Rhythms

*Recent discoveries suggest that the mysterious biological
clock phenomenon results from a continuous interaction
between organisms and the subtle geophysical environment*

The knowledge that living things are rhythmic doubtless harks back to the dawn of man's consciousness. Primitive man could witness rhythmic activities related to day and night, the ebb and flow of the ocean tides, and the annual passage of the seasons. The concept of "biological clocks" arose, however, much more recently and was based upon observations that the rhythmic changes in organisms could persist even when creatures were shielded from variation in every rhythmic factor of their environment to which they were known to be sensitive.

Other observations revealed that the persistent daily rhythms could be set arbitrarily to any relationship with clock hour of the day by appropriate light changes and thereafter persist with the new setting. The persisting

Frank A. Brown, Jr., Morrison Professor of Biology at Northwestern University, offers a sequel to his 1959 American Scientist article "The Rhythmic Nature of Animals and Plants" (47:147-68). The current article was developed out of his 1968 Sigma Xi National Lecture. After receiving his Ph.D. in zoology at Harvard in 1934, the author conducted for more than fifteen years his pioneering investigations of the endocrine system of Crustacea. He then became intrigued with what was shortly to become the well-known and much-studied biological clock phenomenon. Following this problem over the past twenty-five years, he and his numerous associates have been led increasingly along a path diverging from that pursued by the majority of scholars in the field. Dr. Brown's researches culminate in the hypothesis advanced in this article. This research, initially supported by the Office of Naval Research and later by the National Institutes of Health and the National Science Foundation, is currently supported by NSF Grant #GB-31010. He is co-author, with C. L. Prosser, of Comparative Animal Physiology and, with J. W. Hastings and J. D. Palmer, of The Biological Clock: Two Views. Address: Hogan Biological Laboratory, Northwestern University, Evanston, IL 60201.

rhythms could possess a regular period slightly longer or shorter than 24 hours. A single light perturbation could often initiate a rhythm in an individual lacking one. Such observations led to the conclusion that the "clock" must be fully independent of any and all rhythms in the physical environment. According to this concept, the observed rhythms generally reflected faithfully the behavior of the underlying clock. Resetting rhythms was interpreted as resulting from a resetting of the organism's clock. Rhythms that were displaying altered periods were considered to be demonstrating altered clock periods.

Numerous and extensive searches over many years for the mechanism of this type of clock have left us as completely mystified as we were when the clock was first postulated. Furthermore, it has been unsettling to find that no evidence, either early or recent, has unambiguously *compelled* the postulation of such a clock. So complete has been the failure of investigators to discover a clock with the requisite properties that doubt has steadily increased that a clock of this particular character really exists at all.

Meanwhile, advances over the past decade or two in our knowledge of properties of clock-timed rhythms together with newly disclosed sensitivities of organisms to their ambient subtle geophysical environment have encouraged a critical reexamination of the original concept of the clocks and their relation to the rhythms that they time. It has now been possible to formulate an alternative hypothesis that accounts perhaps even more satisfactorily than the classical one for all the described characteristics of the phenomenon.

The new hypothesis encompasses all the clock-timed rhythms—i.e. those that display the unique property of a high degree of period stability, including complete or nearly complete temperature-independence of their periods. It includes all the reported periods, ranging from solar-day, through tidal and monthly, to annual ones. The rhythmic patterns are postulated to comprise genetically and environmentally determined behavioral sequences that have evolved to fit within the natural geophysical periods. Furthermore, these sequences are proposed to depend upon the subtle rhythmic geophysical variations both during their individual development and their on-going precise timing.

In terms of this alternative paradigm, the clocks are environmentally timed and hence always accurate. The observed rhythms are readily set, or reset, relative to the stable clock, and a rhythm can possess a period different from that of the clock upon which it depends. The latter condition can be effected by systematic resetting, cycle by cycle, of the rhythm's temporal relationships to the clock.

It is important to note that the phenomena which underlie this alternative hypothesis do not include the long-elusive, and still-controversial, inherent, stable oscillators. Instead, there are included only the mechanisms of resetting the overt rhythmic processes agreed to in principle by all students of the rhythms, together with a responsiveness of the organisms to the natural electromagnetic forces of their rhythmic physical environment. Such responsiveness is now well established, and our knowledge of its remarkable properties is expanding rapidly.
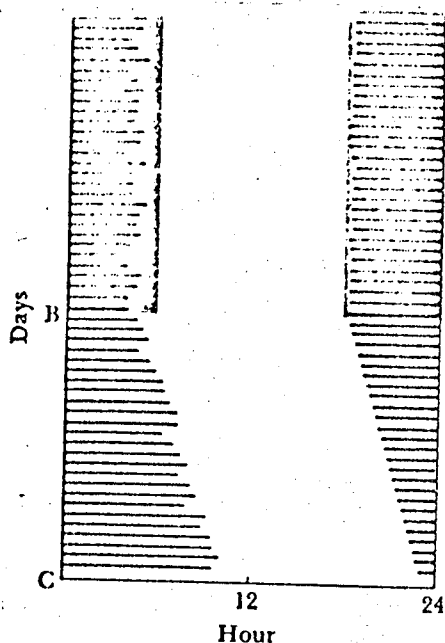
Figure 1. The times of locomotory activity of a generalized *nocturnal* mammal during a 30-day sojourn in a 24-hour light-dark regime (*days A to B*) and during a continuous period in unvarying illumination (*days B to C*). Shaded areas indicate time of darkness. Horizontal lines show times of activity. In continuous illumination a free-running period is typically longer than 24 hours.

Circadian rhythms

Biological rhythms that continue with a period of about a day (18 to 33 hours) with all obvious environmental factors constant have been given the term *circadian* (*circa*—about; *dian*—a day). This term was coined by Halberg (1959) to replace the formerly used daily, diurnal, diel, 24-hour, and nycthemeral, which implied that these particular rhythms were always 24 hours. It was true that rhythmic variations occurring in the natural environment or in artificial 24-hour light-dark cycles were always 24 hours (Figs. 1 and 2, days A to B). It was clearly not so, however, for the same solar-day patterns when the organisms were retained in unvarying light and temperature (Figs. 1 and 2, days B to C). Under the latter conditions, the observed period of the recurring patterns could clearly deviate in a highly significant manner from 24 hours and were said to be "free running."

The periods under these conditions could be either longer or shorter than 24 hours, nearly constant in length over extended periods, or could "spontaneously" change abruptly or systematically with time. The periods could also differ from one individual to another under the same conditions, indeed, even among organisms housed in the same enclosure. The periods also were usually altered slightly when levels of temperature or light were changed. The recurring behavioral, physiological, and biochemical patterns, which in normal circumstances were adaptively attuned to the day-night changes, now were systematically drifting over all clock hours of the day.

Included within the broad definition of circadian was another kind of biological rhythm, the lunar-tidal, whose periods in nature follow the moon-dominated tides of the oceans and hence have, in organisms that live in the natural seashore environment, a mean period of 24 hours and 50 minutes (24.8 hours) between the double tidal cycles of consecutive days. These lunar-tidal rhythms can persist with their normal frequency even in the laboratory away from the tides when the organisms are held in the natural variations of illumination or in artificial 24-hour light-dark regimes. Figures 3 and 4, days A to B, illustrate diagrammatically the simultaneous 24-hour skin-darkening rhythm and the 24.8-hour locomotor-activity rhythm for a fiddler crab under such laboratory conditions. When, however, the periods of darkness are discontinued (Figs. 3 and 4, days B to C), the observed color-change periods commonly become longer than 24 hours, while the lunar-tidal rhythm of activity may exhibit periods longer than 24.8 hours.

