8. The 16th harmonic of a fundamental 24-hour periodicity is 90 minutes (1440 minutes/16 = 90) according to standard usage [*McGraw-Hill Encyclopedia of Science and Technology* (McGraw-Hill, New York, ed. 3, 1971), vol. 14, pp. 490–492]. The authors' reference to a 90-minute period as a "fourth harmonic" of a 24-hour rhythm (1440 minutes/2^4 = 90) is totally unacceptable in period analysis and can only lead to confusion.

21 November 1977; revised 6 March 1978

Kronauer *et al.* use an independent mathematical analysis to conclude that there is no synchrony among the control ultradian cortisol rhythms that we reported (*1*). Their comments fail to address the issue of the exact concurrence of peaks and troughs of these rhythms when compared across both grouped control data and values collected during infusion of adrenocorticotropin (ACTH) [figure 1, B and D, in (*1*)]. If no synchrony existed, it would be highly unlikely that these two series of data collected over 18 months would show such close temporal correspondence. Thus, a major focus of our original report which demonstrated the persistence of an ultradian cortisol rhythm during continuous ACTH infusion and its apparent synchrony with control oscillations remains undisputed.

Two other observations support the apparent validity of these grouped data as an indication of synchrony across real time. First, the same predominant 85 to 90 minute periodicity was observed when we compared the individual power spectra [figure 2A in (*1*)] with the power spectrum from these control data grouped across real time [figure 2C in (*1*)] as well as with the grouped data from ACTH-infused animals [figure 2D in (*1*)]. Second, as mentioned (*1*), the pharmacokinetic estimates of the duration of cortisol secretion and clearance from the grouped data correspond well with published values for individual monkeys (*2*, *3*).

Essentially, there are two perspectives from which one can evaluate the possibility of synchrony in such time-series studies. The approach taken by Kronauer *et al.* represents one reasonable way to analyze this problem. Their cosinor analysis of individual data shows individual variability in period, amplitude, phase, and time of first acrophase among monkeys. We have employed an analysis using multiple complex demodulation (MCD). This technique synthesizes a series of digital filters which may be used to examine nonstationarities in time series. Our results in estimating time of the first acrophase as well as individual periodicities with this method agreed remarkably well with those of Kronauer *et al.* in their table 1. In addition, the individual filtered outputs from the MCD analyses were entered into a pairwise covariance analysis. Of all of the possible pairs of individual animals only two showed significant covariance.

A second perspective from which one can evaluate synchrony is to analyze simultaneously the collective rhythms of all monkeys using grouped data. That was our approach in (*1*). In response to our request for a further evaluation Cleveland (*4*) devised a simplified method of statistically evaluating these data by an ensemble technique, and found that there was some, but not totally convincing, evidence that these control cortisol data contain synchronized rhythms. Although such evaluations of grouped data may be suitable in predicting their collective responses, changes in time series parameters for individual animals become obscured.

We suggest that the rather larger variability in our individual control animal data presented by Kronauer *et al.* should be expected because of the low signal-to-noise ratio and short data series in our original data. Halberg (*5*) suggested that daily rhythms in individual biological systems are not exactly 24 hours but instead are approximate (*circa*dian), thus it is probable that individual variability in ultradian rhythms should also be expected (*circ*ultradian?).

The strongest evidence for or against synchrony in biological ultradian oscillators would be the demonstration of phasic consistency in other studies of rhythmic behaviors. Tannenbaum and Martin (*6*) have reported a light-entrained, synchronized ultradian growth harmonic rhythm in rats. One of us (B.H.N.) has recently published evidence which suggests synchrony of plasma norepinephrine ultradian oscillations in monkeys (*7*) as well as in ultradian patterns of feeding and drinking in this species (*8*). Unlike Kronauer *et al.*, we believe that the collective evidence discussed herein suggests the existence of some synchrony in biological ultradian rhythms which, according to Cleveland, "is a possibility which ought to be looked for in future experimentation and after which it seems reasonable to try to find an explanation in theoretical terms."

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References and Notes

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4. W. S. Cleveland (personal communication) describes what he terms an "incomplete and not totally satisfactory analysis of the data." Initially, a least-squares, straight-line fit was subtracted from each of the eight monkey control series. Ignoring for statistical purposes the effects of this detrending, the following simplified model was hypothesized:

$$y_{it} = \alpha \cos 2\pi\omega + \beta \sin 2\pi\omega t + \epsilon_{it},$$

for $i = 1, \ldots, 8$ and $t = 0, \ldots, 18$, where y_{it} is the detrended value for monkey i at times t; α, β, and ω are unknown parameters; and ϵ_{it} are independent normal variables with mean 0 and variance σ^2. "The estimates of the parameters, using least squares, and their standard errors, using a linearization technique in which it is supposed that the mean function is nearly linear in a neighborhood of the true value, are $\hat{\sigma} = 2.23$, $\hat{\sigma} = -.55 \pm .26$, $\hat{\beta} = -40 \pm .30$, $\hat{\omega} = .235 \pm .007$. In a complete analysis the exact standard errors would be computed and an analysis of residuals would be carried out to see if a small fraction of the data was substantially affecting the results. The F statistic for the regression is

$$\frac{(TSS-RSS)/3}{RSS/(136-3)} = 2.14,$$

where TSS is the total sum of squares of the y_{it} and RSS is the residual sum of squares. Again, we can approximate this, using the linearization assumption, by an F distribution with 3 and 133 degrees of freedom. The .05 and .1 percentage points for an F with 3 and ∞ degrees of freedom are 2.68 and 2.08."
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9. We thank W. Cleveland (Bell Laboratories) for evaluating our data, and F. W. Hegge and H. C. Sing for the multiple complex demodulation and covariance analyses.

29 June 1978

1003-1032 (mk)

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Science **202** (4371), 1002.
DOI: 10.1126/science.202.4371.1002