals. These results include a P-value (derived from a test of zero-amplitude), estimates of the rhythm's mesor (M, rhythm-adjusted mean), amplitude (A, half of the peak-trough difference) and acrophase (ϕ, timing of the high point in the curve best approximating all data). Symbols for special events, such as menstruation, domestic flights in the continental U.S.A. (across less than 2 time zones within a week) also are given along the chronologic time scale of the CSS. It should be realized further that midnight (in Paris time) remains the reference time for all analyses on the data of this study.

Each analytic result is plotted at the midpoint of the interval it represents. Thus, there is a diluting effect exerted upon any value summarizing data from an interval covering different stages of the study. For instance, a value plotted on the day before a known event actually may be based on considerable data from the span following the event. Therefore, there may be a deflection in the plot of values commencing at the time when a diluting effect of the subsequent treatment span appears. Such artifacts of analyses caused by the equivalent of a moving average of several items must not be misinterpreted as an "anticipation" of the event (such as a flight).

P-values, e.g., in row 2 of Figures 1–8 and 12

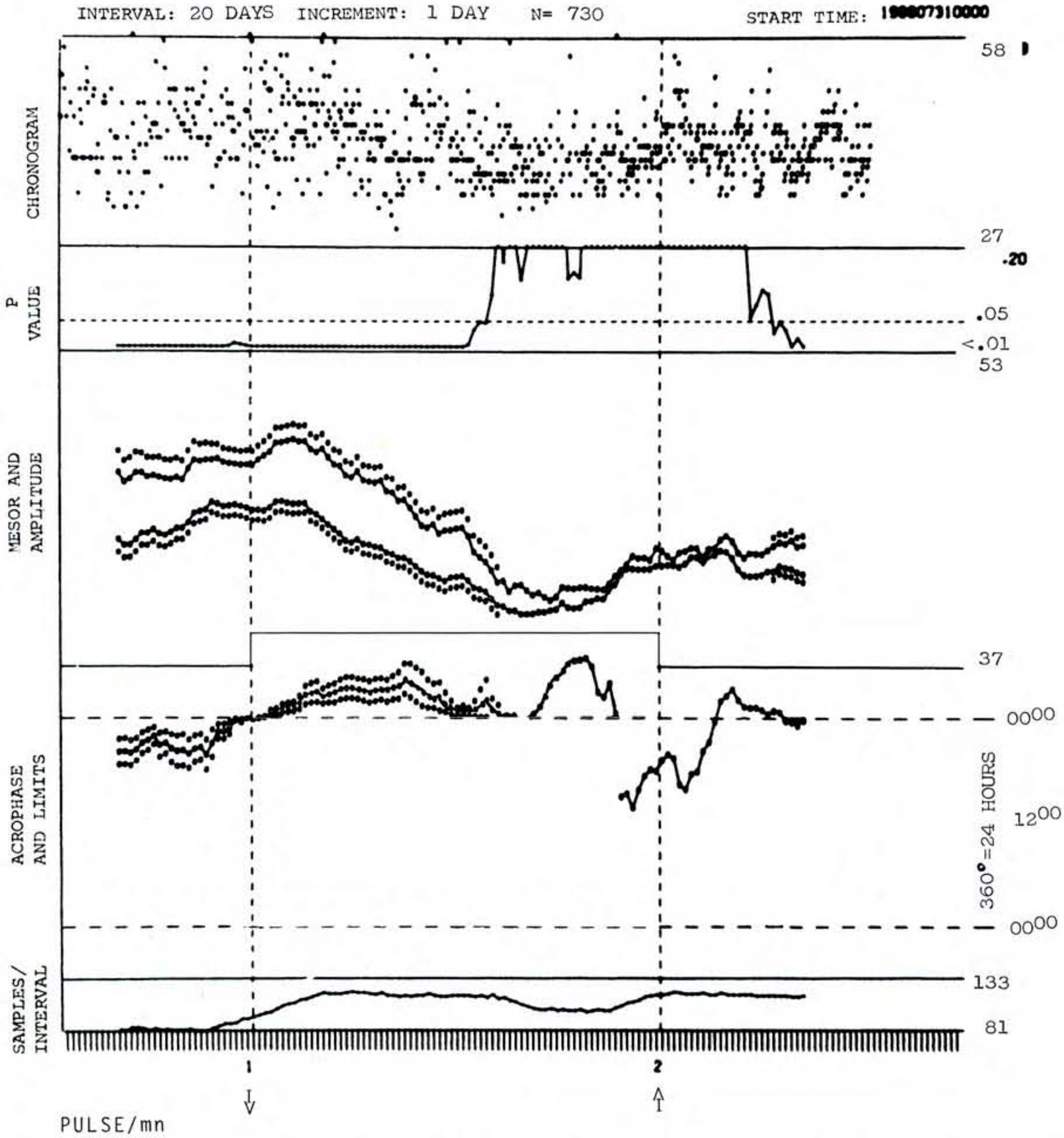


Fig. 7. Circadian rhythm in pulse (beats/minute) of a presumably healthy young woman before and after westward (1) and eastward (2) flights across 6 time zones

are plotted on a scale from $\leqq 0.01$ to $\geqq 0.20$; values $\leqq 0.05$ are regarded as indicating a statistically significant rhythm. In a row portraying mesor and amplitude (e.g., row 3 of Figure 1) the ordinate is in the units used also for the chronogram. The lower line in such a row represents the mesor. Dots below this line show by their distance the standard error of this mesor. The distance from the (lower) mesor line to the upper line represents the amplitude and the distance from that upper line to the dot above it represents one standard error of the amplitude. These standard errors of the amplitude and the mesor are omitted whenever the P-value for zero amplitude is above the 5% level—a procedure adopted for presentation of all results on all rhythm characteristics.

Acrophase estimates are shown in a separate row containing 2 horizontal dashed lines (e.g., second row from the bottom in Fig. 1). Each dashed line represents a chosen reference time (in this study 00^{00} in Paris, France) and therefore the vertical distance between them corresponds to the period of the rhythm (24 h in this study). Results from each cosine-fitting are plotted as a dot bracketed vertically by 2 other dots. The position of the middle dot relative to the horizontal reference lines indicates the timing of the rhythm's high values. The bracketing dots indicate 95% confidence limits for this estimate.

