Reply to R. E. Kronauer and P. H. Gander

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compare very well with the data published by Wever (9). These predictions and comparisons have recently been expanded (Gander, Kronauer, Czeisler, and Moore-Ede). In brief, we have taken the model with parameters derived from free-run data and added a periodic zeitgeber drive. Wever (9) cites 10 appropriate examples of subjects exposed to zeitgebers with various periods. Two different protocols were employed. For one protocol the subject was allowed the use of a reading lamp and consequently was free to override the darkening of general room illumination. We characterize this as a "weak" zeitgeber and assign a moderate drive from z to y in the model. For the second protocol where strict darkness was imposed, we characterize this as a "strong" zeitgeber and used a z-y drive three times stronger than for the weak z. For each of the 10 examples we estimated values for the intrinsic period of the x and y oscillators from the periods and phases of the temperature and sleep-wake rhythms in each subject. All the x periods are in a narrow range (24.2–24.9 h), whereas the range of y periods was large (22.4–32.7 h). All other model parameters were held fixed for the 10 examples. The model simulates qualitative and quantitative data features with remarkable subtlety.

Concluding Remarks

The model proposed by Daan et al. is appealing in the directness with which the single variable S is presumed to regulate sleep. This model also accommodates very well to the extreme case of subjects confined for 60 h to bed in a dark, clockless room (sect. IV*B*) by simply reducing the threshold level for sleep onset. Although we could achieve comparable results in our model by dramatically shortening the period of y, we see no equally simple explanation for doing so. However, by associating the decrease of S with the occurrence and intensity of slow-wave sleep, the authors will have to devise some complicated explanation for the recurrence of slow-wave sleep in subjects who are asked to sleep for a long time and succeed in doing so (4).

The model of Daan et al. has brought forward stimulating new concepts and is further valuable in that it highlights many current issues in the modeling of human circadian rhythms. Whether or not the two oscillators constitute "true" pacemakers, this model and ours share important similarities, particularly with regard to the mechanism of spontaneous internal desynchronization.

REFERENCES

1. ALBERS, H. E., R. LYDIC, P. H. GANDER, AND M. C. MOORE-EDE. Gradual decay of circadian drinking organization following lesions of the suprachiasmatic nuclei in primates. *Neurosci. Lett.* 27: 119–124, 1981.
2. CZEISLER, C. A., J. C. ZIMMERMAN, J. RONDA, M. C. MOORE-EDE, AND E. D. WEITZMAN. Timing of REM sleep is coupled to the circadian rhythm of body temperature in man. *Sleep* 2: 329–346, 1980.
3. FULLER, C. A., R. LYDIC, F. M. SULZMAN, H. E. ALBERS, B. TEPPER, AND M. C. MOORE-EDE. Circadian rhythm of body temperature persists after suprachiasmatic lesions in the squirrel monkey. *Am. J. Physiol.* 241 (*Regulatory Integrative Comp. Physiol.* 10): R385–R391, 1981.
4. GAGNON, P. Extended sleep patterns. *Symp. Abstr. Assoc. Psychophysiol. Study Sleep Meeting, July 21, 1983.*
5. KRONAUER, R. E. Modeling principles of human circadian rhythms. In: *Mathematical Models of the Circadian Sleep/Wake Cycle*, edited by M. C. Moore-Ede and C. A. Czeisler. New York: Raven. In press.
6. KRONAUER, R. E., C. A. CZEISLER, S. F. PILATO, M. C. MOORE-EDE, AND E. D. WEITZMAN. Mathematical model of the human circadian system with two interacting oscillators. *Am. J. Physiol.* 242 (*Regulatory Integrative Comp. Physiol.* 11): R3–R17, 1982.
7. REPPERT, S. M., M. J. PERLOW, L. G. UNGERLEIDER, M. MISHKIN, L. TAMARKIN, D. G. ORLOFF, H. J. HOFFMAN, AND D. C. KLEIN. Effects of damage to the suprachiasmatic area of the anterior hypothalamus on the daily melatonin and cortisol rhythms in the rhesus monkey. *J. Neurosci.* 1: 1414–1425, 1981.
8. WEVER, R. The circadian multi-oscillator system of man. *Int. J. Chronobiol.* 3: 19–55, 1975.
9. WEVER, R. A. *The Circadian System of Man. Results of Experiments Under Temporal Isolation.* New York: Springer-Verlag, 1979.