The frequency range of the lunar-tidal rhythms, whether 24.8 hours or free-running, lies within the general range defined by the term circadian. The periods of the free-running tidal patterns, like those of the free-running solar-day ones, may vary among individuals retained under the same constant conditions and even in the same individual in the course of time.

The rhythmic solar-day and lunar-tidal patterns in the natural environment are said to be period-synchronized and phase-adapted to the natural day-night and ocean-tidal environment. This is accomplished by responses to such factors as the changing natural light and temperature for the solar-day patterns, and
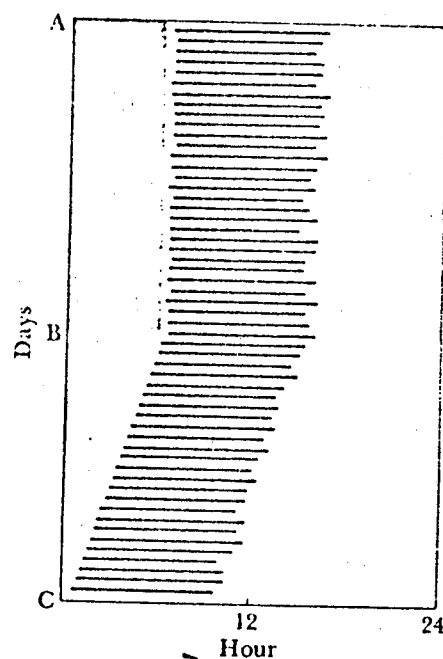

Figure 2. The relation of activity times to light and darkness in 24-hour cycles (*days A to B*) for a generalized *diurnal* bird or lizard. In constant illumination (*days B to C*) the organism typically adopts a free-running period shorter than 24 hours.

some still largely unidentified physical factors correlated with the ebb and flow of the ocean tides for the lunar ones. The factors playing this kind of role are termed phase setters, synchronizers, or *Zeitgeber*.

It is readily apparent that the Zeitgeber for the natural 24.0- and 24.8-hour rhythms must differ from one another, and the properties of free-running lunar-tidal rhythms might be expected to differ from free-running solar-day rhythms. Indeed they do, and in a most fundamental manner. Under natural conditions the foraging schedule of crabs conforms to the tides, which rise fifty minutes later day by day, while the color changes of crabs are an adaptation to the light-dark cycles. As expected, the color changes will follow 24-hour light-dark cycles; the activity will not. The crabs have two clocks, a daily and a tidal. Hence, we must subdivide circadian rhythms into two major classes: solar-day circadian rhythms and lunar-tidal circadian rhythms.

Solar-day circadian rhythms

The tendency for a solar-day circadian rhythm to deviate from

hours under conditions of deprivation of all periodic solar-day Zeitgeber was acknowledged from the time of the now-classical studies of Wilhelm Pfeffer on plants early in this century. Since each individual plant under the same controlled environmental conditions could possess its own overt period, or degree of deviation from 24 hours, it was postulated that each organism contained its own private timer. This timer simulated closely, but not exactly, the period of the earth's rotation relative to the sun. The timing systems for these circadian periods later became known as biological clocks, and more recently as circadian clocks. It was rationalized that the clocks could not be expected to be precise, and that under natural conditions the daily cycles in Zeitgeber would constantly correct the day-by-day errors to provide the usual 24-hour precision.

There have been innumerable investigations disclosing rhythmic biological phenomena throughout the plant and animal kingdoms that are coupled to such postulated clocks. Even unicellular forms may have circadian rhythmicity. The literature describing

examples has become enormous and still rapidly grows. Using the results of investigations of these clock-timed rhythms, the discovered properties of the rhythms have been projected directly to describe attributes of the underlying clock itself. The departure from 24 hours of a solar-day circadian rhythm in constant light and temperature has been widely accepted as establishing that the clock upon which it depends is also displaying the same circadian frequency, and hence its mechanism must be independent of any natural environmental periodicity of close to the same frequency.

In reality, however, it has not yet been possible to devise an experiment that can resolve the issue between *two* still tenable hypotheses for the timing of the circadian periods: (1) the rhythms are timed by some means that is *fully independent* of all environmental rhythms, and (2) their timing is *dependent* upon concurrent subtle geophysical rhythms.

I shall now describe how an environmentally dependent system for the timing of solar-day circadian rhythms is compatible with all our knowledge of the properties of these rhythms. This hypothesis can account for the timing of these rhythms whether they are 24-hour or free-running. Indeed it accounts for some properties for the first time, and other properties as plausibly and consistently as does the classical hypothesis of an autonomous circadian clock.

Light, the dominant Zeitgeber

Let us consider the known characteristics of the processes by which an organism adjusts the phase of its circadian rhythmic pattern to the time of day. The genetic, and environmentally modified, recurring circadian pattern responds to phase setters or Zeitgeber, and the phases of the circadian cycle become shifted to some preferred phase relationship to such Zeitgeber cycles.

It is generally conceded that the dominant Zeitgeber is light. Nocturnal organisms, for example, typically set the times of initiation of their activity periods to onset of darkness (Fig. 1), and diurnal creatures to onset of light (Fig. 2). Other environmental rhythms, such as those

of temperature, feeding, sound, and social interactions, may also sometimes play the role of Zeitgeber, but characteristically with less influence than light. The mechanism of phase adjustment of the circadian rhythm to light involves the presence and operation of a circadian phase-response variation (DeCoursey 1961), which can be illustrated as a phase-response curve.