Results

For all variables CSS were made first with 10-day intervals. In a number of cases results with this inter-

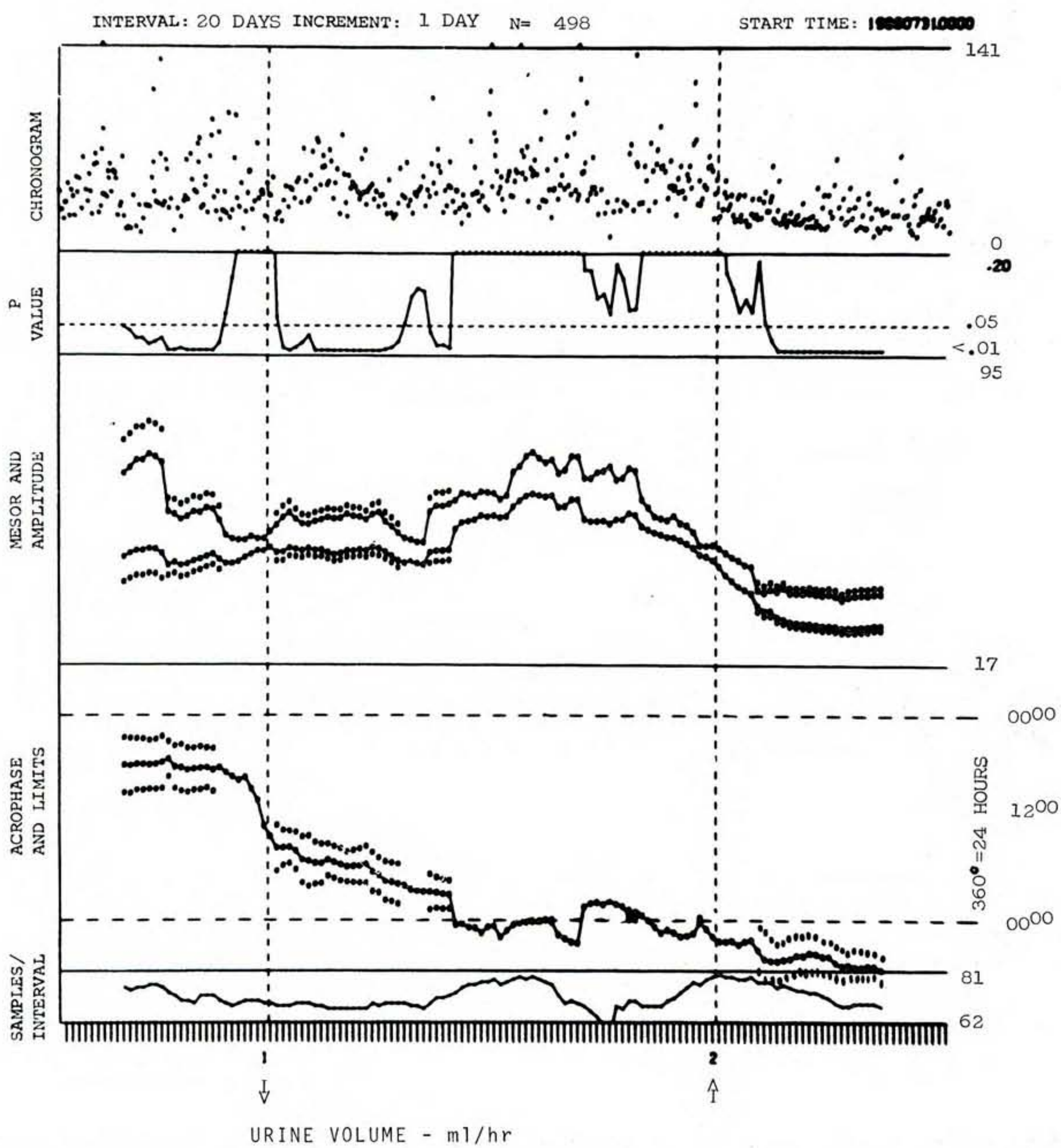


Fig. 8. Circadian rhythm in urinary volume of a presumably healthy young woman before and after westward (1) and eastward (2) flights across 6 time zones

val were so noisy that all analyses were repeated with 20-day intervals. Whatever its length, the analysis-interval was displaced consistently with one-day increments through the entire time series.

Figure 1 on top shows a chronogram of the oral temperatures self-measured during the 3 study-stages investigated: stage-1 while the subject was in France (before the first dashed vertical line indicating the transmeridian flight to Minnesota, U.S.A.), stage-2 while the subject was in the USA (during the span demarcated by the 2 dashed vertical lines, the second line denoting the return flight from the U.S.A. to France) and stage-3 after the subject's return to France. From inspection of the chronogram certain temperature elevations can be seen but a clear periodicity as a function of the menstrual cycle described earlier for body core temperature and other variables is not readily apparent in the particular display presented in Figure 1. An evaluation of menstrual rhythm adjustment or more broadly of circatrigintan and circadian rhythm interactions will be of interest in itself and also in relation to transmeridian flights as discussed by Preston, Batement, Short, among others, and Wilkinson (1974), Halberg (1974) and Haus and Halberg (1970).

For this presentation sufficient data seem to be available to consider certain features of circadian rhythmicity but the data are sparse and too limited

Table 3. Comparative physiologic studies on shifting of 24-hour-synchronized circadian rhythms reveal structured adjustment in the form of differences in rates of rhythm advance and delay—a socalled polarity or chronoasymmetry

Organism	Variable	Extent of shift in synchronizing lighting regime		Hours to adjust to regimen			Reference
		Hours (on a 24-hour cycle)	Degrees	Advance	Delay	Difference	
				Faster advance			
Albizzia julibrissin (silk tree)	Pinnule angle	4[a]	60	24	52	28	Koukkari et al. 1973
Fringilla coelebs, (chaffinch)	Jumping activity	6	90	60	120	60	Aschoff and Wever 1963
				Faster delay			
Tribolium confusum (flour bettle)	O_2 consumption	6	90	48	24	24	Chiba et al., 1974
Sprague-Dawley rat	Intraperitoneal temperature	6	90	312	120	192	Halberg, Nelson et al., 1971
Monkey (several species)	Axillary temperature	6	90	120	72	48	Halberg 1969
Man	Oral temperature[b]	6	90	312	192	120	Halberg 1969

[a] 4 hours = $^1/_2$ the dark span in Albizzia; 6 hours = $^1/_2$ the dark span in rat, monkey, and chaffinch

[b] In social setting. Studies by Aschoff on men isolated in a bunker reveal faster advance than delay