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Reply to R. E. Kronauer and P. H. Gander

THE DETAILED COMMENTARY of R. E. Kronauer and P. H. Gander on our contribution reveals several controversies. The following summarizes our position on the issues raised in the various sections of their critique.

We have not argued against the existence of multiple circadian oscillators. A major outcome of our simulations is, however, that internal desynchronization can occur in a system involving a single circadian pacemaker, as anticipated by Eastman (1). The S process may be termed an oscillator, but one should be aware that the whole organism and its behavior are part of this oscillator and that going to bed and getting up are key elements in its causal loop. Emphasizing the oscillator metaphor may lead to what Kronauer and Gander feel to be semantic confusion and in the past led to the misinterpretation of internal desynchronization as proof of the existence of at least two circadian pacemakers in the human (2).

Our model does not directly address entrainment. Special hypotheses shall be necessary to incorporate effects of light on the system. Such hypotheses may effectively be advanced once these effects—especially phase-response curves—have been measured. They will certainly include phase shifts of the circadian pacemaker as well as effects on decisions to go to bed [e.g., when absolute darkness is imposed (3)], which in turn affect the subjective perception of the light cycle (see Fig. 1, Daan et al.). It is probable that such complex action of light can eventually explain some of the details in spontaneous sleep timing which are the subject of differences of opinion: phase angle difference change in free run after entrainment, period change with internal desynchronization, and rare instances of regular variations in sleep timing during free run (of which Kronauer and Gander present a nice example in their Fig. 3*B*). We have not yet found it useful to simulate these phenomena without having recourse to independent data on the action of light in the human circadian system.

Our suggestion that circadian amplitude of the S thresholds may be reduced in free run compared with entrainment was based on a variety of plant and animal experiments. We find no reason to propose special explanations for the case of the human temperature rhythm, which is anyway not identical with the S thresholds.

Kronauer and Gander ascribe the absence of average periods in the ranges 21–23 and 27–30 h in Wever's experimental data (3) to two hypothetical causes. We can only repeat that these data, as well as our simulations, do show such periods [reanalysis by Zulley (4)]. The record sections selected by Wever on the basis of circadian period understandably do not show them.

A model can be used to generate new experimental designs and can be tested by comparing prediction and empirical results from such novel experiments. This strategy for testing is not identical with a post hoc consistency between available data and model properties. That is not to say that such consistency is unimportant. Indeed we feel that a useful model should be consistent with a broad variety of empirical data, as in the case of human sleep timing, with the results not only of temporal isolation, but also of experiments such as sleep deprivation and continuous bed rest. If extended sleep really leads to systematically increased EEG power density toward the end of sleep, our model will have to be modified. The currently available evidence has not yet forced us to take this position.

REFERENCES

1. EASTMAN, C. The phase-shift model of spontaneous internal desynchronization in humans. In: *Vertebrate Circadian Systems. Structure and Physiology*, edited by J. Aschoff, S. Daan and G. A. Groos. Berlin: Springer-Verlag, 1982, p. 262–267.
2. KRONAUER, R. E., C. A. CZEISLER, S. F. PILATO, M. C. MOORE-EDE, AND E. D. WEITZMAN. Mathematical model of the human circadian system with two interacting oscillators. *Am. J. Physiol.* 242 (*Regulatory Integrative Comp. Physiol.* 11): R3–R17, 1982.
3. WEVER, R. *The Circadian System of Man.* Berlin: Springer-Verlag, 1979.
4. ZULLEY, J. Die circadiane Steuerung des Schlafes. In: *Klinische Psychologie, Depression und Schizophrenie*, edited by D. Vaitl, K. Ferstl, and E. R. Rey. Weinheim, FRG: Beltz, 1983, bd. 3. In press.

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