A phase-response curve illustrates the amount of phase shift, and its direction, observed following exposure of an organism to a stimulus administered at various times of day. The phase-response curve in Figure 5A represents the varying amounts and directions of shifts obtained for nocturnal animals adjusted to the light-dark cycle shown and subsequently exposed to test light periods at various times of day. Maximum delay occurs near the time of onset of evening activity, and maximum advance is associated with the time of morning termination of activity. Figure 5B represents the predicted effect of changing the time of the dark phase of the light-dark cycle so that it occurs 6 hours later. The
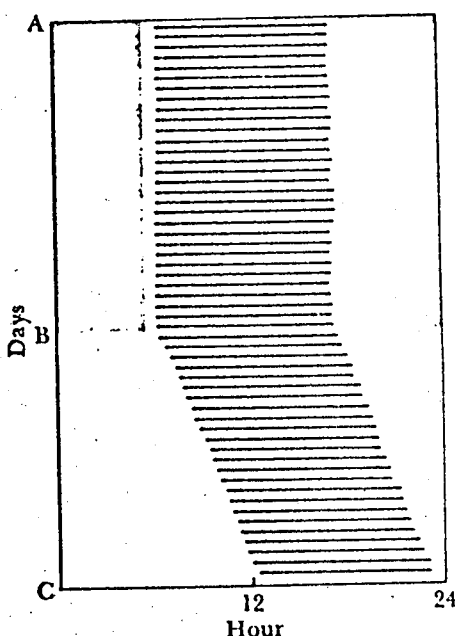
Figure 3. Horizontal lines indicate the times of darkening of the skin of a fiddler crab in 24-hour cycles of light and darkness for a 30-day period (*days A to B*). Shaded areas indicate time of darkness. When conditions are changed to continuous illumination (*days B to C*), a free-running rhythm is adopted.
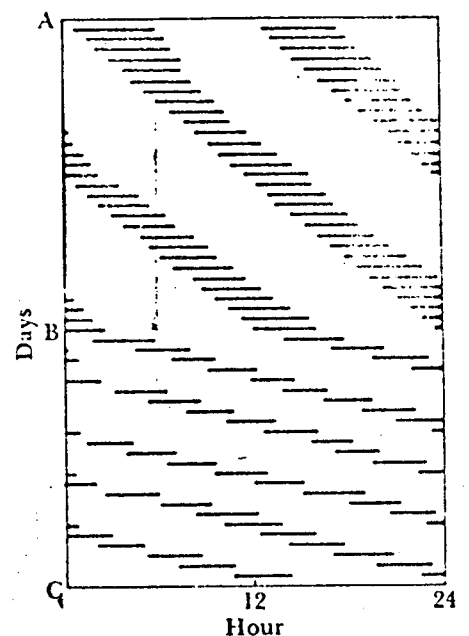
Figure 4. The lunar-tidal rhythm of locomotory activity in a crab under the same conditions as in Figure 3. Note that a lunar-tidal frequency which exists in the 24-hour light-dark regime (*days A to B*) becomes free-running, with a longer period, in continuous illumination (*days B to C*). Both solar-day and lunar-tidal rhythms may occur concurrently in the crabs.

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organism would be exposed to light at the time when the stimulus exerts a maximum delaying effect. Figure 5C similarly shows the predicted effects of shifting the dark phase 6 hours earlier so that exposure to light occurs when there is a maximum advancing effect.

Circadian phase-response curves have been described in varying degrees of detail for many organisms—plant, animal, and microorganism. There is ample reason to presume that these are invariable concomitants of the circadian rhythmic systems and indeed essential for phase adjustment.

When the animal's activity cycle is in final phase adjustment with its ambient daily light changes (Fig. 5A), light near the end of one daylight period occurs during the phase-delay portion of the cycle and nudges the onset of activity toward the dark period. Light at the beginning of the succeeding daylight period occurs during the phase-advance portion of the curve and nudges the cycle toward the preceding dark period. The animal, therefore, effectively maintains a relationship of its rest-activity cycles o the light cycles which depends upon balancing phase delays and advances. Exactly where the activity pattern becomes stabilized with respect to the illumination cycle can be seen to depend upon the detailed relationship of the light phase-response curve to the activity pattern with which it is firmly phase-associated.

The manner of operation of this circadian activity-phase-response complex in response to an abrupt phase shift in the environmental light cycle is self-evident. Figure 5B describes an abrupt westward displacement at the equator by about 6,000 miles as well as the equivalent light-regime change in the laboratory. Figure 5C describes the situation resulting from comparable eastward displacement. Usually within a few cycles the circadian system has become gradually restored to equilibrium in adjustment with the new illumination phases by being nudged more strongly in one direction than the other during each light cycle until the two directions again become juated.

For a given experimental phase change in light-dark cycles, the rate of phase shift is a function of the brightness of the illumination. It is also a function
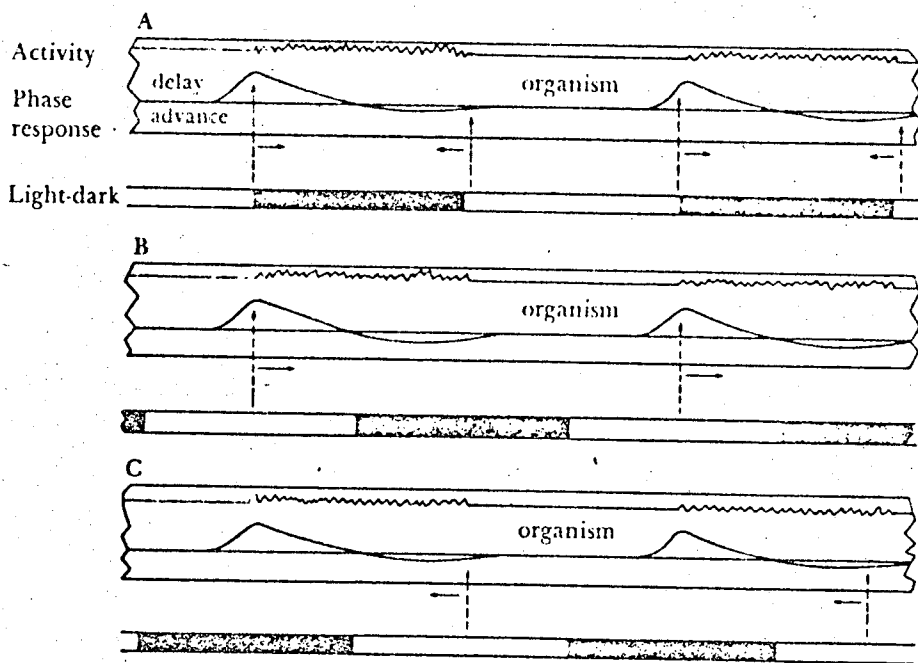

Figure 5. (A) The relationship between the activity rhythm of a nocturnal mammal and its closely associated phase-response curve, together with the relationship of these to the environmental light-dark cycles. The animal's rhythm has become fully adjusted to the light. (B) The relationship immediately after an abrupt phase delay in the environmental light cycle such as would result from rapid displacement westward a quarter way around the earth. (C) The relationship immediately after an abrupt phase advance in the light cycle, as would occur after comparable eastward displacement. Horizontal arrows indicate the expected phasing influences of light at times in the biological cycles shown by the vertical arrows.

of the demanded shift direction as, for example, in response to east-to-west or west-to-east geographic translocation. It is evident that this system which effects gradual phase adjustment to an altered light cycle is highly efficient in permitting the continuance of relatively smooth functioning of the complexly integrated organism during the transition (Fig. 6). It is also nicely adapted for response to the natural diurnal variation in illumination with its relatively long, graded twilights at dawn and dusk, and varying nighttime illumination. Despite natural 24-hour light cycles' lacking precisely timed points, the circadian

rhythms can still become cleanly reset and resume a relatively stable and precise 24-hour periodicity.