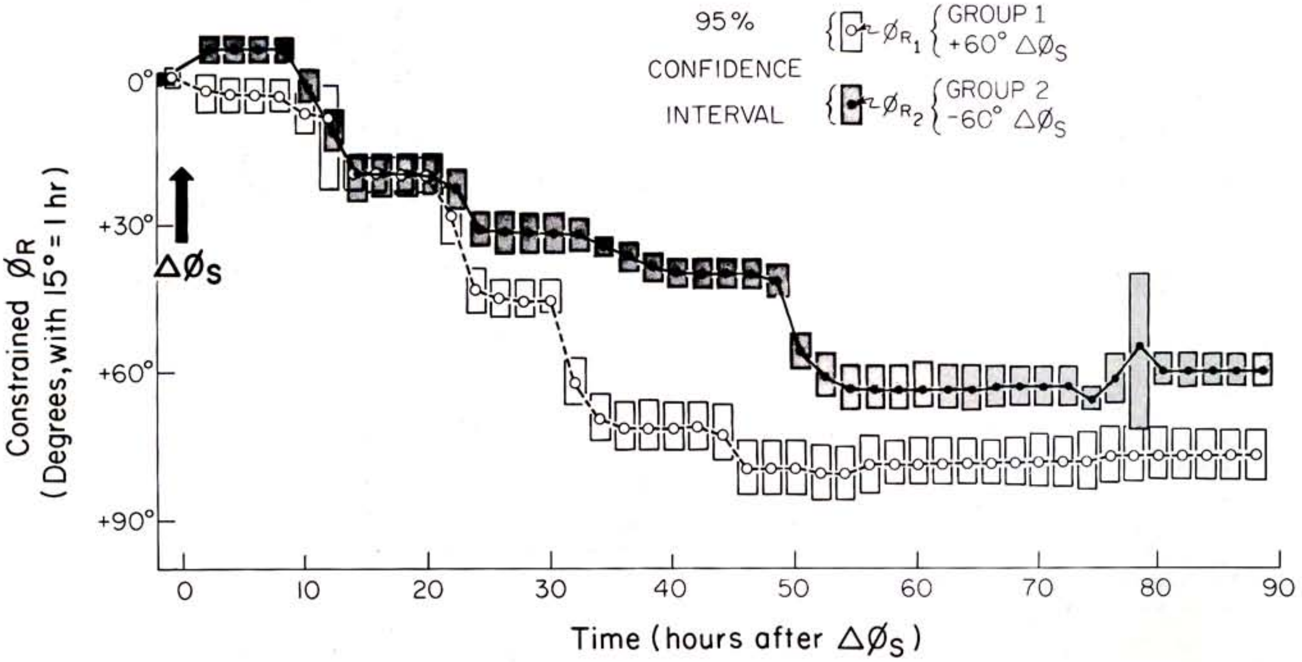


Fig. 9. Difference in change of circadian acrophase, ϕ_R, for pinnule movement of *Albizzia* after synchronizer advance (+) or delay (−)[$\Delta\phi_S$]. 2 groups each of 3 plants, 4 pinnae/plant; mean angle of 3 pinnule pairs (5,6,7) from each pinna

in the number of menstrual cycles covered to assess menstrual rhythms as such or any effect modulating circadian rhythmicity.

The second row in Figure 1 shows P values obtained by a test of zero amplitude for the circadian rhythm in consecutive 10-day data sections. During the first stage in France the zero amplitude assumption is consistently rejected below the 5% level of statistical significance. However, this is not the case during the other two stages; the results on acrophase obtained with a 10-day interval of analysis are altogether omitted.

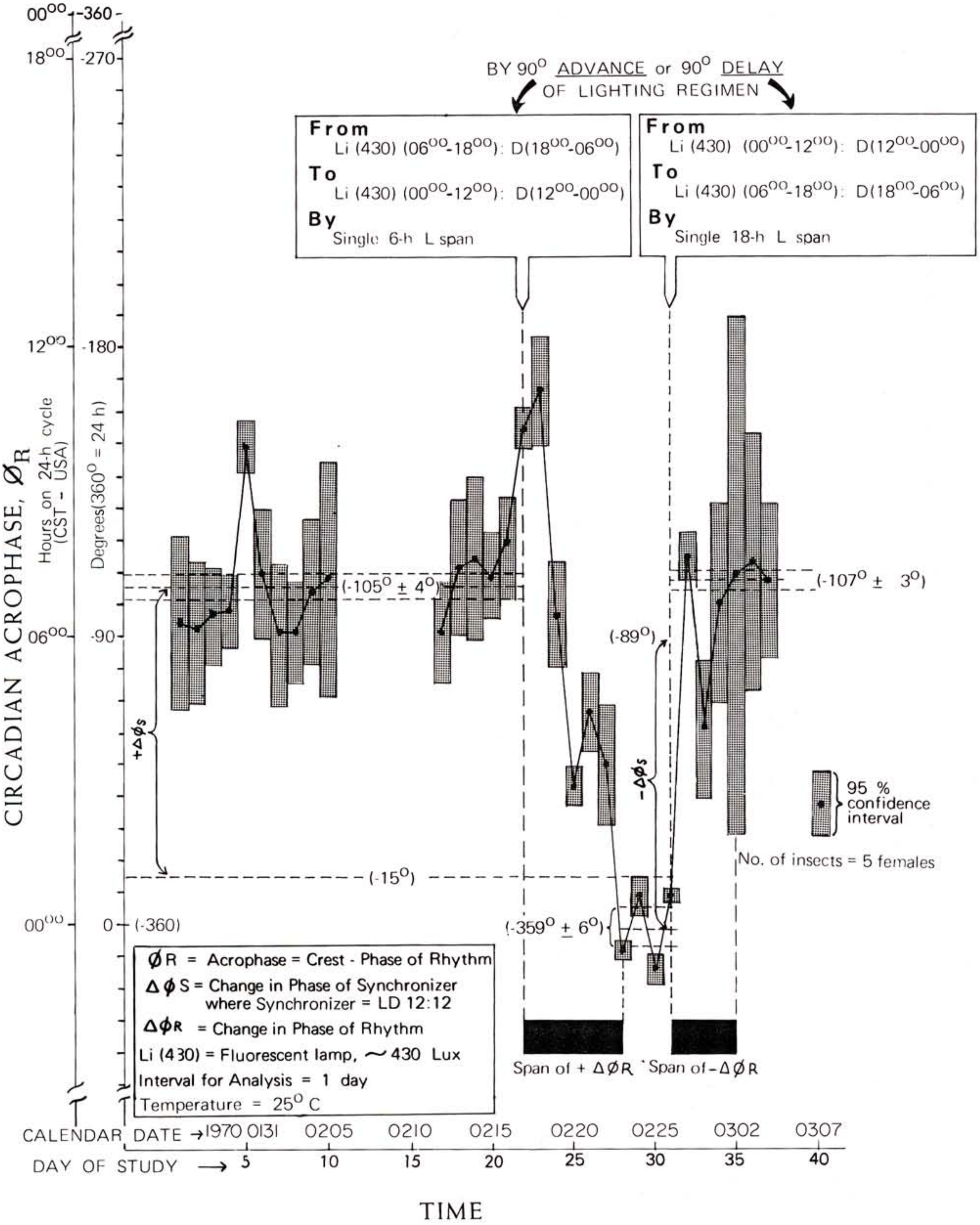
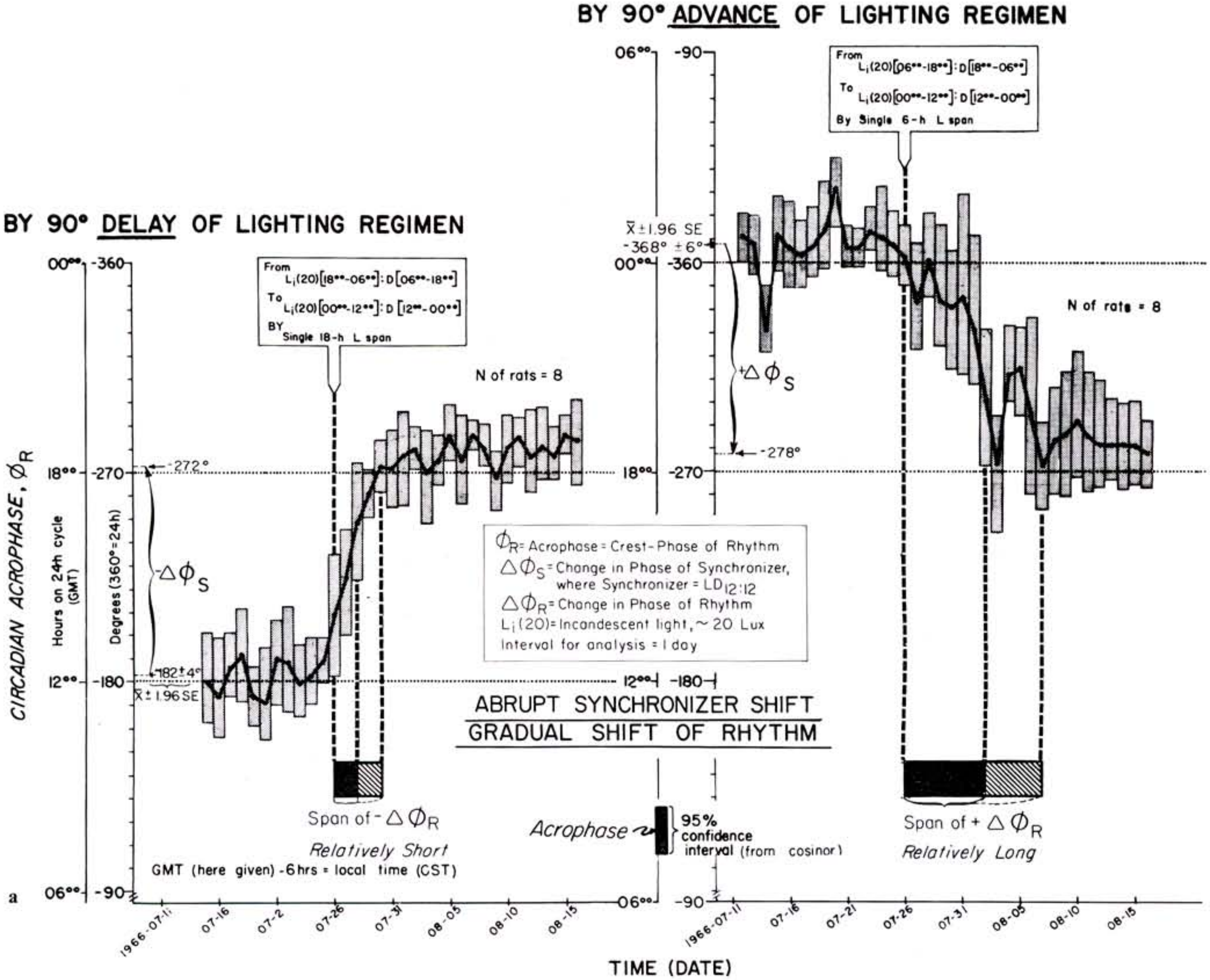


