BIOLOGICAL RHYTHMS AND ANIMAL BEHAVIOR

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He appointed the moon for seasons: the sun knoweth his going down. Thou makest darkness, and it is night: wherein all the beasts of the forest do creep forth. The young lions roar after their prey, and seek their meat from God. The sun ariseth, they gather themselves together, and lay them down in their dens. Man goeth forth unto his work and to his labor until the evening.

Psalm 104: 19–23

INTRODUCTION

The rhythmic or cyclic nature of animal behavior has been appreciated by man since early in recorded history (158). Formerly, attempts to understand daily cycles of activity, annual reproductive rhythms, and the seasonal occurrence of migration and hibernation emphasized changes in the external environment as the causative or driving forces underlying periodicity. This view predominated well into the present century and assigned a more or less passive role to the organism displaying the rhythm; only within the last quarter century have biological clocks within living organisms been widely recognized as major determinants of behavioral and physiological rhythms. The potential adaptive significance of these

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rhythms and their probable mode of evolution have been considered in several reviews (69, 124, 150).

Psychologists have long been interested in the timing of behavior and have struggled with behavioral periodicity in their theories of motivation. An issue here is why a given animal is active at one time and quiet at another; why it eats, copulates, sleeps, or fights at one time of day and not at another. In general, animal behaviorists within the American psychological tradition have not given adequate weight to the role of biological clocks in their answers to these questions. Thus, one of our main goals in this article is to emphasize the importance of biological clocks for the general understanding of behavior and more particularly in the design and interpretation of studies concerned with behavioral phenomena. We have dealt primarily with vertebrate and especially mammalian behavior, but have not attempted to cite all the relevant recent literature. Limitations of space have often forced us to cite a single review article rather than several original research reports. We have emphasized daily and seasonal cycles in behavior and physiology and have not considered rhythmic components of human performance, nor the involvement of biological clocks in periodic illness.

A number of books on biological rhythms are of special interest to students of animal behavior. Broadest in scope are the volumes edited by Aschoff (9) and by Menaker (125), and the reviews by Cloudsley-Thompson (42), Luce (113), and Bunning (37). The most recently published volume of The Neurosciences contains several articles of interest and provides an excellent introduction to biological rhythm research (127, 152, 189). Several more specialized monographs describe human circadian rhythms (43, 46) or individual research programs (170). Articles on biological rhythms are found in scores of scientific periodicals. Two recently founded journals, *Journal of Interdisciplinary Cycle Research* and *Chronobiologia* are devoted to reports on biological periodicity.

**Definition of Terms Used**

The novice is frequently intimidated by the unfamiliar mathematical symbols used to describe parameters of rhythmic behavior. The analogy between biological clocks and physical oscillators has prompted the wholesale adoption of a complex terminology and methods of data analysis (148); these are useful but not essential to an understanding of basic principles. The main concepts and symbols encountered are listed below, this brief description is based on a report by Aschoff et al. (16) *LD cycle* Alternating periods of light and darkness (or brighter and dimmer phases) whose durations are given as in LD 14, 10. This designates a cycle of 14 hr of light, alternating with 10 hr of no measurable light (darkness). The intensity of illumination during the respective phases is often indicated *LL, DD* Respectively, continuous illumination and continuous darkness *Zeitgeber* A periodic environmental factor that entrains a biological rhythm, the LD cycle is the paramount example of a zeitgeber.

*Endogenous rhythm* One requiring no periodic environmental input to maintain its periodicity, a self-sustaining oscillation.
**Entrainment:** The coupling of an endogenous rhythm to a zeitgeber such that both display the same period (synchronization).

**Period:** The duration of a single cycle; i.e. the time between successive recurrences of a specified phase of a cycle. Designated as \( \tau \) for the biological rhythm and \( T \) for the zeitgeber.

**Frequency:** The reciprocal of the period; i.e. if \( \tau = 0.5 \) hr then the frequency is 2 cycles per hr.

**Phase:** The instantaneous state of an oscillation. Any point within a cycle.

**Phase angle** The value on the abscissa corresponding to a particular phase of a cycle, this is given as some fraction of the total cycle (hours, degrees, radians) and is represented by \( \phi \) for a biological rhythm and \( \Phi \) for a zeitgeber.

**Phase angle difference:** The difference between corresponding phase angles of two coupled oscillators.

**Phase shift:** A displacement of an oscillation along the time axis, designated \( \Delta \phi \) and \( \Delta \Phi \) for biological rhythms and zeitgebers, respectively. A shortening of the period is a phase advance while a lengthening is a phase delay.

**Free-running rhythm:** A self-sustaining rhythm not entrained to any zeitgeber and therefore displaying its spontaneous period, usually under constant conditions.

**Circadian rhythm:** An endogenous rhythm with a period of approximately 24 hr. The range of deviation permitted for classification as a circadian rhythm is undefined, but limits between 21 and 27 hr are usually suggested.

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**CIRCADIAN RHYTHMS**

**General Considerations**

The analogy between circadian clocks and physical oscillators has been fruitful both in generating empirical research and in providing a theoretical framework for biochronometry (9, 152, 200). The basic principle of this analogy is that rhythmic behavioral and physiological functions can be analyzed in terms of the known properties of linear (pendulum-like) and nonlinear (capacitor-like) physical oscillators (201). There is now abundant evidence that multicellular organisms contain many oscillators, each of which may have different characteristics and periods. A human subject under constant environmental conditions may simultaneously display free-running periodicities of 33 hr duration for the sleep-wakefulness cycle and of 25 hr duration for the rhythm in body temperature (12).

A single rhythmic function (e.g. locomotor activity) may reflect the operation of two or more independent oscillators that normally are strongly coupled but may in fact show different natural frequencies and different sensitivities to light (152). One oscillator can only be phase-advanced by light and the other only phase-delayed. Together these oscillators can account for effects that have hitherto been interpreted in terms of a single oscillator with differentially sensitive phases. The dual-oscillator model is supported by the "splitting" of an apparently uniform rhythm into two independent components. Under special constant conditions, viz.
very dim illumination for tree shrews (*Tupaia belangeri*) (90) or very bright light for hamsters (*Mesocricetus auratus*) (152) or after hypothalamic lesions in the latter species (see 206a) these oscillators may become dissociated and free-run relative to each other. Starlings (*Sturnus vulgaris*) may show similar splitting of their activity rhythms when injected with testosterone (75a). Other evidence supporting this model includes the effects of contracting "skeleton" photoperiods (152) and the ubiquity of bimodal activity patterns throughout the animal kingdom (11).

The gross behavioral measures commonly used and the strong tendency for oscillators to remain coupled have prevented the more frequent detection of multiple oscillators for each measurable rhythmic function. The integrated cyclic behavior of multicellular organisms can be conceived as resulting from a complex interaction among oscillators possessing circadian and noncircadian frequencies. The neurophysiological basis for the interaction within and between oscillatory constituents remains unexplored (152).

Much of what is known about circadian clocks has been learned from observing the effects of light on rhythmic behaviors. Some of these relations have been summarized by Aschoff (9). His *Circadian Rule* states that as the intensity of constant illumination increases, the frequency of the free-running rhythm increases for day-active species and decreases for night-active animals. These effects predict the behavior of oscillators under entrained conditions as well, thus any manipulation that increases the frequency of the circadian clock relative to that of the zeitgeber will cause the animal's oscillator to phase lead the zeitgeber by increasing amounts [e.g. this will occur in L-active animals when light intensity is increased (10)]. These principles have been confirmed in many species and disconfirmed in several others (88).

The *Circadian Rule* is useful in interpreting the effects of various experimental manipulations. For example, a treatment which "decreases nocturnality" in a LD cycle may in fact decrease the $\tau$ of the underlying activity rhythm and thereby cause a phase advance relative to the LD cycle. Alternatively, the treatment could increase or decrease sensitivity to light in the entrainment pathway, and thereby alter the phase angle of activity onset without effecting a reduction in rhythm amplitude per se.

Kavanau (101) has suggested that species are physiologically adapted to be active at a particular "optimum level" of illumination. Intensities above or below this level will decrease activity, so the linearity implied by the *Circadian Rule* may apply only in the middle range of illumination intensity (101). Both laboratory and field observations support Kavanau's position in demonstrating that many species are most active at moderate illumination intensities (twilight) rather than during the brightest or darkest part of the day-night cycle (42). Kavanau's somewhat untraditional methods of data analysis, his measurement of activity over rather limited time spans, and the lack of uniformity between his analyses and those used in establishing the *Circadian Rule* weaken his criticisms of the latter (101). Nevertheless, his testing of animals over a broad range of light intensities, use of controlled twilight transitions, and investigation of a diverse array of species are all
features that recommend his work (102); the prediction of an optimum species-specific illumination intensity, frequently in an intermediate range, is worthy of rigorous testing.