Now arises the question of how such a circadian activity-phase-response complex might be expected to behave when the organism is subjected to carefully regulated deprivation of all periodic variation in factors that normally serve as stronger and weaker Zeitgeber. What will the complex do if a nocturnal organism is held in continuous unvarying illumination (Fig. 7)? We have learned that illumination near the time of activity onset causes maximum delay in the circa-
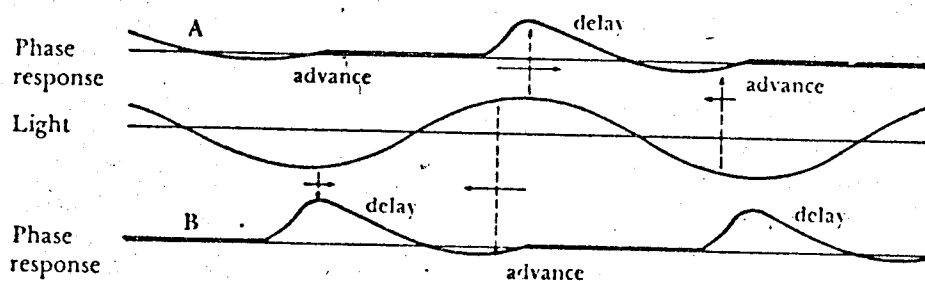

Figure 6. The expected reactions of the activity-phase-response system to gradual 24-hour variations of environmental illumination. The diagram suggests how phase adjustment is normally attained by equating phase delays and advances in the twilight hours of lower intensity. Initiation of phase adjustment is shown from two points, one with activity onset at midday (A) and the other at midnight (B). Horizontal arrows indicate the expected phasing influences of light at times in the biological cycles shown by the vertical arrows.

dian-cycle phase. Light during the time of activity termination advances the cycle phase. When the illumination does not vary in intensity, the amount of sequentially occurring phase delay and advance in each cycle will be expected to reflect the relative strengths that may be described by the areas circumscribed by the delay and advance portions of the curve and the line of zero response for that individual.
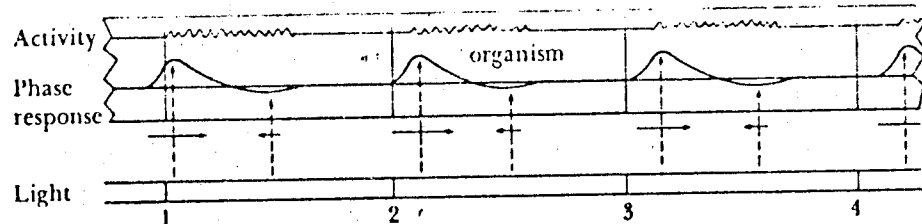

Figure 7. The expected phase-shifting behavior of a nocturnal organism in constant light. There are repeated daily phase shifts, or autophasing, in response to the light, which is normally a Zeitgeber but is here held constant. The numerals mark successive 24-hour periods. Horizontal arrows indicate the expected phasing influences of light at times in the biological cycles shown by the vertical arrows.

Phase-response curves vary in detailed form from one individual to another (DeCoursey 1961; 1964). It is evident that if the phase-*delay* response to a given illumination intensity is stronger than the phase-*advance* one, as appears to be typical for nocturnal mammals, the animal will be expected to generate a period longer than 24 hours (see Fig. 1). This would result from an overall daily phase delay effected by the same organismic mechanism that in nature serves as such an efficient phase-adjusting one. It should be reemphasized at this point that the phase-response cycle, being a component of the circadian one, would be undergoing a parallel phase shift.

Autophasing

An individual whose phase-advance portion of the response curve chanced to be more pronounced than the phase-delay part would be expected to generate a circadian period shorter than a day, by cumulative daily phase advances. Such postulated phase shifting in response to constancy of all Zeitgeber fields, strong and weak, has been termed *autophasing* (Brown 1959). In any population of animals held under the same controlled environmental constancy we would expect many different circadian frequencies since there are many individually different phase-response-curve forms, and we observe this actually to be the case.

The foregoing rationalization can be very readily transposed to a diurnal organism such as a sparrow, finch, or lizard. In these animals, contrary to nocturnal animals, the area of the phase-response curve encompassing phase advance would be expected to be greater than that for the phase delay. Indeed, this has recently been demonstrated for a sparrow (Eskin 1971). With such a responding system, the diurnal animal's activity is effec-

tively held in the daylight phase of the environmental cycle. Diurnal vertebrates (see Fig. 2) in continuous unvarying illumination typically generate cycles shorter than 24 hours (Aschoff 1960), quite as one might predict if the advancing phase response to light were stronger than the delaying one.

A long-known characteristic of circadian rhythms for which there has not been any postulated explanation to date finds a simple explanation in terms of the foregoing model. This characteristic is a relationship between intensity of the field of continuous illumination and the length of the free-running circadian period. This was first reported by M. Johnson (1939) for the deer mouse. The period for nocturnal vertebrates usually lengthens as the illumination increases, while that for diurnal vertebrates becomes shorter (Aschoff 1960).

It is evident that any asymmetry in the amounts of phase delay and advance in response to one level of illumination can be expected to persist as the illumination level is altered. Hence, for example, as the rates of both delay and advance are proportionately increased or decreased in response to a light level change, the algebraic sum for the two will be expected to vary in a direct relationship with the change. The observed period of free-running rhythms should reflect this. If the period is shorter than 24 hours, the higher the illumination, the shorter the period (as, for example, in a finch); whereas, if it is longer than 24 hours, the higher the illumination, the longer the period (in a mouse, for example). This is the state of affairs generally observed and is incorporated in what is known as Aschoff's rule.

Two other light-related properties of circadian rhythms also find a con-

sistent explanation in terms of the autophasing model for genesis of free-running circadian rhythms. The first is a report by Aschoff and Wever (1966) that the period of free-running in a finch is correlated with the specific equilibrium location of the finch's activity pattern in relation to a light-dark (12:12) cycle. The specific equilibrium state would be expected to reflect the form of the individual's phase-response curve and its specific phase relationship to the activity pattern. The greater the phase-advance response, relative to delay, the more advanced, other factors being equal, is the onset of activity, relative to the particular light cycle. Parallelly, the shorter we would expect the free-running cycles to be for the individual bird in constant illumination, and this is the case.

The second property explained by autophasing is the very recent finding by Natalini (1972) that the mean free-running periods of kangaroo rats in continuous light were directly correlated with the amount of their phase shift in response to light at or near the time of activity onset (Fig. 8). Of the eleven rats studied, all eight displaying periods longer than 24 hours exhibited phase delays near activity onset, and the three with free-running periods shorter than 24 hours showed phase advances. It would have been most interesting to learn whether these three rats would have tended to be diurnal in habit, contrary to the predominantly nocturnal habit of the species.

Another well-established property of circadian rhythms is that the length of the free-running rhythm is in part genetically determined. This was shown by the classical studies on Bünning (1935) for sleep movements (daily elevation and lowering of the leaves) of bean seedlings. Very recently, inheritance of period has been

confirmed for *Drosophila*, with further refinement from the discovery that single gene changes could effect significant alterations in free-running periods of this fly (Konopka and Benzer 1971).

The forms of phase-response curves are definitely inherited in some measure. The forms for nocturnal species obviously differ strikingly, and in an inherited manner, from those for diurnal ones. Furthermore, within any sample of a natural population there are differences from one individual to another, as DeCoursey has described for the flying squirrel and Natalini for the kangaroo rat. We would expect the free-running periods of circadian rhythms to reflect genetic differences through contributions of the genome to the forms of the individual response curves.

"Spontaneous" changes in the free-running period commonly occur in presumed unvarying conditions in the laboratory. Semimonthly, monthly, and annual variations in period have also been reported. These can be explained by postulating spontaneous, or systematic, changes with time in the detailed forms of the individual's phase-response curve.

In the absence of light, the dominant Zeitgeber, the unvarying fields of normally weaker Zeitgeber can be assumed to substitute for light in eliciting autophasing. It can be presumed that phase-response variations comparable to those for light exist for the other Zeitgeber. Postulated autophasing in reaction to a constant-temperature field, for example, will be discussed later.

