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General Homeostasis of the Frequency of Circadian Oscillations

(*Leucophaea maderae*/temperature)

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ABSTRACT **Some well-defined statistical regularities characterize the change in period (τ) of cockroach circadian oscillations subjected to a large temperature step. These are explainable in terms of the well-known temperature-compensation (homeostasis) of τ of circadian oscillations. The same regularities are detectable in published data on the effect of several other variables affecting several other circadian oscillations. The proposition is then developed that the temperature-compensation of τ is only a special case of a general homeostatic conservation of the frequency of circadian oscillations in the face of all changes they are likely to encounter in the cell. Such a general homeostasis of τ is a functional prerequisite for an oscillator to function as a useful "clock."**

The initial discoveries of Kramer (1, 2) and von Frisch (3) that birds and honey bees could measure time in using the sun's azimuth as a compass had a significant impact on the study of circadian oscillations. In 1954 (4) it led to the hypothesis, fully validated by Hoffmann (5), that these oscillations were in fact the clocks used in time-compensated sun orientation. It was this intuition that prompted one of us (4) to re-examine published conclusions that the period (τ) of circadian oscillations was temperature dependent: a cellular oscillator with a temperature-dependent frequency would be no more useful as a chronometer than a pendulum uncompensated for temperature change. It was in fact found (4) that the steady-state frequency of the circadian system in *Drosophila pseudoobscura* was essentially invariant over a wide range of temperature, thus meeting the functional prerequisite of an oscillator adequate for measurement of sidereal time. The temperature compensation of τ has been established as a universal property of circadian oscillations: they are indeed clocks, not only in the exotic case of sun orientation, but more generally in providing a framework for an innate temporal organization of metabolism that is an evolved match to the daily periodicity of the external world (6–8).

Given the fact of temperature compensation, and its functional significance, we should long ago have turned to a more general proposition: if circadian oscillations are to function as a reliable framework for a temporal organization of cellular function relative to sidereal time, *their frequency* (or period, τ) *must be essentially invariant in the face of all variations they encounter in the cellular milieu.* One should have foreseen that compensation for temperature variation was only a special case of a more general phenomenon. Our attention to the general homeostasis of τ has been prompted by new results in our laboratory and by reevaluation of many published facts. First, we have found that τ in *Drosophila pseudoobscura* is as relatively unaffected by D_2O as it is by temperature (9). Second, we have found some clear empirical regularities in the oscillator's response to large temperature steps which we interpret in terms of the well-known temperature compensation of τ: they reflect, we believe, the operation of a homeostatic mechanism conserving τ within a narrow range. Since these same empirical regularities are found in the oscillator's response to large steps in several variables other than temperature, we conclude that the homeostasis of their frequency is a general property of circadian oscillations. That conclusion is then supported by the finding that the range of τ variation realized is small in *all* deliberate attempts to change τ.

MATERIALS AND METHODS

Our experiments reported here concern the dependence on temperature of τ of the circadian rhythm of locomotion in the cockroach *Leucophaea maderae*. Its activity is measured in a machined lucite running-wheel cage. The wheel, delicately balanced by adjustable counterweights, rotates on ball bearings and operates a frictionless (proximity) magnetic switch. Its rotations are registered on an operations recorder. The period of the activity rhythm (and hence the cellular oscillations responsible for it) is estimated by eye-fitted curves to the succession of activity onsets. An empirical study of the reliability of this procedure based on estimates of τ made by four different people analyzing 98 freerunning rhythms shows it is reliable to within 1.73 min (Caldarola, in preparation). The freerunning rhythm from which τ was estimated lasted, on the average, 21 days and never less than 10 days.