**Functional Significance**

Biological clocks may have evolved to time behavior in relation to the external environment. For example, the initiation of eclosion activity several hours prior to dawn is such that the emergence of adult *Drosophila* from pupae coincides with the optimal humidity level (150). Certain circadian timers can also function as true clocks, that is, they can be consulted at any time. The sun-compass orientation of birds (89) and bees (197) allows animals to modify their flight direction relative to the sun's position, exactly as if they had access to time of day information; thus they respond to where the sun "should" be at a given time. Such information may be crucial for navigation during migration. Circadian clocks are used by some species to measure daylength and thus are useful in timing seasonal events (see *Seasonal Rhythms*).

Timing is also crucial in relation to other organisms; predators hunt when prey are most active, and related species that feed on similar diets can avoid certain types of competition by foraging at different times of day (cf 145, 194, p 343). Ostriches (*Struthio* sp.) provide an example of the function of daily rhythms in relation to camouflage. In their usual desert habitat the black-plumed male sits on the nest at night while the pale brown female incubates the eggs by day (119a). Ringdoves (*Streptopelia risoria*) show a similar temporal division of labor (Whitman, cited in 107a).

The internal milieu is a temporally integrated system whose continuity depends on biological clocks and their coupling as well as on feedback relations. In *Drosophila* longevity is considerably decreased on 21 or 27 hr LD cycles. Presumably cycles that differ from 24 hr cause dysfunctional internal phase relations among various rhythms (156). The synchronization of enzymatic activity in various organs and the synergistic actions of hormones that depend on precise temporal patterns of secretion are but a few examples of the need for synchronization of internal processes.

Menaker (124) notes that very little is known concerning the adaptive significance of particular rhythms in particular organisms, but concludes that "rhythms will eventually be shown to confer many different kinds of selective advantage on organisms which possess them."

**Physiological Basis for Entrainment by Light**

**Receptors** The existence and functional significance of extraocular photoreceptors in nonmammalian vertebrates is well established (127). But none of the adult mammals studied to date show signs of entrainment by light after removal of the eyes. Since only nocturnal species have been studied systematically, it remains possible that direct penetration of light through the skull (70, 208) and extraocular photoreceptors could entrain rhythmic functions in diurnal mammals (cf 126). On
the basis of current information it is most likely that ocular receptors are the principal, if not the exclusive, mediators of light entrainment in mammals. The specific retinal elements involved in entrainment are unknown, whether unique classes of receptors underlie visual perception and entrainment by light also remains to be established. hitherto unsuspected receptors are apparently involved in both processes. Excellent light-dark discrimination has been demonstrated in albino rats (Rattus norvegicus) after complete destruction of the retinal receptor layer by exposure to LL (5), although in one study 50% of the LL rats did not consistently perform above chance levels and the remaining animals required more trials to reach criterion than controls (22). Degeneration of photoreceptors induced by exposure to constant illumination of moderate intensity is usually complete after one month (5), and is not reversed when rats are returned to a LD cycle (55). The optic tract and lateral geminate nucleus of most of these animals show no response to photic stimulation (143).

Nevertheless, these animals can entrain their corticosterone rhythms to the LD cycle (55) and show light-dependent reproductive and pineal responses (167). It is not known whether these functions are performed by a few residual rods or by an entirely different kind of receptor (e.g. bipolar or ganglion cells). The hardener ans, located within the orbital cavity directly behind the eye, do not appear to be the photoreceptors involved in these processes (166). Reiter has speculated that some cellular element within the eye other than the classical photoreceptors transmits information to the hypothalamus and that a humoral agent secreted by the eye also may be involved (166, 167).

According to Caley et al (39), mice (Mus musculus) with retinas devoid of classical photoreceptors manifest circadian rhythms in feeding that differ from those of control animals, the latter show the usual nocturnal feeding cycles whereas the rodless animals reportedly have a "freely running rhythm" relative to day and night (39). This observation, if confirmed, would imply that entrainment of feeding by the illumination cycle is mediated by the rods. Unfortunately, the only published records of feeding rhythms in CBA/Ki mice (110) do not support the conclusions of Caley et al. the feeding patterns of these animals (110, Fig 6) appear to be well within the normal range for nocturnality. The existence of free-running rhythms would be difficult to prove given the frequency with which feeding was recorded. Mouse strains with various ocular abnormalities (180) provide an excellent and to date unexploited opportunity for the analysis of receptor mechanisms underlying entrainment, photoperiodicity, and visual perception.

PHOTOPIGMENTS The photopigments involved in entrainment are unknown: systematic studies of action spectra and thresholds for entrainment are almost completely lacking (127). Green light is most effective as a zeitgeber for the rat's circadian body temperature rhythm, with red and ultraviolet wavelengths relatively ineffective (119). Short wavelengths are most effective for phase-shifting the daily rhythm of torpor in pocket mice (Perognathus penicillatus) (71). The correspondence between the rhodopsin sensitivity curve and the efficacy of var-
ious wavelengths for entrainment (119) suggests that rhodopsin may be involved in the latter process. It would be useful to test this hypothesis on rats deprived of photoreceptors by prior exposure to constant light.

Wavelengths corresponding to blue and green light most effectively influence locomotor activity of mice (183) and also constitute the components of white light mainly responsible for the degenerative changes induced by constant illumination (4). The possibility that a given wavelength range is maximally effective for entraining all rhythmic functions in a given organism is intriguing and worthy of experimental verification. This seems to be the case in the moth *Pectinophora gossypiella* in which effective spectral components for phasing several behaviors are similar but different from those involved in photoperiodic time measurement (155). The wavelengths most effective in mammals with good photopic vision are completely unknown.

Photopigments involved in entrainment may be distinct from those that mediate other light-dependent functions (e.g., the visual perception of objects). Thus carotenoid depleted *Drosophila* have retinules grossly deficient in rhodopsin and their visual receptors show a 3 log-unit reduction in light sensitivity; nevertheless, the sensitivity of their circadian emergence rhythm to the phase-shifting effect of light flashes appears to be normal (205).

**CENTRAL VISUAL PROJECTIONS** Light impinging on the mammalian eye almost certainly acts via the established visual projections to entrain the central oscillators underlying rhythmicity. A neurohumoral mechanism for entrainment seems at best a remote possibility.

The central visual projections have been most extensively studied in the albino rat, information on this species is summarized by Moore (131). He notes that all visual input from the eye enters the optic chiasm via the optic nerve. Of the three pathways leaving the chiasm the largest is the primary optic tract (POT) which consists of uncrossed and decussating retinal components that terminate in the superior colliculus, pretectum, and lateral geniculate. The superior accessory optic tract (SAOT) runs within the POT and terminates in the midbrain tegmentum. A third visual pathway that leaves the chiasm, the inferior accessory optic tract (IAOT), consists entirely of crossed retinal fibers; after leaving the chiasm it runs in the ventral part of the brain along with fibers of the medial forebrain bundle and eventually terminates in the medial terminal nucleus of the midbrain tegmentum (81). The IAOT has been traced in a number of mammalian species but apparently is not present in the golden hamster (56).