The autophasing concept can also account easily for any observed influences of drugs or other chemicals on the free-running period. The well-established influence of heavy water, D_2O, in lengthening the period (Bruce and Pittendrigh 1960; Suter and Rawson 1968; Dowse and Palmer 1972), for example, could be exerted through an action on the phase-response system.

Influence of temperature

One of the most extraordinary properties of the free-running rhythms is the apparent complete, or nearly complete, temperature independence of the periods. Periods show only a
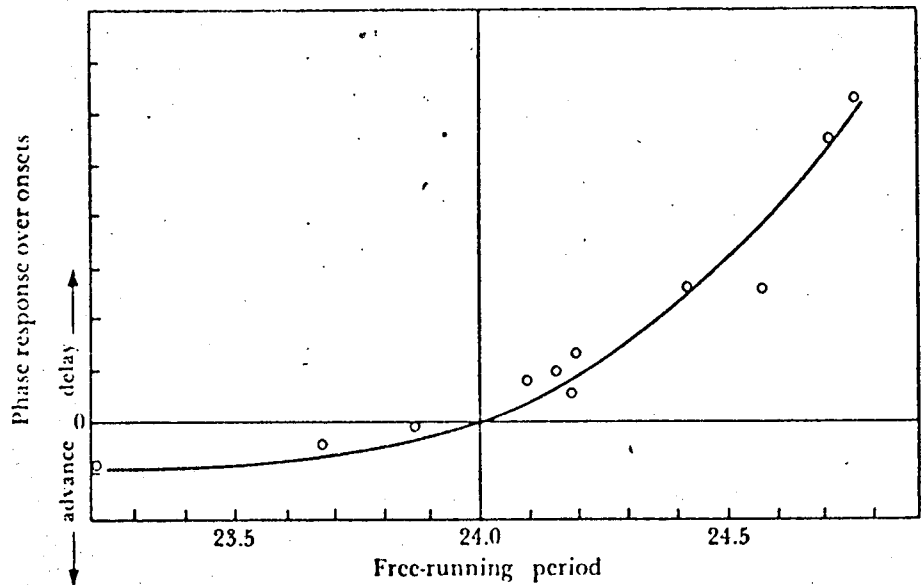

Figure 8. The relationship between the measured phase responses over activity onsets of the members of a population of 11 kangaroo rats and each individual's observed mean free-running period while in continuous unvarying illumination (Modified from Natalini 1972.)

small difference, or none, over even a 20°C range or greater. Q_{10} values (the frequency at one temperature divided by the frequency at a temperature 10°C lower) seldom appear to range beyond 0.8 to 1.2. This is quite foreign to the expectations aroused by temperatures exercising an ordinary kinetic influence upon a typical biological or chemical system. Rates in such systems typically double or triple over a 10°C range; the clocks, therefore, would be expected to increase their rate 2 or 3 times for a 10°C temperature rise ($Q_{10} = 2$ to 3).

Perhaps the very small observed temperature effect commonly noted is *not* a simple kinetic effect on the basic timer for the circadian cycle. Instead, it may be an influence of temperature upon the phase-resetting mechanism. Temperature is also known to be a Zeitgeber, albeit a weaker one than light. Therefore one can predict with reasonable confidence that a circadian phase-response variation for this Zeitgeber will be found to be of rather general occurrence. The existence of a phase-response relationship has already been indicated for several species, including the fiddler crab (Stephens 1957) and bean plant (Moser 1962).

The influence of temperature on the free-running period can be expected by either of two routes: (1) autophasing of the circadian period by a reaction of the organism's free-running activity phase-response curve for temperature, and (2) a kinetic effect of

the temperature changes upon the amount of daily phase shift during response to any given unvarying Zeitgeber intensity, whether the Zeitgeber is light or even temperature itself. The extent of daily phase shift of the free-running cycle would be very small in relation to the total daily cycle. The kinetic effect of temperature (Q_{10}) could, therefore, be well within the normal range for general biochemical phenomena, namely 2.0 to 3.0, if the basic timer of the non-phase-shifting 24-hour cycle were completely temperature independent. A very significant discovery was that the Q_{10} for crabs exhibiting a free-running period indistinguishable from 24.0 hours appeared to be 1.0 (Brown and Webb 1948).

If the influence of temperature were restricted to the phase-shifting processes, shortening of the durations of the overall daily phase delays and phase advances with increasing temperature would contribute, respectively, Q_{10} values slightly greater and slightly less than 1.0 for the total circadian cycle. For example, for a 24.5-hour free-running period, a cumulative total of only 30 minutes of timing out of the 1,470-minute cycle would be involved in the phase-shifting processes and hence be subjected to the normal kinetic influence of temperature.

Even for a 27-hour or a 21-hour cycle there would be effectively only 180 minutes of temperature dependence. Calculated Q_{10} values for the total

...low and of the general magnitudes of those usually reported. Temperature might also influence the free-running period by altering forms of phase-response variations for light and other Zeitgeber.

The foregoing illustrations of how free-running rhythms may be accounted for by phase resetting of the 24-hour patterns are simply elementary and suggestive. Elaboration of the concept of autophasing can permit interpretation of all reported observations of properties of free-running rhythms in its terms.

Role of geophysical rhythms

Where does the hypothesis now leave us? If the genesis of the modifiable free-running periods in absence of all Zeitgeber rhythms involves phasing phenomena, with reference to what kind of an underlying clock are the phase shifts being effected? One is no longer required to postulate that the basic clocks are circadian and variable in period. We are now free to seek basic period-givers or biological clocks of any frequencies. We can seek the most dependable one that might be available to the organism. The most dependable of all, theoretically, are the periodicities of the external atmospheric environment itself, with whose frequencies the organism's rhythms must normally harmonize to achieve optimal adaptation.

It may be significant to recall at this point that the biological rhythms involving behavioral patterns that adjust the organism to the natural geophysical cycles, termed geophysically correlated rhythms, are the only ones that exhibit all the unique clock properties. And these are the principal rhythms whose periods it would be almost essential for the organism to measure by a means relatively independent of the great variations in temperature, light, and chemical content in the environment. Central dogma of the classical hypothesis postulating environmentally independent clock-oscillations interprets this state of affairs as the selective basis for the evolution of an internal timer. However, the same facts can be interpreted quite differently; namely, the geophysical rhythms constitute a temperature-independent clock system comprising an essential foundation for the rhythms.

tories (e.g. Lindauer and Martin 1968; Brown 1971; Stütz 1971; Keeton 1971; Wiltschko and Wiltschko 1972; Rommel and McCleave 1972; and many others) have disclosed that organisms including protozoans, worms, snails, bees, birds, and mammals possess a capacity to differentiate geographic direction and/or geophysical time in the absence of all obvious cues. The capacity has been traced to an extraordinary and apparently highly specialized sensitivity of living creatures to the earth's natural four-dimensional electromagnetic field of space-time. Responsiveness has been shown for extremely weak electric and magnetic fields as well as for radiation ones.

In all investigations of circadian rhythms, the organisms have never been in constant conditions. They have been continuously in subtle rhythmic fields, to many parameters of which they have now been shown to be sensitive. Indeed, evidence indicates that the sensitivity is highly specialized for reception of the extremely weak natural fields. Responsiveness to some of these fields has already been described to exhibit 24-hour rhythms and 24.8-hour and related synodic monthly rhythms, as well as annual ones. The creatures of the earth, therefore, appear to have available continuously a 24-hour timing system whose periods are independent of ambient temperature and of all imposed chemical alterations.