RESULTS

Response of the Leucophaea Oscillator to Large Temperature Steps. An initial experiment in 1971 showed that nine animals in constant darkness at 20° had an average period ($\bar{\tau}_1$) of 1382.9 ± 10.50 min. After an abrupt stepup to 30° their average period ($\bar{\tau}_2$) was 1421.2 ± 5.56 min. The increase in period ($\Delta\bar{\tau}$) of +38.3 min is highly significant and indicates that the temperature coefficient (Q_{10}), *for this 10° step*, is less than one (0.97). The response to the step, however, involves greater complexity than this change from $\bar{\tau}_1$ to $\bar{\tau}_2$. First, while there is a great range of interindividual variation in the periods (τ_1) expressed at 20°, the range of values (τ_2) at 30° is not only shifted up the τ scale but *greatly compressed* (Fig. 1, *top right*). The ratio of the standard deviations ($SD\tau_2$/$SD\tau_1$) is 0.53. Second, when the $\Delta\tau$ ($= \tau_2 - \tau_1$) *for individual animals* is examined, it is found to be highly correlated with τ_1 (the correlation coefficient, C, = −0.89), and the regression of $\Delta\tau$ on τ_1 has a slope (S = −1.017) very close to 45° (Fig. 1, *top left;* Table 1).

TABLE 1. *Relationship of τ_2 and $\Delta\tau(=\tau_2 - \tau_1)$ to τ_1 for the 10° temperature stepup and stepdown in Leucophaea maderae*

	n	$\bar{\tau}_1$	SD_{τ_1}	$\bar{\tau}_2$	SD_{τ_2}	$\frac{SD_{\tau_2}}{SD_{\tau_1}}$	Regression of τ_2 on τ_1			Regression of $\Delta\tau$ on τ_1		
							s	c	P of c	S	C	P of C
20° → 30° Stepup												
1971 Group	9	1382.9	31.51	1421.2	16.69	0.53	−0.02	−0.04	0.1	−1.02	−0.89	0.01
1972 Group	16	1404.1	23.29	1416.1	8.58	0.37	−0.22	−0.60	0.02	−1.22	−0.97	0.001
30° → 20° Stepdown												
1971 Group	12	1422.9	12.56	1376.6	23.12	1.84	0.41	0.22	0.1	−0.58	−0.31	0.1
1972 Group	16	1416.1	8.58	1377.8	30.54	3.56	−0.76	−0.21	0.1	−1.76	−0.45	0.1

SD is the standard deviation for each average τ ($\bar{\tau}$). s = slope of regression of τ_2 on τ_1; c is the corresponding correlation coefficient. S and C are comparable statistics for the regression of $\Delta\tau$ on τ_1. (*P of c*) and (*P of C*) are the significance probabilities for the correlation coefficients c and C, respectively.

After some weeks of other experimental treatments (deuteration), these same animals (with some replacements for deaths) were again allowed to freerun (drinking H_2O as before) at 30° in darkness and after 25 days at this temperature were subjected to an abrupt temperature stepdown to 20°. Their period at 30° (now designated τ_1) was very close (1422.9 ± 3.63 min) to what it had been weeks earlier at this temperature, and the range of τ variation at 30° was again small. At 20° the average period (now designated τ_2) was again smaller (1376.6 ± 6.68 min) and, though very close, actually "overshot" the previous value at 20°. At 20° the range of τ variation was again decompressed (Fig. 1, *top right*). However, the similarity of responses to the stepup ends there: while there is some (very weak) regression of $\Delta\tau$ ($= \tau_2 - \tau_1$) on τ_1, it is clearly not significant (C = −0.31) (Fig 1, *bottom left;* Table 1).

All these facts are accommodated by the propositions summarized schematically in Fig. 1 (*bottom right*): (*1*) the period of the circadian oscillation driving the activity rhythm is

TABLE 2. *Dependence of the slope (S) of the regression of ($\tau_2 - \tau_1$) on τ_1 and their correlation coefficient (C) on the correlation coefficient (c) of τ_2 and τ_1 and the ratio (x) of their standard deviations (SD_{τ_2}/SD_{τ_1})**