A fourth visual pathway, the retinohypothalamic tract (RHT) provides a direct connection between the retina and the suprachiasmatic nuclei of the hypothalamus. This projection is bilateral even in rodent strains in which all other components of the retinal projection are crossed (83). Input to the contralateral suprachiasmatic nucleus (SCN) is about twice as heavy as to the ipsilateral side; most retinal fibers terminate in the ventral part of the SCN where they form asymmetric synapses either on small dendritic branches or on dendritic spines (83). The distribution, receptive fields, and discharge properties of the retinal
ganglion cells that project to the SCN are unknown (83) Although a retinohypothalamic pathway had previously been described (137), the definitive proof of its existence in mammals required the use of autoradiographic tracing techniques and was accomplished only within the past 4 years (83, 130, 131) The RHT remains difficult to detect with conventional tracing procedures such as silver impregnation (111). A thoughtful discussion of problems involved in this analysis is contained in (83) To date the RHT has been described in mammals representing several orders, including rodents, carnivores, marsupials, and primates (130) It also exists in birds (123) and other nonmammalian vertebrates (137)

There is no firm evidence that pathways other than the retinohypothalamic tract are essential for entrainment of mammalian circadian rhythms. Lessons that bi-laterally interrupt the primary and/or accessory optic tracts do not eliminate steady state nocturnal drinking rhythms of albino rats maintained on a LD 12:12 cycle (187) or locomotor rhythms of pigmented rats (3) It was also reported that POT transection did not affect the phase-shifting of the drinking rhythm after a 12 hr shift in the illumination cycle (187) Subsequent observations show that lesions aimed at the lateral geniculate nuclei to interrupt the primary optic tracts retard the rate of phase-shifting of the hamster wheel running rhythm. re-entrainment requires 3 times as long as for controls (206a). Final steady state entrainment is comparable to that of unlesioned hamsters Failure to observe similar changes with respect to the rat's drinking rhythm may be due to procedural differences between the studies

 Interruption of the primary and accessory optic tracts also does not interfere with steady state adrenal corticosterone rhythms or with the pineal rhythm of N-acetyltransferase (131) Entrainment of these rhythms as well as the circadian locomotor rhythm of rats (186) and the locomotor and drinking rhythms of hamsters (see 206a) is disrupted by lesions that destroy the retinohypothalamic projection Knife cuts posterior to the SCN also disrupt entrainment of the adrenal corticosterone and the pineal N-acetyltransferase rhythms (131, 132), perhaps by interrupting efferents from the SCN. Although this pathway has not been adequately described. Krieg (105) suggests that SCN axons course dorsally and then caudally in the periventricular system

 The retinohypothalamic projection is probably necessary and sufficient for photic entrainment of mammalian circadian rhythms, and the primary optic tracts may influence these processes by virtue of their indirect connections with the suprachiasmatic nuclei (190)

Zeitgebers Other than Light

Light is the acknowledged dominant zeitgeber for mammalian rhythms. In our own species, however, social factors may synchronize free-running rhythms (13) and experimental instructions can override illumination effects (142). In social isolation some human rhythms may free-run in the presence of "adequate" LD cycles to which other animals would entrain (13) Social stimuli may be more important synchronizers of human rhythms because we control our environment to a greater extent than do other mammals, this could have reduced the biological
significance of the illumination cycle. Caution should be exercised in drawing such a conclusion because animal subjects are rarely tested in social situations and the effectiveness of social cues in entraining their rhythms is largely unknown. The likely efficacy of social stimuli is indicated by the observation that nondominant rats in a seminatural setting modify their eating and activity rhythms to avoid conflict with dominant animals (40). The changes observed in animal activity rhythms after human disruption of their environments (101) also suggest an important role for nonlight factors in modifying mammalian rhythms.

A sparrow housed in constant dim illumination has been entrained to the sight and/or sound of a conspecific; recorded bird song can also entrain the activity rhythms of some sparrows, but this zeitgeber is far weaker than an illumination cycle (128). The cycle of maternal behavior has been proposed as a social stimulus that may contribute to the development of rhythmicity in the young (1). However, rat pups reared with constant access to maternal care, supplied by mothers on opposite LD cycles, show the normal development of rhythmicity (69).

Perhaps the most extensively documented social influences are connected with reproductive rhythms. In some species synchronization of estrus can be effected by the presence of males; female mice exposed to the odor of males tend to come into heat and to ovulate on the same day of the estrous cycle (34). Pheromonal mechanisms may also be involved in the reported synchronization of menstruation in women who live together in college dormitories (118). There has been virtually no experimental exploration of the influence of conspecifics on daily rhythms of mammalian behavior.

Other weak zeitgebers include electrical fields (202) and cyclic pressure changes (80). Some stimuli may affect specific rhythms without necessarily acting as classical zeitgebers; e.g., limited daily temporal access to food or water rephases rhythms of locomotor activity (29), adrenal corticosterone secretion (98), sleep (134), and metabolic cycles (28). Handling of animals at the same time each day may induce gonadal degeneration or growth, depending on when it occurs relative to the animal’s day-night cycle (122). The neural mechanisms by which environmental stimuli other than light gain access to biological clocks that govern rhythmic behavior have not been delineated.

Temperature cycles, although effective as zeitgebers for poikilotherms, are ineffective for mammals (161). Mammals, in common with other animals, show excellent temperature compensation in preserving periodicity within narrow limits. Although the biological clock is presumably chemical in nature, the rate of change of \( \tau \) as temperature changes (\( Q_{10} \)) is extremely small compared to that of other chemical reactions (161).

**Neural Control**

Although circadian rhythms can occur in plants and in protozoa lacking nervous systems, the generation of these rhythms in metazoa probably is accomplished primarily via nervous mechanisms. Even among mammals, however, the adrenal gland (6) and the intestine (37) can display endogenous daily rhythms of secretion and contraction, respectively, in complete isolation from neural influences. In the
intact organism phasing of these rhythms is subject to control by central neural pacemakers.

**NONMAMMALIAN SPECIES** Neural control of rhythms has been studied mainly in nonmammalian species, and the perspective gained from this work is useful in evaluating and guiding research with mammals. The optic lobes of insect brains have been implicated in the generation of activity rhythms and other circadian cycles (32, 112) The early view that a neurohumoral agent was involved in rhythm generation has been vigorously challenged (32) but has also received renewed support from the demonstration of interanimal transfer of rhythmicity in parabiotic cockroaches (48). The distinctive circadian rhythm of cocoon emergence (ecdysis) can also be transferred by brain transplants between two closely related moth species (192). Truman's elegant studies showed that the timing but not the motor pattern of ecdysis was affected by brain transfer. this effect was accomplished even when the brain was implanted in the abdomen of the pupa and therefore in the absence of normal neural connections Although this suggests neurohumoral mediation of rhythmicity, it is important to distinguish between nonhumoral clock mechanisms and humoral linkage of the neural clock to motor systems that express rhythmical behavior.

Circadian rhythms of neural activity have been demonstrated in a single neuron of the *Aplysia* parietovisceral ganglion (189) and in the optic nerve discharge of the excised *Aplysia* eye (94) Jacklet & Geronimo (95) cut away portions of the eye in vitro and observed normal circadian rhythmicity in optic nerve activity when only 20% of the eye was left intact. When a larger portion of the eye was destroyed, the period of the rhythm decreased, with 2% of the eye remaining, only ultradian (\( \ll 24 \text{ hr} \)) frequencies of electrical discharge were expressed. One interpretation of these findings is that the cells whose fibers form the optic nerve are themselves pacemakers independently generating ultradian rhythms and that a minimal number of such mutually coupled oscillators interact to produce a circadian rhythm of spike discharge (95) This view emphasizes circadian rhythmicity as an emergent property of the interaction among oscillators The alternative proposal is that the reduction in the period of the *Aplysia* optic nerve rhythm involved the fortuitous destruction of crucial circadian pacemaker cells within the eye which synapse chemically onto optic nerve neurons (189) The issue is unresolved, but there is strong evidence indicating that chemical synapses are not involved and that oscillators in this preparation are electrotonically coupled (94).

The avian pineal may possibly be a clock for generating activity and body temperature rhythms (127) Pinealecotomized (pnx) sparrows display a normal rhythm of body temperature and perch-hopping activity when exposed to a LD cycle, however, in DD where normal birds generate clearcut free-running circadian rhythms, pnx birds are hyperthermic and continuously active and show no signs of circadian rhythmicity in these functions (26, 27) The pineal may be a master oscillator that hierarchically entrains other oscillators, each of which is responsible for circadian rhythmicity in a particular function (127), alternatively the pineal may be a coupling device between a master driving oscillator located
elsewhere and other light-sensitive damped oscillators that in turn drive overt circadian rhythms (127).