Many creatures, including birds, salmon, and eels, inherit behavioral patterns that incorporate migrations in particular directions at specific times in their lives. No one questions that a bird inheriting a tendency to migrate, say, southwest from a specific site in the fall has inherited both the specific behavioral pattern and the capacity to employ spatial cues, obvious or subtle, to determine the southwest direction. Clearly the bird cannot inherit southwest as a purely endogenous feature. Both heredity and environment are essential, continuously operating components.

Just as there is a *geographically* differentiated environmental field of subtle factors so is there simultaneously a fully comparable *temporally* differentiated one, which involves the same geophysical parameters. Indeed, the determinations of points in both ter-

...real space and time depend ultimately upon celestial relationships. These comprise a space-time continuum. Are the clock characteristics a consequence of the inherited sensitivity of living systems to their ambient rhythmic physical environments? Could it be that the biological system possesses the capacity to "read" time from its four-dimensional subtle-field environment and to employ this information to time its adaptive, recurring physiological patterns?

The salient suggestion that the biological clock involves such a reading of time from the environment has been derived from investigations of lunar-related light responsiveness. Patterns have been reported which appear to be remarkably similar for organisms as diverse as planarian worms, clams, snails, guppies, and rats. When, for example, planarian worms crawling geographically northward in the laboratory are exposed to light coming from the east, a characteristic monthly pattern of variation in strength of turning from the light is disclosed. This pattern becomes *instantaneously* phase-shifted by 180° (Fig. 9) by the simple expedient of rotating the whole assay system, including the light source, by 180° to shift the worm's crawling direction to south and the light source to west.

It is important to note that the 180° phase shift is not simply a cycle inversion but is instead a "temporal" phase displacement of a characteristic asymmetrical monthly cycle. The organism acts as if it were employing the horizontal magnetic vector as a spatio-temporal reference for reading the monthly period from still other unidentified parameters of the subtle-field complex and phase-relating the 360° monthly cycle in each instance to the horizontal magnetic vector. A fully comparable 180° phase shift can also be instantaneously effected simply by experimentally reversing the direction of the ambient horizontal magnetic vector for the organism by means of a bar magnet (Brown and Park 1965).

In addition, the worm appears to be able to associate a light stimulus with a point along the 360° compass cycle identified solely by means of the subtle geophysical parameters and to "remember" the relationship for at least several minutes (Brown and Park 1967). It seems probable that clock-

time rhythms involve a fully comparable capacity for organisms to associate genetic and learned 24-hour patterns of events with points along the 360° temporal, solar-day cycle of variation in subtle geophysical parameters.

Geophysically dependent 24-hour variations

Let us carry our reasoning further and picture the 24-hour circadian rhythms in nature. Such Zeitgeber cycles as those of light and temperature are synchronized with the 24-hour periodic complex of innumerable subtle electromagnetic parameters. The genetically determined circadian pattern has been appropriately phase-adjusted to sun time by influence of the Zeitgeber complex. In addition, superimposed on the inherited activity-rest pattern are other components reflecting "learned" responses to the previous daily stimulus patterns of the organism's specific niche. No continuous correction of an inaccurate endogenous clock to 24-hours is demanded. All is in rhythmic harmony; all temporal stresses have been minimized.

The earth's electromagnetic fields contribute not only to the organism's external environment but to its internal as well. Fluctuations in these fields can convey information concerning the well-known solar-day tides of the atmosphere. The fluctuations may also reflect in more direct manner changing angular relationships of the sun and its fields relative to any given terrestrial locus, as well as steadily varying activities within the sun itself. The atmospheric fields also bear information concerning the more erratic and less predictable movements and characteristics of weather systems.

The organism would be expected to compensate, through the multifold servomechanisms involved in homeostasis, for any biological influences that might arise from the fluctuations. There would, however, still be organismic fluctuations reflecting the subtle environmental changes. These would be expected to be evident both as quantitatively varying energy demands for compensations for their effects and as uncompensated residual variations resulting from imperfections in the organism's regulatory ability.
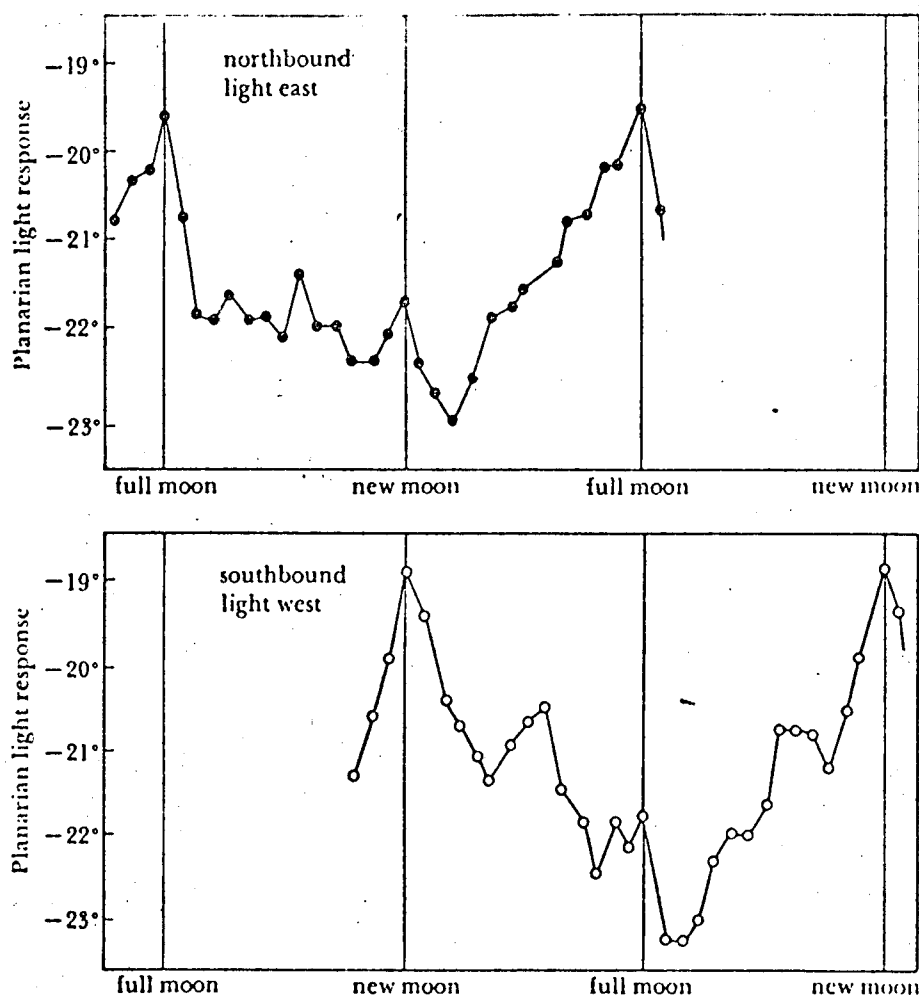

Figure 9. The variation with phase of the moon in the strength of negative phototaxis of planarian worms. Closed circles (*above*) show the worms crawling north with a light to the east; open circles (*below*) show how this is altered instantaneously by rotating the test field by 180°, thereby changing the crawling direction of the worms to south and the light source to west. The larger the negative values on the ordinate, the stronger the response. (Modified from Brown and Park 1967.)