	(S) as a function of (c) and (x)				
x/c	−1.0	−0.5	0.0	0.5	1.0
0.0	−1.00	−1.00	−1.00	−1.00	−1.00
0.2	−1.20	−1.10	−1.00	−0.90	−0.80
0.5	−1.50	−1.25	−1.00	−0.75	−0.50
1.0	−2.00	−1.50	−1.00	−0.50	0.00
1.5	−2.50	−1.75	−1.00	−0.25	0.50
2.0	−3.00	−2.00	−1.00	0.00	1.00
	(C) as a function of (c) and (x)				
x/c	−1.0	−0.5	0.0	0.5	1.0
0.0	−1.00	−1.00	−1.00	−1.00	−1.00
0.2	−1.00	−0.98	−0.98	−0.98	−1.00
0.5	−1.00	−0.94	−0.89	−0.86	−1.00
1.0	−1.00	−0.86	−0.70	−0.50	0.00
1.5	−1.00	−0.80	−0.55	−0.18	1.00
2.0	−1.00	−0.75	−0.44	0.00	1.00

* Values in the table are derived from the following relationships in which the notation $\mathrm{cov}(\cdot,\cdot)$ is used for covariance and $\mathrm{var}(\cdot)$ for variance. To obtain the entries in Table 2 first note that $\mathrm{cov}(\Delta\tau,\tau_1) = \mathrm{cov}(\tau_2,\tau_1) - \mathrm{var}(\tau_1)$. The correlation coefficient C between $\Delta\tau$ and τ_2 is then $C = \mathrm{cov}(\Delta\tau,\tau_1)/\sqrt{\mathrm{var}\,\Delta\tau\ \mathrm{var}\,\tau_1}$. This reduces to $C = (cx - 1)/\sqrt{1 - 2cx + x^2}$ where, as in the table, c is the correlation between τ_2 and τ_1 and $x = \sqrt{\mathrm{var}(\tau_2)}/\sqrt{\mathrm{var}(\tau_1)}$. To calculate the regression coefficient of $\Delta\tau$ on τ_1 we use $S = C\sqrt{[\mathrm{var}(\Delta\tau)/\mathrm{var}(\tau_1)]} = C\sqrt{1 + x^2 - 2cx} = cx - 1$.

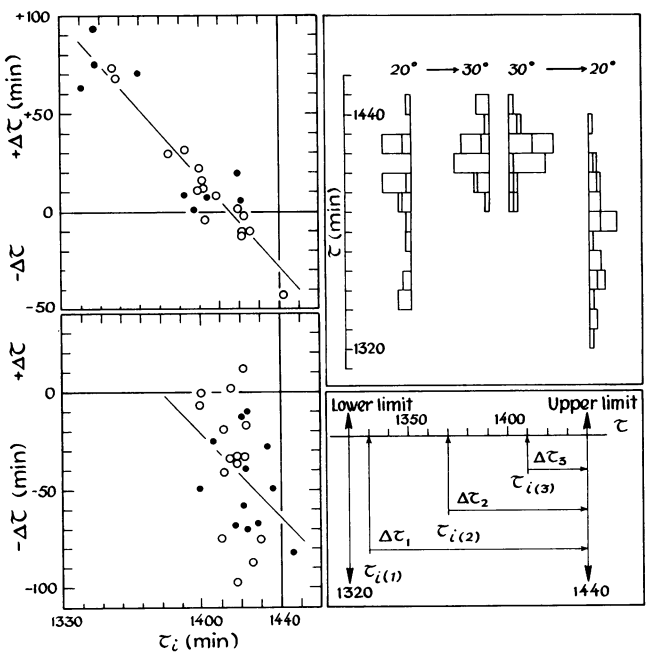

FIG. 1. *Top left:* Change in the freerunning period ($\Delta\tau$ in min) after a 10° temperature stepup (20° → 30°) as a function of the initial period at 20° (τ_1 in min) in *Leucophaea maderae*. Each point represents an individual animal; (●) 1971 group, (○) 1972 group. The *straight line* is the computed linear regression for the combined data; S = Slope = −1.14; C = correlation coefficient = −0.94 See *text* for details, where values for slope and correlation coefficient are given for the 1971 data alone. *Top right:* Frequency distribution showing the range of steady-state values of τ_{DD} (min) for individual *Leucophaea* for the temperature stepup from 20° to 30° and the return to 20°. 1971 and 1972 groups are combined. *Bottom left:* Change in the freerunning period ($\Delta\tau$ in min) after a 10° temperature stepdown (30° → 20°) as a function of the initial period at 30° (τ_1 in min) in *Leucophaea maderae*. S = −1.05; C = −0.39. *Bottom right:* Schematic representation of a homeostatic regulator which sets lower and upper tolerated limits to τ variation.