MAMMALS The effect of selective lesions of the mammalian nervous system on rhythmicity has most often been studied only under entrained conditions. Any alteration in the temporal pattern of a single physiological or behavioral parameter studied in a LD cycle is subject to a variety of interpretations and cannot be used to localize a clock within the destroyed brain region. The changes that have been described after brain lesions include a temporary reversal in the phasing of the peak in corticosterone release in dogs without olfactory bulbs (7), temporary elimination of the rat’s corticosterone rhythm after transection of the fornix (109), and elimination of this rhythm after basal hypothalamic isolation (74). Lesions of the ventromedial or dorsomedial hypothalamus reduce the normal day-night differences in feeding (18, 23), while lesions of the lateral hypothalamus accentuate the nocturnal feeding rhythms of rats (99); medial septal lesions exaggerate the apparent nocturnality of activity rhythms of hamsters (87) and the drinking rhythms of rats, and increase the rate at which rat drinking rhythms phase shift after a change in the LD cycle (Rusak & Zucker, unpublished observations, 1972) Superior cervical ganglionection retards the rate of entrainment of feeding behavior in rats (20), and lesions interrupting the primary optic tracts of hamsters slow the phase shifting of the locomotor activity rhythm (206a).

The problems inherent in such studies are exemplified by one performed in our laboratory (see 206a): lesions of the raphe nuclei of rats increased overall wheel running activity and greatly reduced the nocturnality of this rhythm. However, when tested in constant dim light these rats generated normal free-running rhythms with $\tau$s of approximately 25 hours, as shown by power spectral analysis. Raphe lesions clearly increased the level of activity but did not eliminate the endogenous rhythmic fluctuations around the higher mean level. Such results emphasize the need for sufficient time series (24, 25) and adequate statistical analysis of data obtained under proper experimental conditions before one may conclude that any neural, chemical, or other manipulation has “eliminated” the rhythmicity of a behavioral system. It should be emphasized that it is far easier to affect motor systems involved in expression of rhythmicity than the clock mechanism itself.

Richter has reported a complete and convincing loss of circadian rhythmicity of eating, drinking, and wheel running activity in blinded rats with hypothalamic lesions of unspecified size and location (171) More recently, suprachiasmatic (SCN) lesions have been reported to eliminate rhythmicity in pooled mean levels of plasma corticosterone sampled at different times during a LD cycle (132). Individual records of wheel running activity and drinking recorded in LD cycles and in constant light showed an elimination of circadian rhythmicity after SCN lesions (186). Our recent studies of hamsters with SCN lesions suggest a complex role for this brain region in the production, coordination, and entrainment of behavioral rhythms (see 206a). Critchlow (47) had earlier implicated the SCN in the control of estrous cyclicity. His observations have been extended in more
recent work which also suggests that the SCN is involved in the control of daily surges in luteinizing hormone and in the timing of ovulation in several species (38, 76). Whether the SCN serves as a master clock, a central coupler of rhythms, or as one complex oscillator in a multioscillator system is unknown. The adjacent medial preoptic area (97) and the lateral hypothalamus (176) both show regular changes in spontaneous electrical activity during lengthy recording sessions. It has not been established that these cycles represent true circadian rhythmicity nor that the rhythmic activity originates independently at each recording site.

The importance of the hypothalamus in the regulation of rhythmicity is supported by human clinical data. Patients with hypothalamic damage show a reversal of normal patterns of electrolyte excretion (107). Another report (146) cites a loss of normal body temperature rhythms after an increase in third ventricular pressure which presumably interferes with the function of midline hypothalamic nuclei.

**Chemical Control**

**Chemical Basis of Clocks**

In multicellular organisms the output of a circadian oscillator may be the product of interactions among a large population of cells. Other cells may couple the oscillator to the external environment or to effectors that express the observable circadian rhythm. Chemicals may operate at any or all of these levels of organization. As a consequence, pharmacological or chemical modification of circadian rhythmicity does not necessarily imply that the oscillator itself has been affected.

The period (τ) of biological clocks reflects the basic process involved in time measurement and is remarkably intractable to a wide range of pharmacological agents, including inhibitors of macromolecular synthesis, anesthetics, hallucinogens, poisons, and other drugs traditionally used in pharmacological research (49, 140, 154, 170). The few agents that have affected τ have done so only within narrow limits, and these successes have not led to a clear understanding of the chemical nature of biological clocks.

Dilute solutions of ethyl alcohol (ETOH) lengthen the endogenous tidal rhythm of the isopod *Euxolana chiltoni* (58). 0.5% ETOH increases τ by an average of approximately one hour and dosage dependence is apparently linear up to 1%. Reliable but considerably smaller lengthening of τ of the hamster locomotor rhythm occurs when blind animals are chronically ingesting 20% ETOH (206a).

Deuterium oxide (D₂O), also known as heavy water, is the only chemical agent that consistently affects the period of many free-running circadian oscillators. It lengthens τ in plants and in a variety of unicellular and multicellular animals (154). In the mouse τ of the locomotor rhythm is increased in proportion to the concentration of D₂O in the water supply; a maximum increase of 7.4% was obtained with a 30% solution. In a LD cycle phase lags of entrainment are frequently recorded, and in some cases the activity rhythm "breaks away" from the illumination cycle and free-runs (54). Pittendrigh et al (154) have summarized some of the effects of D₂O on biological systems. Partial deuteration slows virtually every biological process and rate depression is explainable by many dif-
ferent potential causes: they postulate that D₂O produces its effects on circadian rhythms by diminishing effective cell temperature. Some preliminary evidence obtained with the Drosophila emergence rhythm supports this view.

Chemical manipulation of unicellular and in vitro systems will not be reviewed here except to cite the frequently stated generalization that the intracellular production of a circadian periodicity may depend on the transmembrane potential and on the permeability of specific ionic channels (59, 140, 189). Alcohol, D₂O, and other chemicals (e.g. lithium) which lengthen the periods of various clocks have all been described as increasing the stability of biological membranes. A recently developed membrane model of the circadian clock (140) suggests that timing is the result of a feedback system involving transmembrane ion gradients and protein-dependent ion transport channels. This model accounts for temperature compensation of τ on the basis of the temperature adaptation of the membrane lipid bilayer. The rate of ion diffusion and of horizontal movement of the proteins responsible for ion transport would both be compensated for temperature change by this mechanism. The fact that K⁺ pulses (59) and valinomycin, which causes an accumulation of K⁺ (37), can produce phase shifts similar to those produced by L pulses suggests a crucial role for K⁺ in the production of circadian rhythmicity and its entrainment by light (140).

The existence of a general homeostasis of τ in the face of all potential perturbations occurring within cells (153) might account for the transitory nature and small magnitude of drug induced changes in circadian systems. The variation in τ effected by all changes in light, temperature, and chemical stimulation is small, usually of the order of 5% and very rarely exceeding 10% (152). As noted by Pittendrigh (152, 153), the apparent homeostasis of τ is a major barrier to evaluating the quantitative effects of any agent used to disturb the circadian oscillator and complicates assessment of the chemical nature of biological clocks.

Chemical Influences on Rhythm Amplitude The degree to which rhythms in brain chemistry affect amplitude of behavioral rhythms remains to be established. Discrete portions of the mammalian nervous system and the brain as a whole display circadian fluctuations in 5-hydroxytryptamine (5-HT), norepinephrine (NE), and possibly in dopamine (DA). The amplitude of these rhythms and their phase relations to the illumination cycle are species-specific (85, 133).

Depletion of 5-HT which is produced by injecting parachlorophenylalanine temporarily reduces the nocturnal feeding, drinking, and activity rhythms of rats: the amplitude of these rhythms recovers to control levels within one week (31, 66, 206a). Similar effects are observed after 6-OH DA treatments that markedly reduce brain NE; the nocturnal activity rhythm is attenuated but not entirely eliminated two to three weeks after treatment (85) and normal three to four weeks later (182). The effects of these drugs on the free-running periods of these behaviors were not reported.

Noradrenergic mechanisms appear to link endogenous rhythms with the cycle of environmental illumination. The β-adrenergic blocking agent 1-propanalol prevents the dark-triggered increase in rat pineal enzyme activity (53). NE de-
pletion also interferes with entrainment of body temperature in a monkey (Cebus albifrons) (203).

The 24 hr periodicity of eating behavior observed in rats maintained in LD 10:14 disappeared when amphetamine was added to the water supply (30). In a similar study rats ingesting amphetamine equivalent to 20 mg/kg of body weight increased their wheel running activity throughout the 24 hr period so that entrainment to the LD cycle seemed to disappear (49). The hyperactivity produced by amphetamine also obscured the free-running rhythm of rats maintained in constant light. The authors conclude that amphetamine disrupted the circadian activity rhythm, but they provide no quantitative estimate of \( \tau \), from visual inspection of their records we conclude that circadian rhythmicity may have persisted under the drug condition.