Variations which appear to be of the foregoing origins have been described for a wide range of organisms held in presumed constant conditions. These variations have been disclosed whether or not any ostensible genetic circadian pattern and Zeitgeber responses concurrently existed in the organism. They have been recorded as rate variations in diverse phenomena, such as standard metabolic rate or O_2 consumption (Brown 1968) or as variations in "spontaneous" motor activity (Brown, Shriner, and Ralph 1956; Terracini and Brown 1962).

These 24-hour biological patterns appear to retain unchanged relations to clock hours of the solar day even under conditions where there is an overt free-running rhythm. They also tend to exhibit similar or related forms for widely different kinds of animals and plants, which suggests little species specificity. For such reasons they are assumed to be the expected direct reactions to the uncontrolled physical

variations and hence have been termed *geophysically dependent* 24-hour variations.

Phylogeny and ontogeny of clock-timed rhythms

Living creatures are exposed to pervasive environmental periodisms wherever they are and at every stage of their life cycles, from reproductive cells through adult. One may speculate that very early in the course of the evolution of life, the recurring solar-day geophysical pattern served as a template upon which were fashioned biological sequences of causally related events. This could yield what Bünning (1964) has termed an endodiurnal organization. The organism's fundamental organization seems to be geared to the very conspicuous solar-daily fluctuations. Even the single-celled organism *Acetabularia* with its nucleus removed can continue to display clock-timed circadian rhythms in

photosynthetic potential for many days (Schweiger et al. 1964).

In short, the 24-hour subtle-field information is postulated not simply to be a timing reference for the adult's individual activity patterns but even to have been responsible for guiding the phylogeny and ontogeny of the circadian patterns themselves. These patterns perhaps only secondarily evolved susceptibility to Zeitgeber phase control, with its consequent liberation of the organism from slavery to its clock system. This liberation also made possible more plastically adaptive circadian patterns that enabled ready readjustment to such factors as seasons, geographic translocations, and individual experiences.

The inherited circadian pattern, when free-running, can now be visualized to be systematically phase-shifting relative to an underlying 24-hour frame of reference whose period remains stable and dependable. Such a frame of reference has the deluxe clock properties of independence of all the temperature, light, and chemical variations in the organism's immediate environment. The adaptive 24-hour patterns have no favored phase setting relative to the exogenous cycle and may be clutched in any temporal relationship or freely shifted, depending upon the environmental conditions. All the well-established clock-timed properties of the solar-day rhythmic system have been accounted for in a consistent manner. All the recent rapid advances in our knowledge of organismic responsiveness to extremely weak electromagnetic fields of the physical environment have been taken into account.

Indeed, evidence at hand has indicated that under some rare conditions subtle electromagnetic-field variations may extend their role from probable simple temporal reference to the level of a Zeitgeber. They may then determine the phase of a free-running circadian rhythm, as reported for embryonic chick respiration (Johnson 1966) and mouse activity (Terracini and Brown 1962), in recognition of which the expression "subtle Zeitgeber" has become increasingly used. More usually, however, the overt Zeitgeber-phase-response system determines the phase of the circadian pattern, while the pervasive subtle fields provide a dependable and accurate clock period.

Lunar-tidal circadian rhythms

Tidal rhythms adapting the activities of littoral organisms to their periodic submergence and exposure are well known. They have been investigated most for unicellular forms (Fauré-Fremiet 1951; Palmer and Round 1967) and crabs (Webb and Brown 1958; Barnwell 1963; Naylor 1958). These rhythms persist in organisms removed from their tidal environment (Fig. 4). In the laboratory or in the field, they do not period-synchronize to 24-hour light-dark cycles. In natural daily light cycles, or in experimental 24-hour light-dark cycles, the mean period of these rhythms is that of the ocean tides, the tidal patterns with two cycles a day of about 12½ hours in length moving over the solar-day patterns at the mean rate of 50 minutes a day.

When the solar-day rhythms of color change in fiddler crabs are phase-shifted by experimentally altering times of light and darkness, the lunar-tidal cycles are shifted by about the same amount of time (Brown, Fingerman, Sandeen, and Webb 1953). When, however, the solar-day cycles become restored to 24-hours, the tidal cycles resume their 24.8-hour periods. The lunar-tidal rhythms can, however, deviate from the lunar-day frequency. This has been demonstrated for fiddler crabs held in continuous illumination of such intensity that the solar-day circadian 24 hours condition the lunar-tidal cycles become longer than 24.8 hours (Barnwell 1966)

It has been postulated that this behavior involves an autophasing solar-day rhythm carrying with each daily phase shift in the lunar-tidal rhythm. E... 50 minute cycle by s... hour light-tidal rhyth... about 25.... 1965). As shifted da... cycle was utes. In... the free-change in... period, th... motor acti... frequency

shift in the lunar-tidal forcing a daily delay of on the crabs' solar-day jecting them to a 24.8-dark rhythm yields a lunar-of spontaneous activity of hours (Webb and Brown the solar-day cycle was by 50 minutes, the tidal turn shifting by 50 minutes continuous darkness, when running rhythm of color the crabs retains its 24-hour free-running tidal cycle of ty retains its normal tidal

The Zei... ber for the lunar-tidal

rhythms responsible for phase-setting the tidal cycles to adapt to the tidal schedules of the crabs' home beach remain more or less obscure. However, that subtle Zeitgeber of lunar-day frequency are sometimes able to do so has been described for both oysters (Brown 1954) and fiddler crabs (Bennett 1963). When placed in continuous dim light or darkness in the laboratory these animals gradually phase-shifted their cycles to have their maxima occur at the time of upper and lower transits of the moon. These are times of maxima in gravitational attraction by the moon on the earth's oceans and atmosphere.

Lunar-day subtle Zeitgeber have also been reported sometimes to synchronize solar-day rhythms in rats and hamsters held in presumed constant conditions in the laboratory (Brown and Terracini 1959; Brown 1965a). Free-running of lunar-tidal rhythms with periods deviating from the natural rhythm of the physical environment would therefore seem to depend upon simultaneously autophasing solar-day rhythms.

The existence of subtle geoelectromagnetic variations correlated with the lunar-day tides of the earth' oceans and atmosphere is well established. Influences of the moon's changing position are also impressed upon the solar-related fields. Therefore lunar-day rate variations in biological phenomena would be predicted and in fact have been described for a wide gamut of animals and plants (Brown 1965b). There appear to be similar, or related, patterns among widely different organisms including both plants and animals, and these seem to be fixed in their phase relations to clock time of the lunar-day. They have therefore been considered to be geophysically dependent fluctuations.

Circamonthly and circannual rhythms

Further support for the general hypothesis that has been presented here for circadian rhythmicity is found in its obvious applicability in principle to longer-period clock-timed rhythms. These include fortnightly, monthly and yearly periods, for which the classical paradigm of independent internal timing becomes increasingly implausible. No fundamental differ-

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periodicities and the circadian is apparent.