Fig. 10. Acrophase-shifting of 24-h-synchronized oxygen consumption rhythm in 5 sterilized female flour beetles, *Tribolium confusum*



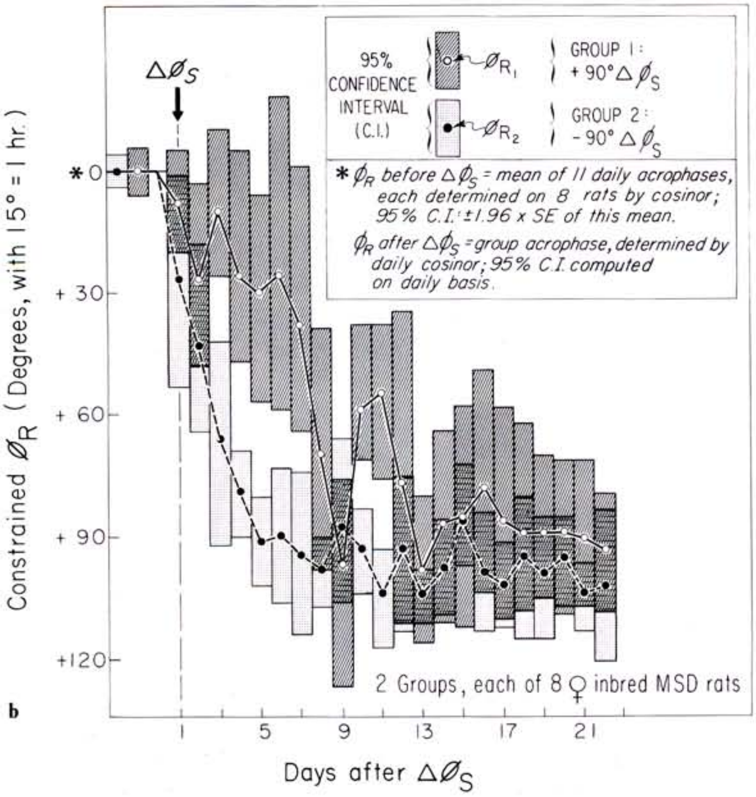


Fig. 11a. Shifting of 24-h-synchronized circadian rhythm in intraperitoneal temperature of female MSD rats

Fig. 11b. Difference in change of circadian intraperitoneal temperature acrophase, ϕ_R, after synchronizer advance (+) or delay (−), $\Delta\phi_S$