Removal of endocrine organs reduces the amplitude of various rhythms including those of body temperature (65), locomotor activity (170), and food and water intake (187, 188). The effects are presumably dependent on chemical-hormonal changes consequent to gland extirpation. None of these procedures appears to affect the periodicity of the underlying behavioral rhythms (160, 170), but see (37, p. 57) for a discussion of adrenal effects on physiological periodicities.

This brief survey illustrates that it is far easier to alter the amplitude of biological rhythms than to affect their periodicity. The specific chemical substrates underlying zeitgeber perception or coupling of oscillators to effector systems are unknown, and the possibility exists that coupling within the mammalian neural clock and between it and other systems may be electrotonic rather than chemical (cf. 95). Electrotonic coupling has been described in several mammalian neural structures, including the visual system (22a).

**DRUG EFFECTS ON BEHAVIOR** Responsiveness to drugs fluctuates with the phase of the organism’s circadian cycle, the timing of crests and troughs of susceptibility can also vary from one drug to the next and depends on the function and species studied.

Mortality of rats after a single injection of amphetamine at different times of day reached a peak of 78% at 0600 hr and a trough of 7% at 0300 hr; these animals were maintained on a LD 12:12 cycle with light onset at 0600 hr (175). Fluctuations of a similar nature have been noted for a wide array of physiological parameters and for various classes of drugs. These findings are of importance in chemical therapeutics where it has often been tacitly assumed that animals are steady state systems whose sensitivity to drugs is invariant across time of day.

An exhaustive review of research in this area (162) and our subsequent literature search indicate that biological time of day has been manipulated as an independent variable in but a few psychopharmacological studies. This is unfortunate since drug effects on behavior are almost certainly as subject to modification by endogenous rhythms as the more traditionally investigated physiological parameters. Insufficient recognition of this point may account for seemingly discrepant findings (cf. 117, 173). Biological time of day is a decisive determinant of the effects of l-NE on food intake. When applied directly to the lateral hypothal-
amus of rats during the L phase of a LD 12:12 cycle. NE increases food intake; in the dark phase NE depresses food consumption (117). This effect may depend on circadian fluctuations in the activity and sensitivity of lateral hypothalamic neurons (176).

The dose-response curve for increasing locomotor activity with amphetamine is steeper in the L than the D part of the illumination cycle (60); sleeping time of rats on a LD 12:12 cycle is a function of the hour of barbiturate administration (162). These findings suggest the importance of controlling for or better yet manipulating biological time of day as a variable in psychopharmacological research. The meager data currently available suggest that the new findings and perspectives gained from such an analysis will be well worth the effort.

SEASONAL RHYTHMS

Photoperiodism

Homeothermic species in temperate and arctic climates must adapt to seasonal changes in temperature, predator pressure, and the availability of food and protective cover. In doing so they undergo hibernation (135), estivation, migration, seasonal and opportunistic breeding, and delayed uterine implantation (174, 194). Social reorganization, daily torpor, and changes in fur quality and coloration are also among the adaptations observed in mammals on a seasonal basis (96, 184, 185).

Physiological and behavioral responses must often be initiated well in advance of the seasonal conditions they are designed to meet. Hibernating mammals store food or body fat long before snow cover and cold make feeding impossible and hibernation essential for survival (194, p. 378). Birds show precise timing of premigratory fattening and development of functional reproductive organs in advance of their arrival at distant breeding grounds (62). Mechanisms that rely exclusively on simple responsiveness to current conditions are inadequate to account for these phenomena; animals clearly use information about time of year to anticipate critical conditions. Most species use the stable and regular annual cycle of change in daylength (photoperiod) to time seasonal events. Photoperiodic time measurement (PTM) is evident in the initiation of seasonal reproduction, but it also mediates other seasonal cycles. An understanding of the formal models proposed to account for PTM is essential to any consideration of research on seasonal rhythms.

MODELS OF PHOTOPERIODIC TIME MEASUREMENT (PTM)

(a) The hourglass model The mechanism whereby an organism may directly measure the duration of a L or D period by accumulating some endproduct during one phase and not the other has been compared to an hourglass. This type of mechanism has been confirmed in a few insects (155) but apparently is not applicable to mammalian PTM.
(b) Bunning's hypothesis This states that an endogenous circadian oscillator mediates PTM. In its role as zeitgeber light first entrains a circadian photosensitivity rhythm, the second function of light is induction of the photoperiodic response. This occurs if and only if light extends into the photoinducible (sensitive) phase of the circadian cycle. If it is assumed that dawn sets a photosensitive phase to occur 14 to 15 hr later, then light will fall in the inducible phase only when days are long (in excess of 14 hr). In this way a short period of light coinciding with a critical photosensitive phase can induce the seasonal changes associated with long days, otherwise the animal will behave as if under short-day conditions. Animals need not experience light continuously for effective PTM. This is an attractive feature in accounting for the excellent PTM observed in fossorial animals who may be exposed to daylight only near dawn and dusk each day.

Photoperiods of any given duration occur twice each year and PTM depends on the animal distinguishing 14 hr of light in the spring from 14 hr of light in the fall. Many animals show a photorefractory period such that photoinduction by long days (spring) takes place only if these days are preceded by an extended period of short days (winter). The specific form of Bunning's hypothesis described above relies on the coincidence of an internal state (photosensitivity) with an external condition (light) and has been called an external coincidence model.

(c) The internal coincidence model This assumes that the sole function of light is to entrain various circadian oscillators such that they bear different phase relation to each other under different photoperiods. PTM and induction depend on a seasonally unique phase relation of these oscillators and no direct inductive role is ascribed to light. Two oscillators entrained respectively to dawn and dusk could serve this function. A corollary of this model is that entrainment by non-light zeitgebers could achieve the proper internal relations among oscillators and thereby effectively mediate "photoperiodic" time measurement in the absence of light such studies are currently in progress with temperature zeitgebers, but the predicted effect has yet to be demonstrated.

(d) The resonance effect Since laboratory tests of PTM frequently use exotic lighting schedules, one cannot conclude that the circadian system is actually involved in PTM merely because the schedules in which L recurs at modulo 24 hr intervals are most effective for induction. A non-circadian mechanism might measure light duration but produce maximum induction only when the animal's physiological mechanisms are synchronized by a cycle approximating the natural frequency. In general an organism is assumed to function most efficiently when its internal oscillators have the proper phase relations and this occurs only when entrained to 24 hr cycles.

Tests of the models Tests of Bunning's hypothesis typically involve noninductive entraining light periods followed by brief "flashes" of light at various intervals during the succeeding dark periods. The pitfalls inherent in interpreting such studies derive from the difficulty in distinguishing entraining from inductive...
effects of light (152). Elliott et al (57) recently attempted to circumvent this problem by concurrently recording locomotor activity and testicular development of hamsters exposed to such LD sequences. When the hamsters' activity cycles were stably entrained to the illumination cycles their testes showed unique daily phases of sensitivity to the inductive effects of light; these phases recurred at 24 hr intervals in accord with Bunning's hypothesis. However, these results may also be amenable to an explanation in terms of light entraining a dawn oscillator one day and a dusk oscillator on another in such a way as to maintain an inductive internal phase relationship, i.e. an internal coincidence model involving only entraining and not inductive actions of light is still not ruled out (57).

Results obtained with the moth *Pectinophora gossypiella* do not support Bunng's hypothesis. In this species, where it is possible to separate the inductive and entraining properties of light, no circadian involvement in PTM was observed (155). Replication of this experiment in mammalian species in which circadian systems seem to be implicated awaits the discovery of light wavelengths and intensities consistent with induction but not with entrainment.

The importance of photoperiodic time measurement and the intricate interaction among biological clocks, hormones, and behavior are most clearly illustrated by Meier's elegant studies on sparrows (120, 121). Injections of corticosterone and prolactin induce premigratory fattening, gonadal development, and *zugunruhe* (directed migratory restlessness) only when they bear a particular phase relation to each other. Prolactin injected 12 hr after corticosterone produces all these effects and the *zugunruhe* is directed northward (spring mode); if prolactin is given 4 hr after corticosterone, only fattening occurs and *zugunruhe* is directed southward (fall mode). Prolactin injections bearing other phase relations to corticosterone are ineffective.