TABLE 3. *Relationship of τ_2 and $\Delta\tau(=\tau_2 - \tau_1)$ to τ_1 in several species and for different agents affecting τ*

	n	$\bar{\tau}_1$	SD_{τ_1}	$\bar{\tau}_2$	SD_{τ_2}	$\frac{SD_{\tau_2}}{SD_{\tau_1}}$	Regression of τ_2 on τ_1 s	c	P of c	Regression of $\Delta\tau$ on τ_1 S	C	P of C
(*1*) *Leucophaea* (roach)	25	1396.4	27.94	1417.9	12.04	0.43	−0.14	−0.32	0.1	−1.14	−0.94	0.001
(*2*) *Leucophaea* (roach)	7	1419.8	16.60	1454.4	7.46	0.45	0.30	0.66	0.1	−0.70	−0.90	0.001
(*3*) *Peromyscus* (mouse)	6	1486.8	17.67	1425.5	4.37	0.25	−0.18	−0.74	0.1	−1.18	−0.99	0.001
(*4*) *Lonchura* (finch)	28	1402.5	17.01	1437.4	8.11	0.48	−0.08	−0.16	0.1	−1.02	−0.90	0.001
(*5*) *Homo* (man)	10	1580.7	73.91	1499.9	33.67	0.46	0.38	0.84	0.01	−0.62	−0.93	0.001
(*6*) *Leucophaea* (roach)	28	1419.0	10.85	1377.2	27.12	2.50	−0.06	−0.02	0.1	−1.05	−0.39	0.05

(*1*) *Leucophaea maderae:* τ_1 at 20°, τ_2 after step to 30°; 1971 and 1972 groups pooled (see Table 1)
(*2*) *Leucophaea maderae:* τ_1 in constant darkness, τ_2 in constant light (250 lux) (ref. 11)
(*3*) *Peromyscus manicu-latus:* τ_1 in constant light (25 lux), τ_2 in constant darkness (ref. 12)
(*4*) *Lonchura striata:* τ_1 in constant light with nesting box, τ_2 after removal of nesting box (ref. 13)
(*5*) *Homo sapiens:* τ_1 when people screened from earth's electrostatic field, τ_2 after removal of screen (ref. 14)
(*6*) *Leucophaea maderae:* τ_1 at 30°, τ_2 after step to 20°; 1971 and 1972 groups pooled (see Table 1)

For definition of abbreviations see Table 1.

allowed to vary only within narrow limits: homeostatic controls set lower and upper tolerated limits to τ variation; (*2*) many variables in addition to temperature affect τ, and at 20° uncontrolled variables other than temperature are responsible for the wide scatter of individual τ_1s within the tolerated range; (*3*) the large temperature stepup pushes τ_2 in all individuals to (or close to) its upper tolerated limit; (*4*) the resultant $\Delta\tau$ is consequently a simple function of τ_1—the further τ_1 (at 20°) is from the upper tolerated limit, the greater is the realizable $\Delta\tau$; (*5*) when the insects are at 30° the range of individual τ variation is compressed because they are all at (or close to) the same tolerated limit; and (*6*) when they are returned to 20° they assume their original τ values and $\Delta\tau$ is now no longer a function of τ at 30°.