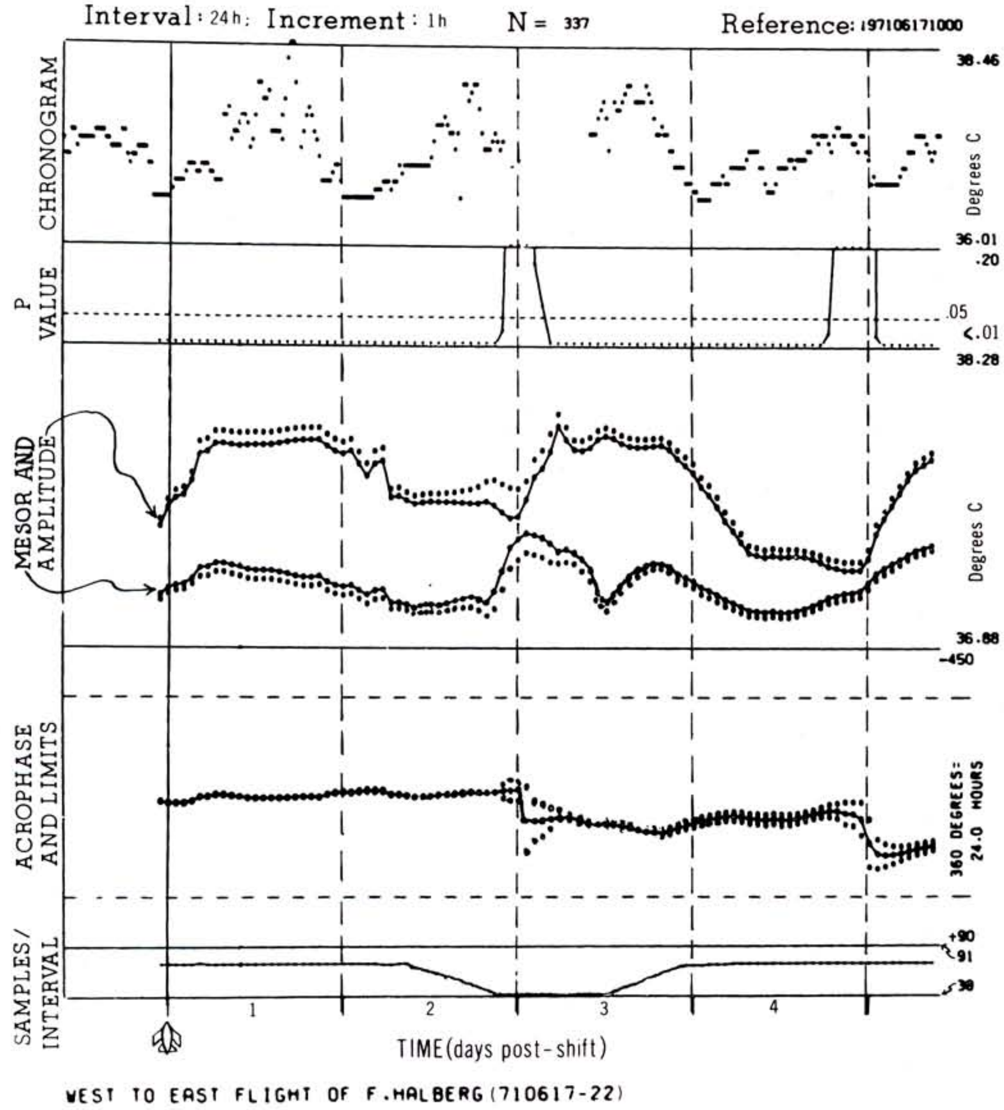


Fig. 12. Rectal thermogram (at 20′-intervals) in relation to transmeridian flight across six time zones (Mpls., Minn., U.S.A. to Bruxelles, Belgium)

The mesor and amplitude results with a 10-day interval are shown in the third row. Mesor estimates in this row reveal rather prominent changes that show a high circadian mesor in mid-menstrual-cycle before the first transmeridian flight. A gradual increase in circadian mesor is also seen during the first two menstrual cycles in Minnesota, with the second cycle in Minnesota involving a seemingly lesser change than the changes seen in the preceding two cycles. On October 15th the death of a beloved grandmother communicated by telephone from Paris probably represented a major psychological trauma added upon the prior burdens of attending school in an unfamiliar setting. Such changes in both mesor and amplitude are greatly attenuated if not partly obscured in the corresponding analyses carried out with 20-day intervals as shown in row 5. Row 4 shows that the 20-day interval (in the case of oral temperature) did lead to the rejection of the zero amplitude assumption most of the time below the 20% level of statistical significance and quite often below the 5% level of significance.

The row before last in Figure 1 shows the major point of the analysis, namely the change in circadian acrophase. Note that midnight in Paris remains the reference time (horizontal dashed lines) even though the subject traveled to Minnesota, as shown in Table 1, thereby being subjected to a schedule change of 6 h (Minnesota was on daylight savings time and Paris, at that time, was not). Some other travel by the subject in the U.S.A. from Minneapolis, Minnesota to Denver, Colorado and San Francisco, California as well as to New York (indicated in Table 1) clearly complicates data interpretation in comparing advances and delays for any one variable, even if the changes in time zones involved relatively short spans of days and deviations of no more than one or two hours from Minnesota time. For this reason

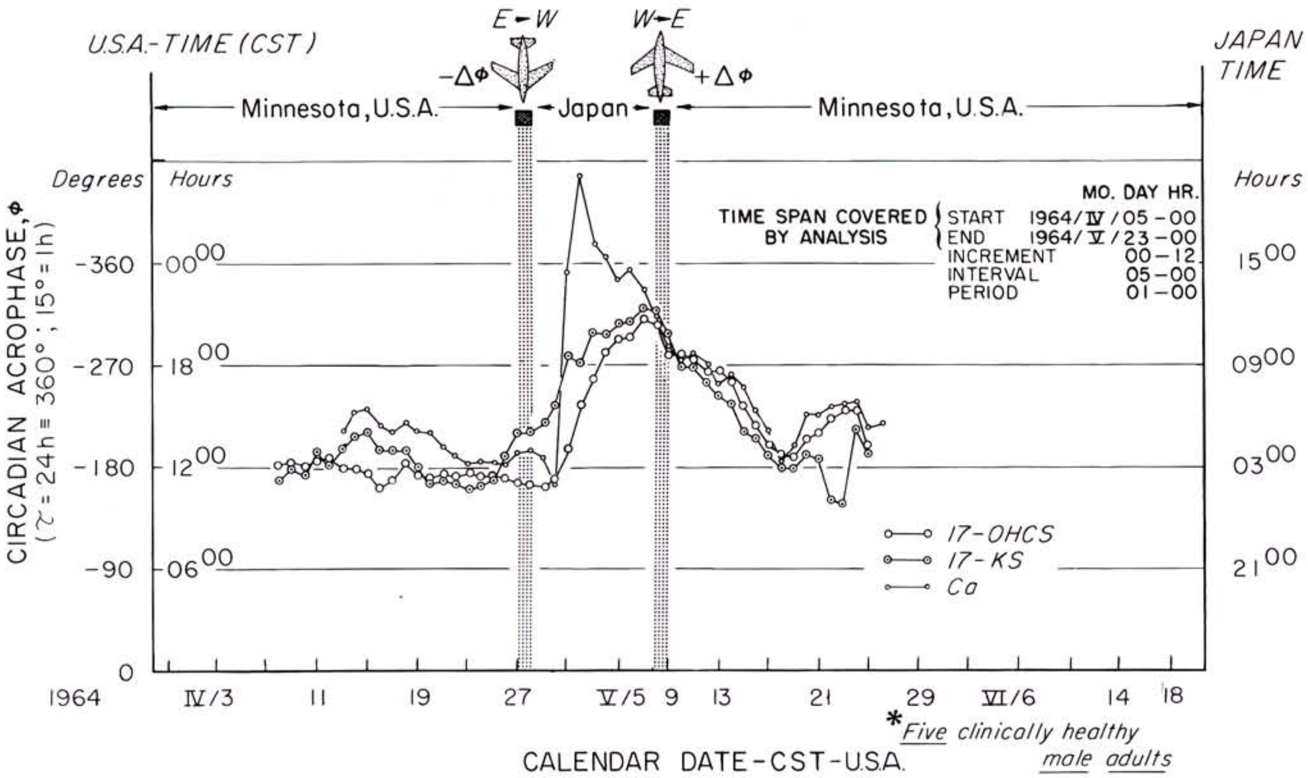


Fig. 13. Differing post-flight behavior of circadian acrophase-shift for different variables* after delay (E→W) but not advance (W→E) of synchronizers

major emphasis in interpreting results is placed upon the differences among the variables investigated.