Meier's evidence suggests that the peak in endogenous corticosterone secretion is followed 4 to 8 hr later by a photoinducible phase during which light can trigger release of luteinizing hormone (LH). A second photoinducible phase 16–22 hr after the corticosterone peak permits light to stimulate release of follicle stimulating hormone (FSH). The maintenance of photosensitivity at these phases depends on entrainment of the prolactin rhythm at an appropriate phase relative to the peak in corticosterone secretion (121). These data are consistent with the following hypotheses: light entrains the circadian rhythms of corticosterone and prolactin release, with daylength determining the internal phase relations between these rhythms; when the proper phase relation occurs, it in turn entrains a circadian rhythm of photosensitivity during which light may act to influence pituitary release of LH and FSH. This results in spermosogenesis, testis growth, and other signs of spring migration, or in the fattening and *zugunruhe* typical of autumn migration. Stress produced by handling sparrows and pricking them with a needle at appropriate times of day can also phase the corticosterone rise so that photomuduction can take place (122).

Careful tests of entrainment of the circadian system with nonlight cues are needed to improve our understanding of the control of seasonal breeding and migration. Such experiments could provide valuable information about the rela-
tive importance of the internal and external coincidence systems already implicated by Meer's findings. They could also provide insights into the physiological mechanisms whereby many internal oscillators can be entrained and phase shifted relative to each other and to environmental cycles.

**Circannual Rhythms**

Endogenous annual oscillations (circannual rhythms) provide a second mechanism, independent of photoperiodic time measurement, for timing of seasonal events. To qualify as endogenous, a circannual rhythm must persist under constant environmental conditions and occur year after year with a free-running period of approximately one year. It is hardly surprising that few studies have adequately satisfied this demanding criterion.

The existence of such endogenous annual oscillations has also been controversial because closely related species differ strikingly with respect to the existence and general form of these rhythms. Unlike daily rhythms, annual cycles are a new evolutionary development of adaptive significance only to relatively long-lived species (63). If, as seems likely, a great diversity of mechanisms evolved independently to mediate annual cyclicity, then the search for unitary mechanisms and models based exclusively on a circadian paradigm may be inappropriate (77).

Among the most convincing examples of circannual rhythms is the hibernation rhythm of blinded ground squirrels (*Citellus lateralis*) maintained for years in a constant environment at 3°C. In one individual the intervals between successive entries into hibernation were 313, 314, and 310 days, respectively (149). Heller & Poulson, studying other ground squirrels (*Spermophilus*), maintain that "regardless of the experimental manipulations we imposed upon the animals, the free-running period length measured from terminal arousal to terminal arousal is generally only slightly less than a year and shows remarkably little variation" (82). In yet another species of ground squirrel the hibernation-weight gain rhythm damps out after one year and few subjects show a second cycle (136). Endogenous annual rhythms may also regulate antler growth in pika deer (*Cervus nippon*) (73), fat deposits in woodchucks (*Marmota monax*) (51), water intake and body weight in ground squirrels (149), and hibernation in chipmunks (*Eutamias*) (82). The evidence that these rhythms are truly endogenous is far less compelling than for circadian rhythms. For example, the detection of circannual rhythms is strongly dependent on the maintenance of a particular daily LD cycle. Some species require a LD 12:12 cycle, while others need a LD 11:13 cycle to express their annual rhythms (77); the annual cycle of antler growth in the pika deer occurs on LD 16:8 or LD 8:16 but not on a LD 12:12 cycle (73).

The peculiarities and advantages of the endogenous timers of different species that have such stringent and divergent requirements remain unknown. A number of annual rhythms may be subject to separate endogenous and exogenous controls. Part of the cycle is entirely independent of external input (*endogenous component*) and a second part requires a particular LD cycle or temperature to trigger or terminate some crucial event. If this *exogenous component* is provided, the annual rhythm is expressed, in its absence the endogenous process is arrested at the blocked phase.
The interaction of endogenous and exogenous controls in seasonal rhythms is clearly illustrated by Reiter's work with golden hamsters. In these animals short photoperiods initiate testicular regression, culminating within 8 weeks in reproductive quiescence. After 25 weeks of continual exposure to the short photoperiod, the gonads undergo spontaneous recrudescence and become functionally mature (164). Testicular development and recrudescence proceed independently of any need for the long photoperiods (168) otherwise required to maintain testicular function, and thus appear to be endogenously controlled. However, a second cycle of testicular regression in short photoperiod conditions will not occur unless the animals first experience many weeks of long-day conditions (164).

These findings are in good accord with field observations cited by Reiter (163). Short laboratory photoperiods may simulate the conditions hamsters are exposed to in the late fall when they enter underground burrows and hibernate in the absence of light until the following spring. The 20-week period of sexual dormancy induced by the short photoperiod prevents delivery of young during the disadvantageous fall and winter seasons; the subsequent testicular recrudescence, independent of light, insures that sexual competence coincides with spring emergence and that young are born during the season optimal for survival (165). The pineal gland has been implicated in these and other seasonal reproductive events, and its contributions are ably documented by Reiter (164).

**Seasonal Influences on Behavior**

In addition to prominent annual rhythms in hibernation and reproduction, there are more subtle but nevertheless important seasonal influences on physiology and behavior (cf 35). One direct seasonal influence is due to the changing availability of foodstuffs. Rodents feeding on the protein-rich spring and summer herbage grow faster and reach sexual maturity earlier than those ingesting the starchy foods available in the autumn (78). Certain opportunistic breeders living in arid regions reproduce only after favorable and unpredictable events such as rainfall (174).

Other seasonal influences are less direct. Goldfish perform better in learning tasks and are more active in winter than during the summer spawning season. Reducing the amount of light to which they are exposed improves summer performances (179). Under natural lighting conditions the occurrence of estrus in pocket mice (*Perognathus penicillatus*) is little influenced by the presence of males; it has a high incidence in spring and summer and low in autumn and winter. However, under constant long or short photoperiods the annual cycle is disrupted and the presence or absence of males becomes an important variable (144). Snowshoe hares (*Lepus americanus*) gonadectomized during their breeding season increase LH and FSH synthesis and release; no such increases in hormone secretion are detected when gonadectomy is performed out of the breeding season (52). Male *Microtus* are more aggressive in paired encounters when captured in their breeding season than at other times of year (193).

The pattern of daily activity often changes with the seasons (194, p. 345). Three species of voles showed a single nocturnal activity peak during summer, but all gradually became diurnal with one or more activity peaks during winter (75). In
spring, arctic deer mice (*Peromyscus maniculatus*) have a pronounced daily activity rhythm which may be related to effective foraging and mating. In winter, they undergo daily torpor and are weakly nocturnal (184). Woodchucks emerging from hibernation in late winter show scattered daily activity. by spring they have a strong afternoon activity peak, in summer a bimodal pattern, and in the fall scattered activity culminating in winter hibernation (33)

Little is known about whether these seasonal cycles persist under constant laboratory conditions, but there is a suggestion that hamsters breed more readily in spring than in winter, even under unchanging light and temperature conditions (164)

The particular conditions of illumination, ambient temperature, and availability and quality of food in laboratory studies may mimic those of a given season. The effects of subsequent experimental manipulations may therefore be affected by the induction or blockade of seasonal phenomena. To select appropriate laboratory conditions, one must be familiar with the ecology of the species being studied. Such knowledge has often been lacking or ignored in psychobiological research.

**RHYTHMS AND BEHAVIORAL FUNCTIONS**

The final sections of this review are concerned with the rhythmic aspects of specific behavioral phenomena. Psychologists and physiologists appreciated that behaviors associated with sleep, activity, food ingestion, and reproduction had an intrinsic cyclicity long before they suspected that other behaviors might be similarly organized. As a consequence, the evidence is far more satisfactory for the former behaviors than for the processes involved in sensation, perception, and learning.

*Eating and Drinking*

The frequency and periodicity of mammalian eating behavior depend on the nature and availability of the diet eaten and may be characteristically quite different for carnivores, herbivores, omnivores, etc. Size and metabolic rate, type of digestive system, endogenous activity rhythms, and numerous environmental factors, *viz.* temperature, illumination, humidity, presence of conspecifics and predators, and reproductive status, also may dictate the distribution and quantity of food consumed. The feeding frequency of smaller nocturnal mammals will also depend on the availability of an insulated nest that reduces metabolic demands imposed by changes in environmental temperature and humidity, and that provides a dark retreat during daytime.