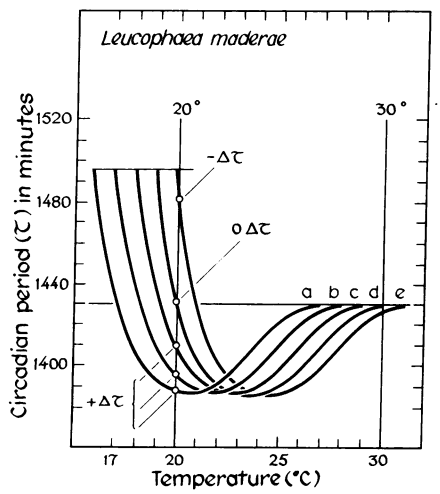

FIG. 2. Schematic representation showing how interindividual variation in the location, on the temperature axis, of the nonmonotonic curve describing $\tau = f(t°)$ for *Leucophaea* accommodates the change in sign for regression of $\Delta\tau$ on τ_1. *Curves* labeled *a* through *e* represent five individuals with different τ values at 20° (*a* shortest, *e* longest). When the animals are switched to 30°, the $\Delta\tau$ for *a*,*b*, and *c* is positive; for *d* then $\Delta\tau$ is zero; for *e* $\Delta\tau$ is negative.

A repetition of this experiment in 1972, with new insects, yielded an identical result but with the added, surprising, feature that for the 20° → 30° stepup the regression of $\Delta\tau$ on τ_1 was maintained even when τ_1 demanded a change in sign of $\Delta\tau$ (Fig. 1, *top left*). In other words, for some individual insects the Q_{10} for the 20° → 30° step was greater than one; but the $\Delta\tau$ expressed by them fell on the same regression line. This new complication led us to the prediction, which was then confirmed experimentally (Caldarola, unpublished), that τ is a nonmonotonic function of temperature. τ is very large at 17°, falls to a minimum between 20° and 30°, at which temperature it has again risen, probably to a plateau. Fig. 2 indicates how, given the nonmonotonic variation of τ between 17° and 30°, the earlier propositions explain the change in the sign of $\Delta\tau$. The interindividual variation of τ at 20° is envisaged as interindividual variation in the location, on the temperature axis, of the curve describing $\tau = f(t°)$. Erkert's study (10) of the dependence of τ on light intensity in horned owls, *Tyto alba*, provides a clear empirical precedent for this interpretation of individual differences in τ in a prescribed environment.

The association of four distinct features of the data is crucial in developing and evaluating our interpretation of the facts: (*1*) the coefficient (*c* in Table 1) of the correlation between τ_1 and τ_2 is small and not statistically significant;

TABLE 4. *Ranges of τ variation (expressed in % of $\bar{\tau}$) realized by change in external variables*

Realized range (in % of $\bar{\tau}$)	Frequency in % Light	Temperature	Drugs	"All"
0.0– 4.9	65.2	75.0	71.4	68.4
5.0– 9.9	17.4	12.5	28.6	18.4
10.0–14.9	17.4	0.0	0.0	10.5
15.0–19.9	0.0	12.5	0.0	2.6
Mean	6.0	5.3	4.0	5.2
No. of cases (n)	23	8	7	38