In studying the time course of the body temperature acrophase, one must realize that the results are based upon a limited number of self-measurements. The bottom row of Figure 1 shows that in a 20-day interval there were at least 83 self-measurements (i.e., on the average, over four per day) and a larger number on occasions. While this is a reasonable measurement density for a person who self-measures and follows an unimpeded routine, modern means of more or less continuous data collection for variables such as heart rate or core temperature allow a much more rigorous scrutiny not only of the circadian acrophase (derived by a fit of a single 24-hour cosine curve) but also of the waveform and its orthophase (based on the concomitant fit of several components—Tong et al., in press; Rummel et al., 1974).

Rather narrow 95% limits for the temperature acrophase in France indicate that the subject may have followed a schedule involving reasonably regular hours and the fact that the acrophase dots themselves are situated within the last quarter of the day are in keeping with the fact that the subject did not usually retire before midnight. For a while in Minnesota the dispersion index of the acrophase remains small but thereafter, including a span of travel to Denver and San Francisco, the acrophase limits are much broader. Such uncertainties notwithstanding, the temperature acrophase eventually clearly shifts from Parisian time to Minnesotan time. Equally clear, this shift is gradual rather than abrupt and much slower than the shifts in urinary potassium and sodium. The latter changes are shown in the penultimate rows of Figure 2 and 3.

The first three figures, as a whole, demonstrate the difference in the time required for the completion of the adjustment of circadian rhythms to a given schedule. This so-called polarity has been documented by a number of authors for a variety of functions and species (Halberg, 1969; Levine et al., 1974). It is of interest that the delay of rhythms required after a flight from east to west is completed seemingly faster for all of the three variables than is the advance of rhythms required after a flight from west to east. For urinary potassium there seems to be an almost immediate adjustment following the flight from east to west, and a slower adjustment in the same function after the flight from west to east. To the extent that this finding can be validated for variables with consistently significant P values (as in the case of body core temperature) it is remarkable that adjustment may be faster after a flight away from home as compared to that after homeward flight.

Figure 4 summarizes data on peak expiratory flow. The rhythm in this variable adjusts perhaps most slowly after flights in either direction. After a month in Paris the acrophase has not as yet returned in stage 3 to the timing exhibited rather consistently prior to the transmeridian flight. This is not surprising

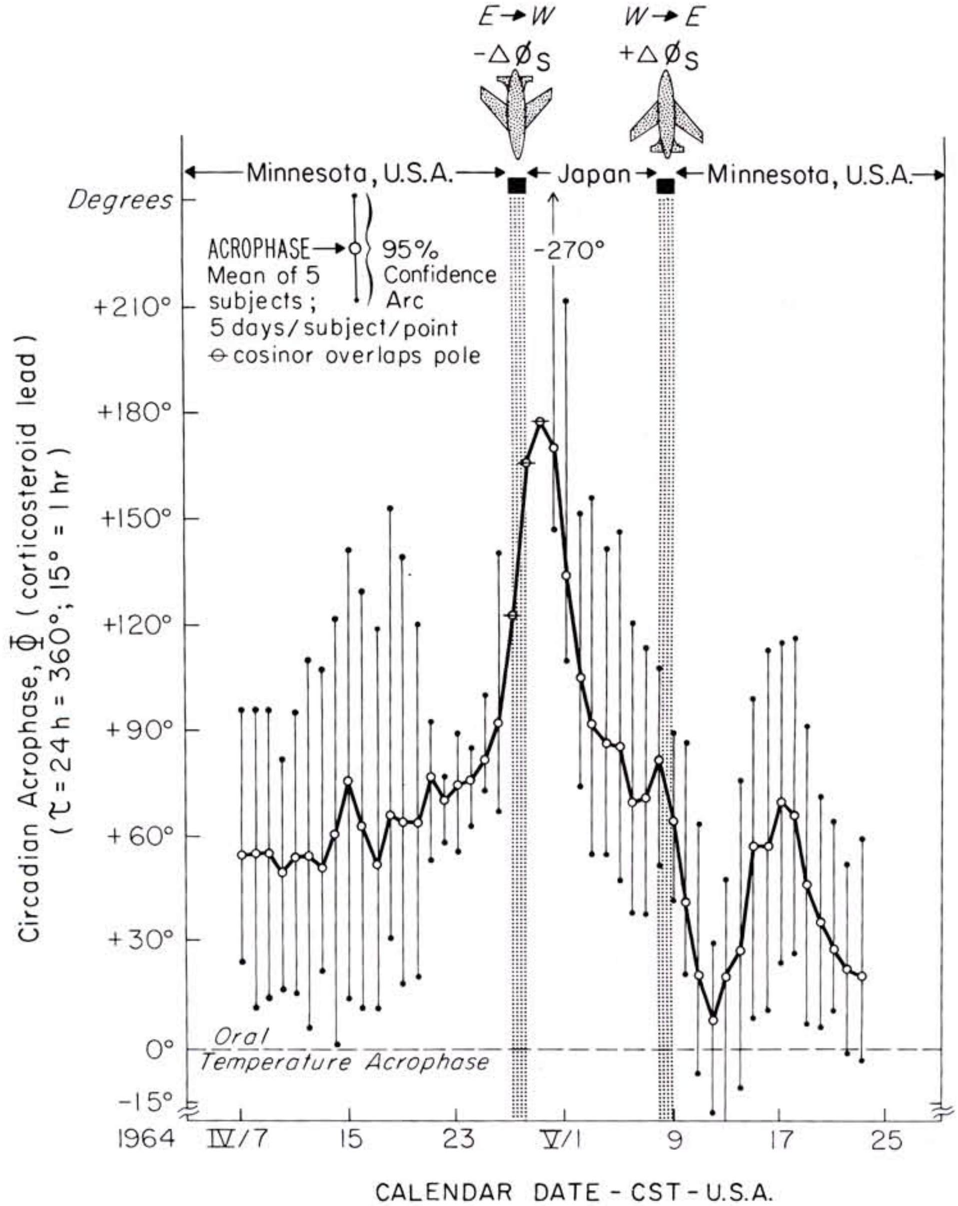


Fig. 14. Internal circadian timing, ϕ, of urinary 17-hydroxy-corticosteroid excretion and oral temperature before and after two intercontinental flights – clinically healthy male adults. $\Delta\phi_S$ = change in phase of synchronizer, where synchronizer = 24-h societal schedule. + = advance, − = delay

since it took over 20 days for the peak flow acrophase to shift from Parisian to Minnesotan time following the first flight. Moreover, it is interesting that the peak flow mesor is statistically significantly higher in suburban Minnesota than in metropolitan Paris.