The survival of mammals and the maintenance of energy balance depend on foraging, hunting, and often returning with food to nests or storage areas. Much of the observable spontaneous activity of mammals in the wild is related to feeding, and it probably is inappropriate to analyze one without considering the other. Eliminating the necessity to search for food may well be a critical factor influencing periodicity of intake. e.g. in nature the activity cycle and feeding behavior of
an insectivorous rodent may be linked to that of the invertebrates that form part of its diet and which themselves show marked fluctuations in daily activity (17).

In typical laboratory studies of eating behavior the periodicity of intake is established while excess food is freely available at all times. A dark nest box is rarely provided, so the nocturnal animal must experience long periods of light or modify its behavior to minimize light exposure (e.g. increased sleeping during the L phase). The addition of a dark place in the cage stimulated a South American rodent (*Oxymycterus rutilans*) to eat a greater proportion of its food during the L portion of the illumination cycle (196). Albino rats given access to a constantly dark tunnel and burrow in addition to an open field where food and water were available under a LD 12:12 cycle altered the temporal pattern of their eating and drinking (Rusak & Block, unpublished observations. 1973).

The study of the effects of food restriction on subsequent eating is complicated by the variety of feeding styles adopted by mammals. Large predatory mammals obtain substantial quantities of easily digestible food at irregular intervals and may gorge themselves during one relatively brief feeding; they are adapted to fare quite well without further food for days. Other mammals, such as those eating diets of low caloric density and high cellulose content, may be compelled to eat relatively continuously throughout the day and night. This would appear to be true of the larger herbivores, including some of the ruminants (17). Some herbivorous animals have very limited abilities to compensate for periods of food deprivation and only slowly regain weight loss during starvation (Silverman & Zucker, unpublished observations. 1973). The degree of depletion induced by starvation and in fact the survival of rodents may depend on the time of day during which food deprivation occurs (138).

**ENTRAINMENT**  Rats with ad lib access to food and water in a bare laboratory cage are nocturnal feeders and drinkers. In a LD 12:12 cycle they eat 75% of their food and drink 85% of their water during the dark phase (206). In LD 14 10 a peak of eating occurs with the onset of darkness and a second peak about 6 hours later (191). The nocturnal drinking rhythm may be partially independent of the nocturnal feeding rhythm (141), and relations between food and water intake may differ fundamentally in the different phases of the illumination cycle (206, 207).

In hamsters drinking is 85% nocturnal on a LD 12 12 cycle, but only 58% of feeding occurs during the dark phase (207). In guinea pigs there is no obvious nocturnal, diurnal, or crepuscular cycle, and the animals appear to eat and drink at regular intervals throughout the day and night (86). Some primates appear to be exclusively diurnal feeders, and observations of monkeys (*Macaca mulatta*) in seminatural conditions suggest that they withdraw to trees and do very little eating between dusk and dawn (195).

**SHORT-TERM CYCLES**  There is a significant positive correlation between the rat's meal size and the interval to the next meal (108). This relation does not appear to be a general description of the rat's feeding behavior; according to Panksepp (147), it holds during specific metabolic states and is a consequence of statistical
procedures of questionable validity. He proposes instead that the “free-feeding pattern of rats is generated by an internal signal of body nutrient depletion-repletion which varies in a circadian fashion” and that the satiating capacity of ingested food and the depriving capacity of intermeal intervals vary across the day.

This concept is supported by other findings: e.g., the effectiveness of the suppression of oral intake by intragastric loading of nutrients depends not only on the number of calories infused but also on the temporal distribution of infusions relative to the normal time of feeding (159). Factors other than total caloric intake thus play a role in determining satiety. Some circadian rhythms in blood amino acids are not directly related to ingestion of dietary proteins and are evident on the day of birth in human infants (64). These rhythms could be manifestations of a neural system that generates a circadian depletion-repletion cycle.

Failure to simulate environmental conditions more representative of those experienced by animals in nature may lead one to generate reliable but invalid laboratory data on feeding patterns. Extrapolation from results obtained with a particular species, tested under a limited set of conditions, to mammalian feeding in general glosses over a wealth of information about species specificities that range from radical differences in intestinal and gastric morphology (41) to elaborate food storage techniques practiced by certain mammals (194, p. 323–24). Consider for example that albino rats, often studied as models of human feeding, reingest approximately 40% of the feces they produce when studied under laboratory conditions. This coprophagy shows a pronounced daily rhythm (114) that permits the recovery of valuable nutrients (19). The influence of this cycle of coprophagy on meal patterns and on the rat’s adjustment to alterations in food availability and in diet quality deserves experimental attention.

Sleep and Activity

Animal rest and activity cycles have been investigated more thoroughly than any other rhythmic function. Such cycles seem to be fundamental to the temporal organization of all animal behavior and are found both in the simplest and most complex organisms. The relative ease with which activity can be continuously monitored over long intervals recommends it to the student of biological rhythmicity. However, measurement of activity in laboratory settings is subject to many of the same problems as were enumerated in the preceding section. The availability and quality of food, the presence of burrows, and the use of gradual light-dark transitions may alter the timing of activity (17, 100, 101; Rusak & Block, unpublished observations, 1973). The distribution of activity as recorded in the laboratory may differ from that in the field (102), particularly if seasonal variations occur.

The methods used for monitoring activity (stabilimeter, activity wheel, photocell, etc.) influence the nature of the results obtained (14, 67, 169). Nevertheless, measures as diverse as chewing, drinking, eating, and wheel running may yield quite similar nocturnal patterns when studied in a single species (171). If one is concerned with the temporal distribution of these behaviors rather than with the
function or topography of the response being measured, then one may be justified in studying one endpoint (e.g. wheel running) as an index of the animal's temporal organization. However, since a given manipulation (e.g. a brain lesion or a drug) can have different effects depending on the type of device used to measure activity (cf 115), it is important to determine the generality of treatment effects by studying a number of different responses. This is obviously necessary where one suspects a multiplicity of clocks for different functions.

Researchers have recognized the importance of circadian and ultradian rhythms in the control of sleep. Kleitman (104) proposed that the arousal level of an individual varies throughout the day and is a function of an ultradian species-specific, rest-activity cycle that persists through the sleep and waking states. The proportion of the various sleep stages recorded depends on when in relation to their circadian cycle individuals first fall asleep (199).

The function of sleep has interested many writers and may be, as some have suggested (181, 199), to prevent wasteful and dangerous expenditure of energy at nonoptimal times of day; the rest-activity cycle would thus ensure that each species is active only when its activity has the greatest potential survival value. The idea that sleep serves primarily this function rather than one of metabolic recovery is supported by data obtained on human (15) and hamster subjects (129); under free-running conditions sleep time is inversely proportional to the length of the preceding period of spontaneous wakefulness. This relation is predicted by a circadian organization of the sleep-wakefulness cycle since the total of rest and active periods must equal a stable \( \tau \) value. The opposite is predicted by any theory that emphasizes the recovery function of sleep. The development of a sleep "need" after periods of sleep deprivation (202a) does suggest that some recovery occurs during sleep; this may be a more recently evolved function superimposed on the basic timing process of the sleep-wakefulness cycle.

Exposing burrow-dwelling rodents to obligatory LD cycles may restrict the amount and distribution of the various sleep stages (68, 134). In constant darkness or when given access to a darkened retreat, rats may make up a chronic sleep "debt" incurred under standard laboratory conditions (68). These findings require further study and confirmation, but they emphasize the need for consideration of species' ecology, particularly in relation to light exposure.

**Reproduction**

The reproductive physiology and behavior of many mammals has an intrinsic rhythmicity. The ovaries of polyestrous spontaneous ovulators pass through follicular and luteal phases of relatively fixed duration, and the cycle is repeated unless interrupted by copulation or pregnancy. The limited life span of ovulated ova makes it essential that mating behavior and insemination be temporally synchronized with the period during which fertilization is most likely to occur. In many mammals the coupling of sexual receptivity and ovulation to the same fixed sequence of hormonal events assures this outcome. Synchronization of ovulation and sexual behavior is mediated in female rats by neural control of the pituitary (61, 72, 204) and may possibly involve adrenal participation (116).
The endogenous nature of the biological clock controlling the hamster estrous cycle has been definitively established (2); in constant illumination behavioral estrous cycles free-run with a period greater than 4 days (a circaquadradian rhythm). The timer that mediates this cycle probably functions with a circadian rather than a circaquadradian periodicity (2). Neural pathways that promote preovulatory LH release do so at 24 hr intervals (103, 139), but ovulation occurs only on the day of the cycle that coincides with high plasma estrogen levels (139). Spontaneous or pharmacologically induced blockade of ovulation extends the cycle by 24 hr rather than by an entire cycle length (2), further supporting a circadian organization of estrous cyclicity. Failure to establish free-running estrous cyclicity in rats housed in constant light does not argue against the endogenous nature of this rhythm. The albino rats used in these studies are abnormally sensitive to the disruptive effects of constant light (36), and the cessation of ovulation and onset of persistent estrus in LL speak to a desynchronization or damping of the various hormone rhythms that contribute to the ovulation cycle (cf 178).