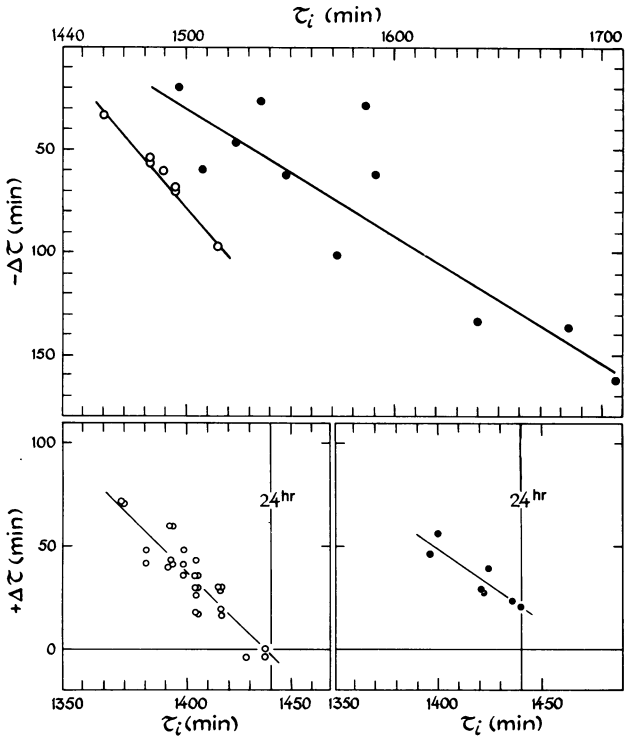

FIG. 3. Regression of $\Delta\tau$ on τ_1. *Top:* O, for the step from constant light (25 lux) to constant darkness in *Peromyscus maniculatus* (12); C = −0.99; S = −1.18. ●, after reinstatement of the earth's electrostatic field in *Homo sapiens* (14); C = −0.93; S = −0.62. *Bottom left:* After removal of dark nesting boxes in *Lonchura striata* (13); C = −0.90; S = −1.02. *Bottom right:* For the step from constant dark to constant light (250 lux) in *Leucophaea maderae* (11); C = −0.90; S = −0.70. Each *point* represents an individual animal. *Straight line* is the computed linear regression.

(*2*) the coefficient (*C*) of the correlation between $\Delta\tau$ (= $\tau_2 - \tau_1$) and τ_1 is, on the other hand, close to −1.0 and statistically highly significant; (*3*) the same is true of the regression [with slope (S) of essentially −1.0] of $\Delta\tau$ on τ_1; and (*4*) the ratio of the variances (expressed as $SD\tau_2/SD\tau_1$) is much less than one, indeed less than 0.5. It was features *3* and *4* that led us to our model, but *3*, especially, is of itself not compelling.

We thank Drs. Serge Daan and Marcus Feldman for the analysis, and its consequences, which are illustrated in Table 2. It concerns any transition from one normal distribution of τ values (τ_1) to another (τ_2) and tabulates the slope (S) of the regression of ($\tau_2 - \tau_1$) on τ_1 and the correlation coefficient (C) between these variables. Both are a function of two other statistics: the correlation coefficient (c) of τ_1 and τ_2 and the ratio (x) of the two variances expressed as $SD\tau_2/SD\tau_1$. A slope of −1 for the regression of $\Delta\tau$ on τ_1 is a statistical necessity when c is small (close to zero) but the combination of small c with S = −1 and C = −1 (which we observe) is only realizable when x is small. That, of course, is what we observe, and is therefore the crucial feature of our observations: it is not a statistical necessity and requires biological explanation. The explanation we offer for this compression of τ_2 variance is a homeostatic mechanism limiting the range of τ variation near an upper (or lower) tolerated limit.

The Same Empirical Regularities Characterize Response to Steps in Other Variables and in Other Species. Table 3 and Fig. 3 show that the same statistical regularities characterize the response of circadian oscillations to several other variables and in a wide diversity of organisms: they are found in the response of *Leucophaea* to light (11); in the response of the deermouse, *Peromyscus maniculatus*, to light (12); in the response of finches, *Lonchura striata*, to behavioral stress (13); and in the response of humans to change in the earth's electrostatic field (14). In all cases c is small and statistically not significant; S and C are close to −1 and highly significant; and *in all cases there is an associated compression of τ_2 values after the step involved* (x *is less than 0.5*). Although the compression of τ_2 variance seen in the above examples, as well as that for temperature steps in *Leucophaea*, occurs as τ approaches 24 hr, it is important to point out that the intercept of the regression $\Delta\tau$ on τ_1 is not exactly 24 hr (see especially Fig. 1, *top left*, and Fig. 3, *bottom right*). According to our interpretation, the intercept of the regression $\Delta\tau$ on τ_1 represents the upper or lower tolerated limit of τ, and in each of the above cases the value of the upper or lower limit is (only) in the neighborhood of (lies close to) 24 hr.