This recent finding amplifies on an original suggestion by Halberg (in the context of the Biologic Program's chronobiology endeavor) that PEF be monitored already within the school system by autorhythmometry with a view of maintaining environmental integrity (Halberg, Lauro and Carandente, 1976). The documentation by Reinberg, Gervais, Halberg and Halberg (1972) of a change in PEF mesor of certain patients with exogenous asthma when introduced into a hypoallergic room leads to the conclusion that some human subjects can be considered as sentinel organisms or biologic detectors of overall pollution. The fact that the airway patency is likely to change as a function of pollution in the subject here studied indicates that with the help of autorhythmometry and other chronobiologic methods, an apparently healthy subject can also be a sentinel organism. However, the speed with which a subject's PEF will respond may be critical for environmental monitoring. In the case of the subject here investigated the response appears to be gradual (partly, perhaps, because it is a gradual response and of course, partly because the chronobiologic serial section uses a reasonably large interval for analysis).

The subject, a non-smoker, had no lung allergy

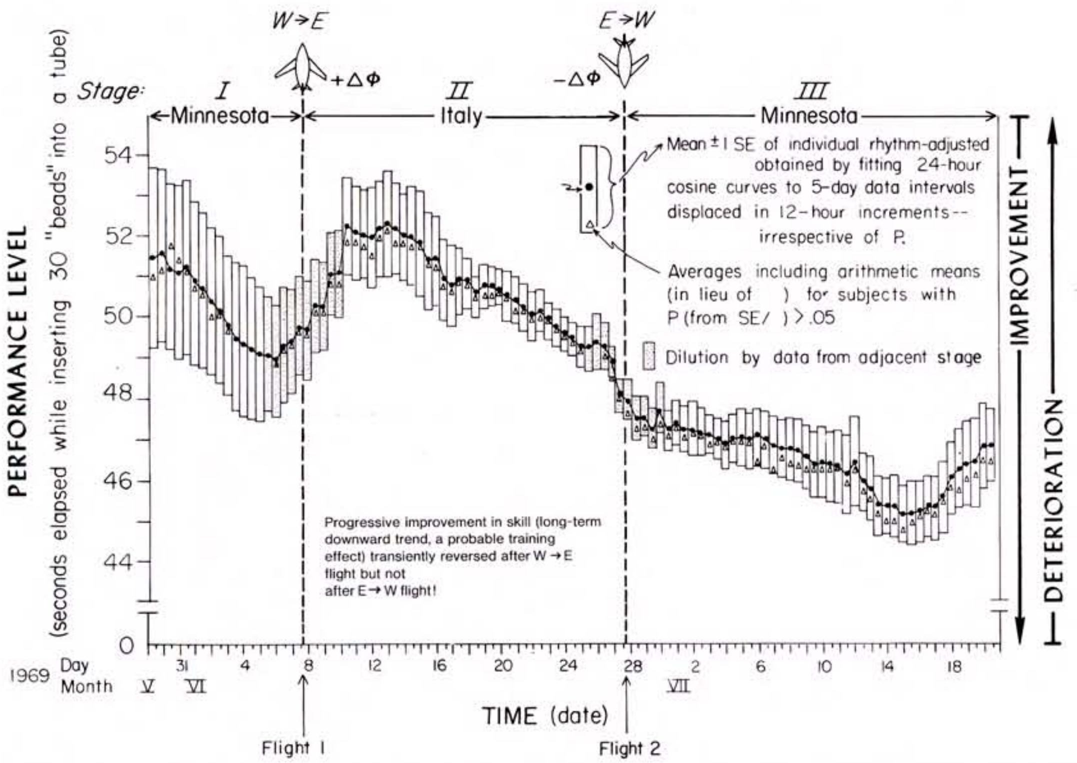


Fig. 15. Transmeridian dyschronism. Eye-hand skill of 7 healthy subjects deteriorates following west-to-east flight (advance of rhythms). Similar decrement not detected after east-to-west flight (delay of rhythms). "Polarity" in effect of transmeridian flight on performance (in small sample surveyed)

yet exhibits allergic responses of the skin to copper, nickel, chromium, and other agents such as perfumed cosmetics. In subsequent tests involving bronchial challenge with acetylcholine her response mesor was in the mesor range of presumably healthy individuals of comparable sex and age (Reinberg et al., 1974). Table 2 lists known pollution data. Figure 5 summarizes results on vital capacity which complement those on peak flow, as a related yet not identical index of lung function. The slower readjustment to Paris is as clear for vital capacity as it is for peak flow, although vital capacity is the noisier function. Differences in the behavior of the mesor for the case of vital capacity as compared to the time course of the peak flow mesor qualify conclusions regarding the latter. An elevation in VC is considered, from a physiologic viewpoint, as a compensatory response to a reduction in airway patency. (The ratio FEV/VC is considered in the method of bronchial challenge according to Tiffeneau (1957)). Therefore, one can anticipate the observed changes in the mesors of both VC and PEF; i.e., a rise in the first is associated with a lowering in the second and vice versa.

Figure 6 demonstrates during part of stage 2 and all of stage 3 a statistically significant circadian rhythm in eye-hand skill. The mesor gradually improves (as a learning effect) following an initial deterioration, since the index used consists of the time needed to complete the task (and hence the higher the value the poorer the performance). In view of the noisiness of this variable at the outset of the study no definitive conclusions are drawn regarding its adjustment rate. It would appear that a change in timing did take place, if one relies on the few statistically significant acrophases recorded during stage 1. By the same token, against this particular reference standard, the adjustment in stage 3 seems to be both gradual and incomplete. Accordingly, the information on the timing behavior of this variable in no way contradicts inferences drawn for the other variables, concerning a polarity in the adjustment of most if not all body functions.

Figures 7 and 8 also deal with quite noisy functions, heart rate and urine volume, respectively. The failure to detect a circadian rhythm in heart rate in part of the Minnesota data may perhaps be related to a long-term effect of the psychological trauma, yet, admittedly, this constitutes *post hoc ergo propter hoc* reasoning. The seemingly free-running rhythm of urine volume has to be qualified by the failure to reject the zero amplitude assumption during the span following the death of the grandmother. It is noteworthy, in addition, that the circadian rhythm in urine volume seemingly adjusts by an acrophase advance to a synchronizer delay. This finding suggests that in the same organism one of the variables adjusted in a direction different from that corresponding to the adjustment of many other variables. An earlier finding of diagnostic interest is in keeping with this observation (Meyer et al., 1974).