One unresolved major question, as noted by Everett (61), is whether the clock for cyclic LH release and ovulation exists in both sexes. According to one view (72, p. 240), the inherently cyclic preoptic area regulates cyclic release of gonadotropins in female rats. In males cyclicity of this neural substrate is thought to be suppressed during perinatal sexual differentiation. The result is that the adult male or the adult female exposed to androgens during the critical period of sexual differentiation is acyclic. An alternative hypothesis is that the clock for cyclic LH release, ovulation, and cyclic behavioral receptivity is present in adults of both sexes. Females may differ from males in the coupling of the clock to the hypothalamic-pituitary-gonadal axis. We propose that hormonally mediated changes in these functions, rather than in the clock mechanism per se, are responsible for the lack of cyclicity in adult male rats. This conclusion is based on the observations that the clock for ovulation is present on the day of birth in rats of both sexes (79) and on the general ineffectiveness of all chemical agents in changing the basic periodicity of biological clocks.

The induction of sexual receptivity in many rodents ordinarily depends on the synergistic action of estrogens and progesterone (157, 204). These hormones act on a neural substrate to promote lordosis and other species-specific components of behavioral receptivity. The extent to which circadian fluctuations in the number of central binding sites for estrogens and progesterone contribute to the time of onset of receptivity is unknown. Binding capacity may remain constant on each day of the cycle and within any given day. Significant diurnal variation in the secretion of hormones could be principally responsible for the behavioral rhythm. The rhythmicity of estrogen secretion is difficult to assess from the published records (93), however, the steady and seemingly continuous rise in estrogen secretion between vaginal diestrus and proestrus reduces the probable functional significance of any such rhythm. The diurnal variation in peripheral plasma progesterone concentrations on each day of the estrous cycle is of adrenal rather than ovarian origin.
(116), and is probably of some significance in determining the onset of behavioral receptivity (178).

The data referred to above are derived mainly from studies of rats and hamsters. two spontaneously ovulating species. According to Conoway (45), this type of ovarian cycle is of restricted occurrence among mammals; induced ovulation is the more widespread phenomenon. In the reflex ovulator, ovulation is induced by copulation and occurs a fixed number of hours after mating; this could diminish the significance of photoperiodic synchronization of ovulation.

Comparatively little has been written about the synchronizing influence of illumination on daily cycles of copulation in male mammals. Beach & Levinson (21) report that male rats tested during the dark portion of a LD 12:12 cycle ejaculate much more frequently than when tested during the L phase. The peak in the male's copulation in this species coincides with the peak in the female's receptivity. Blind female rats cohabiting with blind males are not impregnated except when the female's free-running period of sexual receptivity overlaps the active phase of the male's free-running rest-activity cycle (171a).

Sadleir (174, p. 160) notes that the modal arrangement among mammals is that the male has a breeding season which overlaps that of the female; in other mammals males are fertile and capable of mating throughout the year and their female counterparts may breed continuously or have discrete breeding seasons. The significance of the males of certain species maintaining breeding capacity during the female's period of reproductive quiescence may relate to other functions of testicular hormones, as for example, in influencing aggressive behavior or population dynamics (174). For an extensive discussion of the role of environmental stimuli in establishing readiness to breed in mammals, the interested reader should consult the excellent monograph by Sadleir (174).

**Sensation**

What little information currently is available suggests that sensory systems undergo circadian fluctuations in sensitivity. In the crayfish (Procambarus) the responses of retinal photoreceptors and of central visual interneurons to repeated light flashes vary across a circadian cycle that depends on the hormonally controlled, endogenously timed migration of retinal pigments (8). Mechanoreceptors of this species also show a daily cycle of sensitivity to stimulation.

The responsiveness of the toad (Bufo bufo) to stimuli which mimic natural prey objects fluctuates seasonally. In summer toads emit more prey-catch responses to a light object moving against a dark background than to a dark object on a white background; in winter responsiveness to the light object is greatly reduced. Firing rates of retinal ganglion cells show parallel seasonal changes in sensitivity to these stimuli. This effect is apparently achieved by centrifugal control of the retina and accomplishes at the sensory level the behavioral changes essential to the toad's annual cycle of feeding and hibernation. The decline in responsiveness to fly-like objects as winter approaches coincides with the cessation of feeding and the animal's preparation for hibernation (61a).

Circulating levels of adrenal corticoids modify sensory thresholds of audition.
taste, and vision in several mammalian species (44, 84). The well-established daily fluctuations in adrenal corticoid secretion (cf 106) encompass a sufficiently large range to measurably affect sensory thresholds in human subjects (84). Increased nocturnal sensitivity to stimuli may also account in part for the greater incidence of stimulation-induced seizures in mice (177) and rats (198) during the dark phase of the illumination cycle.

Learning and Memory

The discovery of a time-sense in bees was one of the first demonstrations of a circadian organization of learning and memory (197). Bees can be trained to return to a particular site at a specific time of day; once trained they return to the food site at approximately 24 hr intervals. They can learn to fly to several different sites to selectively obtain food at different times of day but cannot be trained to return to a given location at long intervals that differ substantially from 24 hr (37, p 160). Such temporal constraints on learning are also evident in rats restricted to feeding for one hour per day. When maintained on a 24 hr illumination cycle (LD 24 24) these animals increase their activity in anticipation of the daily feeding (29); they do not show activity in anticipation of feedings given at 19 hr or 29 hr intervals, even if raised from birth on 19 and 29 hr illumination cycles (29).

A starling was trained at a fixed time of day to obtain food in a circular arena from the one feeding dish among 12 that lay in the direction of the sun. When tested at other times of day the bird did not simply fly towards a feeder in the direction of the sun, but compensated for the sun’s movement and flew to a feeder in the same compass direction to which it had been trained. Thus the starling did not readily learn a simple association of food with a salient environmental stimulus (the sun), but rather learned a complex rule about the direction of food availability relative to the sun’s position and its own internal clock (89, 104a).

Rats acquire and retain passive avoidance tasks more readily at some times of day than at others (50). Regardless of the actual clock time of training, performance of active and passive avoidance behaviors is best 24 hr after training and at multiples of 24 hr (48 and 72 hr). Retention is also fairly good at 12 hr multiples after training and very poor at intermediate times (91, 92). These effects are independent of the actual time of day at which original training takes place. Apparently, rats tested in passive and active avoidance tasks learn not only a spatial relation, i.e. that a particular area is safe or dangerous for them, but also when the area has these properties. The apparent temporal coding of such learning has only become evident within the past few years and adds an entirely new dimension to the interpretation of learning phenomena (cf 91, 92).

The circadian involvement in learning is advantageous in that it permits bees to visit flowers only during the limited periods each day when the latter secrete nectar. For rats the temporal modulation of what is learned may serve to increase the plasticity of behavior. An animal need not universally avoid the place where it was frightened or driven off by a competitor: it can return regularly at another time of day when the competitor is absent and feed unmolested (cf 40).
CONCLUSIONS

The importance of the temporal organization of behavior is difficult to overestimate. In nature a premium is placed on animals performing responses at appropriate times of the day and seasons of the year. We have tried to indicate the central role of biological clocks in the integration of the animal's internal milieu and in the synchronization of these functions and of behavior to environmental periodicities.

Biological clocks are inherited (69, 172), manifested in the adult animal independently of specific postnatal "learning" experiences (150), and provide the substrate for the inherent rhythmicity of most animal behavior. The treatment of living animals and their behavior as steady state systems invariant across time of day has been common in many branches of psychology and biology but can no longer be justified (162). As a research strategy, ignoring biorhythmicity may confound the effects of other independent variables, or at least increase the variance associated with any given experimental procedure.

Biochronometry has much to offer psychologists in understanding behavior as a cyclic phenomenon whose periodicity serves important functions. By providing methods of analysis and a theoretical framework it gives us the tools to deal with and understand the temporal organization of behavior.

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