As with the circadian, the synodic monthly rhythms commonly involve genetically determined patterns such as complex reproductive cycles and breeding behavior. These may often be phase-adjusted in a species-specific manner with rhythmic changes in the natural physical environment. Synodic monthly reproductive rhythms timed to specific moon phases have been described for many organisms of the seacoast and suggested for some wild primates.

The synodic month obtains its mean 29.5-day period from the systematically changing temporal relations between solar and lunar days. Times within the month may be defined in degrees. It is 0° at new moon, when the moon reaches its highest point near solar-day noon, and 180° at full moon, when the highest point occurs near midnight. Indeed, timing of monthly or semimonthly reproductive activities to occur at highly specific times of tide on the organism's home beach bespeaks the simultaneous roles of solar-day and lunar-tidal Zeitgeber in determining the time of the events. This kind of adjustment to local time of tide in semimonthly cycles has been observed for the grunion of the California coast and for the brown alga *Dictyota*.

The synodic month also involves the systematically varying amount and time of night illumination. Systematically changing daily light cycles may serve as a monthly Zeitgeber for organisms with mechanisms sufficiently stable and precise to resolve these minute day-to-day differences. At the same time, and probably of great importance, information concerning the synodic month is steadily available as fluctuations in the atmospheric electromagnetic fields. As might be predicted, therefore, geophysically dependent monthly patterns have been described, with cycle forms that seem to be largely independent of species or biological phenomenon (Lang 1965).

Numerous organisms have genetically determined circannual patterns of growth, reproduction, and other behavior, including migrations. Experiments have shown that a prominent, if not the dominant, Zeitgeber for

annual patterns to time of year is the changing relative lengths of daylight and darkness (photoperiodism). Parallelly, there are relatively large-amplitude, apparently geophysically dependent, annual variations which persist under conditions of constancy of all obvious factors that could signal the yearly period. These variations have been reported for a variety of phenomena and kinds of animals and plants. There is a close similarity in times of year of occurrence of maximum and minimum even among species as distantly related as an alga, a potato, a planarian worm, and a mammal (Brown, Hastings, and Palmer 1970).

For the circamonthly and circannual patterns, the Zeitgeber determine the phase relations for extremely complex, drawn-out series of cause-effect events. It is self-evident that these long cycles would always demand for their integrity a good degree of clock-timed orderliness. This demand would exist even during phase-shifting by experimentally altered daily photoperiods.

It seems reasonable to postulate that, like the circadian, these long cycles are dependent upon an external timing reference of the corresponding natural geophysical frequency. The steady inflow of geophysical information would provide the templates for the evolutionary development and individual ontogeny of the circamonthly and circannual patterns. Such dependence would furnish the best means for fitting biological cycles within these long periods of the planet with minimum stress or tension. The often-reported deviations in the periods from the natural month or year, under experimental conditions of constancy of the normal Zeitgeber, are postulated to be a consequence of autophasing of the inherited patterns adapted to the natural monthly or annual cycles.

In summary, recent discovery of a highly specialized sensitivity to the natural electromagnetic fields has raised serious doubt about the existence of an inherited, independent internal timing mechanism with all the well-known clock-properties. This discovery together with present knowledge of the response system employed in phase-shifting, clock-timed rhythmic patterns has permitted an alternative

by a the unprovocative classical one. As with many other biological phenomena in the past, the "clock" seems destined to pass from its years of controversy involving heredity versus environment to a recognization of continuous interaction of the two factors.

The usual concept of the organism within its rhythmic physical environment must now be supplemented by a concept of the rhythmic physical environment steadily contributing to the internal environment of the organism. No clear boundary exists between the organism's metabolically maintained electromagnetic fields and those of its geophysical environment. In terms of the hypothesis for biological clocks that has been presented here, the clocks themselves, being environmentally dependent, possess high mean precision. It is suggested that the peculiar properties and activities of the organism's natural phase-shifting mechanism have been responsible for the long-held but probably erroneous notion that an independent internal clock system is present.

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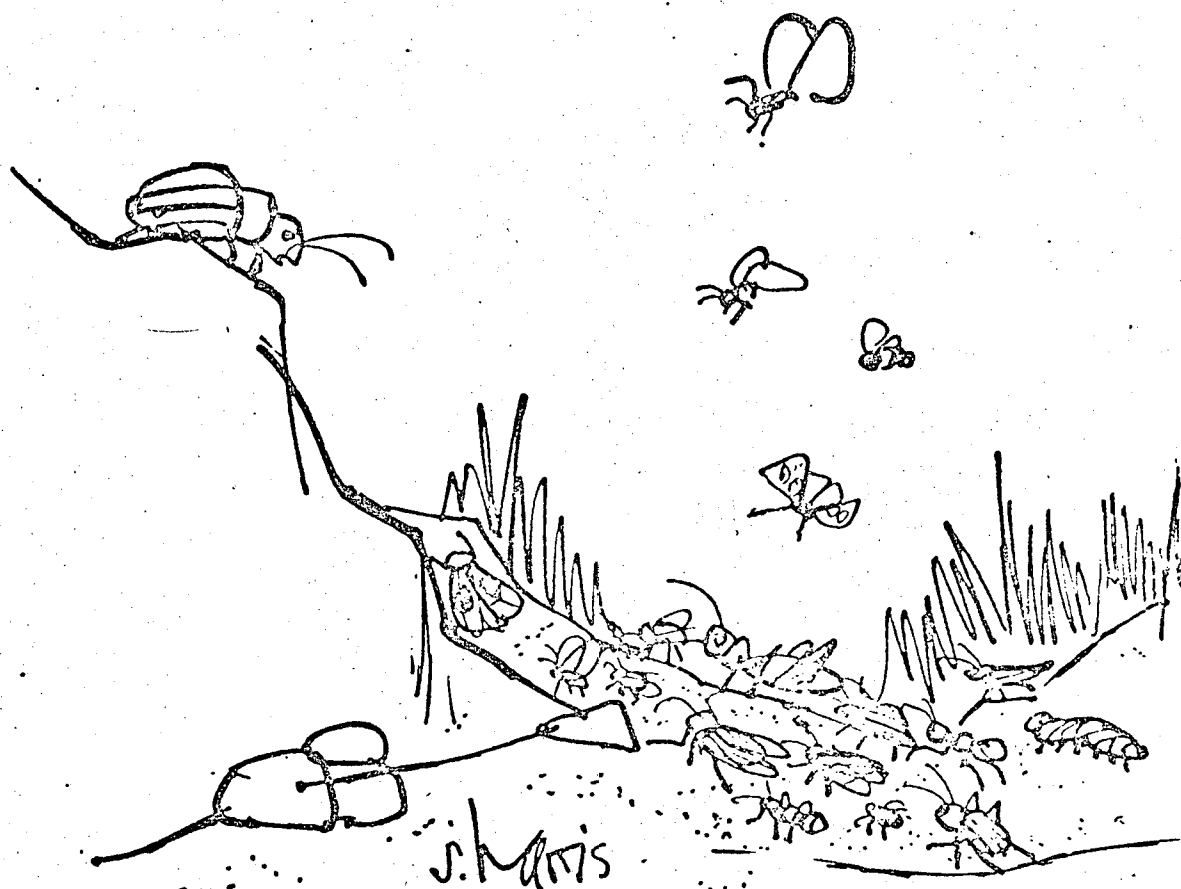
"If we ever intend to take over the world, one thing we'll *have* to do is synchronize our biological clocks."