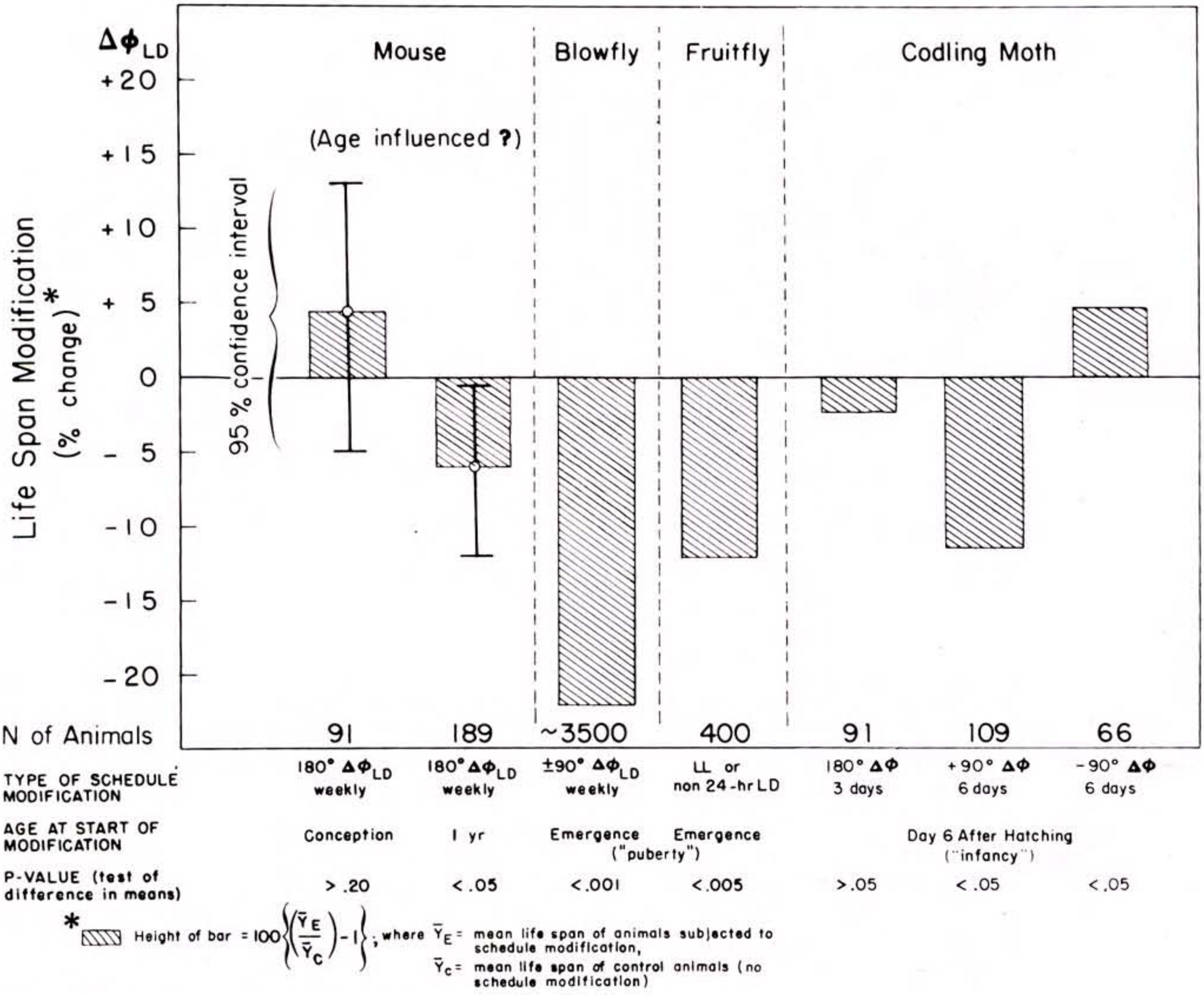


Fig. 16. Life span changes on modified schedules

Discussion

Table 3 lists extensive evidence for the polarity so characteristic of the adjustment by most forms of life to changes in the routine of living. The present data on a presumably healthy female subject extend the scope of such observations. In addition to polarity, the results document further the drastic intervariable differences in adjustment time. Metarhythmometry (i.e., the study of rhythm adjustment) can serve physiology, medicine and ecology. We had earlier proposed the long-term monitoring of air pollution by autorhythmometry of peak expiratory flow. This case report supports the suggestion.

The polarity of circadian rhythms or the assymmetry in their adjustment can differ among various functions of the same individual, among individuals and most prominently among species. To amplify on Table 3, which leads to the pertinent literature, a faster advance than delay of rhythm was reported for chaffinches by inspection and study of data plots in 1963 by Aschoff and Wever. A yet earlier (1905–1906) study of the same problem in the nonhuman primate by Simpson and Galbraith yielded data suggesting that a delay of rhythm is faster than an advance. This point was objectively ascertained by rhythmometric data analysis (Halberg, 1969).

Figure 9 shows again a difference in speed of rhythm adjustment for the silk tree, *Albizzia julibrissin*. In this very rapidly adjusting plant, a difference of a few hours is found by serial mean cosinors: advances are somewhat faster than delays (Koukkari and Halberg, 1973).

Figure 10 shows that for several flour beetles the delay of a circadian rhythm is achieved faster than an advance, as documented again with serial mean cosinors by Chiba, Cutkomp and Halberg (1973).

Most extensive data and analyses on the phenomenon of polarity have been obtained by intraperitoneal temperature telemetry at 10′-intervals in the rat, as demonstrated by Figures 11a and 11b. It can be seen that a delay is achieved within 4 days, whereas an advance may take twice or even three times that span. Not only are the rat data impressive by the difference in rhythm-shifting and its reproducibility but they are the more important since they seem to correspond to the behavior during rhythm-shifting of most human beings.

In turning to human beings, modern instrumentation permits the more frequent recording of body temperature automatically and thereby, one can, for human beings, reproduce more thoroughly the findings made in the case here reported by self-measurement. Before turning to differences between advances and delays, Figure 12 reveals again by a chronobiologic serial section, that the adjustment after a transmeridian flight of the body core temperature rhythm in a man is gradual rather than abrupt. Figure 13 shows that different functions in the same human individuals can take different adjustment spans. Thus their time relations to one another change in a different fashion after advances and delays of a synchronizer, Figure 14. This phenomenon is the more relevant in human beings since an actual performance decrement, Figure 15, can be noted after flights in one direction but not after flights by the same individuals in the opposite direction (Halberg, 1969; Halberg, Nelson, Doe, Bartter and Reinberg, 1969; Halberg, Katinas, Chiba, Garcia Sainz, Kovats, Künkel, Montalbetti, Reinberg, Scharf and Simpson, 1973).

Figure 16 shows that in long-term studies on rodents and insects, even lifespan can be affected by the frequency of schedule shifts. This effect of the frequency of shifts has been noted to differ as a function of whether one carries out advances or delays and also as a function of whether one shifts schedules more or less frequently, say once every 3 or 6 days or once or twice a week in the codling moth and mouse, respectively (Hayes, 1976; Halberg, Nelson and Cadotte, 1975) but not in the blowfly (Aschoff, Hoffmann, Pohl, and Wever, 1975; Aschoff, Saint Paul, and Wever, 1971).

However, the speed of adjustment can differ among individuals. In selected shift-workers, Reinberg, Chaumont et al. (1973) and Reinberg, Vieux et al. (1976) have shown that these subjects were able to adjust rapidly a set of circadian rhythms to a new timing, both after a synchronizer advance and a delay. Differences of speed were not statistically significant. It is likely that in these experiments the phenomenon of polarity was obscured both 1) by the rapid adjustment which minimizes the difference between advance and delay and 2) by the the sampling procedure for time series which does not allow the detection of a statistically significant difference when this latter is small. For work on experimental animal models regarding shift-schedules and blood pressure disease, the interested reader can be referred to Halberg J. et al., 1977; for problems of ulcerogenesis and shift-work, to Carandente, F. et al., 1976 and in press.

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