To the extent we are correct in interpretation of these regularities, they imply that the period, or frequency, of circadian oscillations is homeostatically protected against major change by several variables other than temperature; that the temperature compensation of τ is only a special case of a more general, teleonomically predictable property of circadian oscillations as clocks. In Table 4 we summarize the ranges of published τ variation that have been effected by manipulating τ with light, temperature, or drugs. The range is small: on average it is about $\bar{\tau} \pm 3\%$. The only exception we are familiar with is Feldman's (15) use of cycloheximide in *Euglena* where he could effect a 25% $\Delta\tau$ with a sufficiently large dose of this blocker of translation in protein synthesis.

DISCUSSION

Our proposition is that the frequency of circadian oscillators is subject to general homeostatic control in the face of all potential perturbations normally encountered in the cell. In retrospect it is remarkable we have failed to perceive the functional necessity of a *general* homeostasis of circadian frequencies. The teleonomic prerequisite for such homeostasis derives, of course, from the oscillator's role as a timing device (4). First, it is clear that were τ extremely labile in the face of change in the cellular milieu, it would readily fall outside the range within which it can entrain to external cycles with a fixed period (T) of 24 hr (7). Second, and more importantly, even were lability of τ limited to just that range within which it can lock on to the external world, its phase relation (Ψ) relative to local time would be unacceptably inconstant. A given phase (ϕ_i) in the oscillation, appropriately occurring at time t_i in the real day, would consistently phase-lead or phase-lag that target time as the oscillator's frequency varied. These functional considerations, now universally recognized as the historical or evolutionary explanation for the temperature compensation of τ (4), are equally pertinent to all other variables in the cellular milieu capable of affecting the oscillator parametrically.

Our proposition of the general homeostasis of circadian frequencies defines significant challenges and raises many obvious questions. What is the nature of the regulatory mechanism involved? No model, formal or concrete, for circadian oscillations is interesting unless it accommodates this

major feature. Is the homeostasis in some sense intrinsic to the structure of the oscillator, or is it effected by ancillary "control circuitry" extrinsic to the oscillator itself? Is there a "regulator" separable from the oscillator? This question has become both timely and tractable in the light of Feldman and Waser's (16) report of a mutation in *Neurospora* which leaves that fungus with a circadian rhythm whose τ is, however, temperature dependent. Has the mutation impaired a *general* regulator? Is τ in the mutant strain also subject to easy manipulation by light and by those metabolic blockers that elsewhere have been found to have so little (essentially no) effect on the period of circadian rhythms? It now seems likely that the failures so many workers have reported in their attempts to manipulate τ chemically reflect, at least in part, the homeostatic protection it enjoys. If there is a separable regulator extrinsic to the oscillator itself—and sensing its frequency as such—one might expect the effects of different agents affecting τ to be additive: if one pushes τ closer to an upper tolerated limit with one variable (e.g., light), is the extent to which another variable that can lengthen τ reduced thereby? The additivity and/or interaction of variables affecting τ has, with few exceptions (17, 18), been nearly ignored in the existing literature. This issue is made especially cogent by the finding of one of us (Caldarola, unpublished) that the effect of D_2O—which lengthens τ—is strongly temperature dependent in *Leucophaea*. At 20° the $\Delta\tau$ effected by 25% D_2O is three times greater than at 30°. On the face of it, this is an especially attractive finding: were the action of D_2O truly temperature dependent, it would immediately exclude several possible interpretations of its primary physical action on circadian oscillations. But the empirical result is now equivocal: at 20° τ is much further from its upper tolerated limit than at 30° and one cannot, therefore, exclude the possibility that the greater effect of D_2O at 20° is due (in a sense trivially) to the fact that at that temperature the oscillator is further away from the upper limit tolerated by its homeostatic controls than it is at 30°; and D_2O, acting similarly at 20° and 30°, simply has a greater opportunity to lengthen τ at the lower temperature before the homeostatic mechanism offsets its effect.

Clearly the general homeostasis of τ raises a serious caveat in the interpretation of dose/response curves for *all* agents that affect the oscillator. Until more is understood, even about the formal properties of the homeostatic mechanism, it stands as a screen between experimenter and oscillator. Mutants, like Feldman's in which homeostasis has been lost, become a prime *desideratum*, removing that screen and opening the oscillator to more direct chemical manipulation.

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