

Social influences on mammalian circadian rhythms: animal and human studies

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ABSTRACT

While light is considered the dominant stimulus for entraining (synchronizing) mammalian circadian rhythms to local environmental time, social stimuli are also widely cited as ‘zeitgebers’ (time-cues). This review critically assesses the evidence for social influences on mammalian circadian rhythms, and possible mechanisms of action. Social stimuli may affect circadian behavioural programmes by regulating the phase and period of circadian clocks (i.e. a zeitgeber action, either direct or by conditioning to photic zeitgebers), by influencing daily patterns of light exposure or modulating light input to the clock, or by associative learning processes that utilize circadian time as a discriminative or conditioned stimulus. There is good evidence that social stimuli can act as zeitgebers. In several species maternal signals are the primary zeitgeber *in utero* and prior to weaning. Adults of some species can also be phase shifted or entrained by single or periodic social interactions, but these effects are often weak, and appear to be mediated by social stimulation or arousal. There is no strong evidence yet for sensory-specific nonphotic inputs to the clock. The circadian phase-dependence of clock resetting to social stimuli or arousal (the ‘nonphotic’ phase response curve, PRC), where known, is distinct from that to light and similar in diurnal and nocturnal animals. There is some evidence that induction of arousal can modulate light input to the clock, but no studies yet of whether social stimuli can shift the clock by conditioning to photic cues, or be incorporated into the circadian programme by associative learning. In humans, social zeitgebers appear weak by comparison with light. In temporal isolation or under weak light-dark cycles, humans may ignore social cues and free-run independently, although cases of mutual synchrony among two or more group-housed individuals have been reported. Social cues may affect circadian timing by controlling sleep-wake states, but the phase of entrainment observed to fixed sleep-wake schedules in dim light is consistent with photic mediation (scheduled variations in behavioural state necessarily create daily light-dark cycles unless subjects are housed in constant dark or have no eyes). By contrast, discrete exercise sessions can induce phase shifts consistent with the nonphotic PRC observed in animal studies. The best evidence for social entrainment in humans is from a few totally blind subjects who synchronize to the 24 h day, or to near-24 h sleep-wake schedules under laboratory conditions. However, the critical entraining stimuli have not yet been identified, and there are no reported cases yet of social entrainment in bilaterally enucleated blind subjects. The role of social zeitgebers in mammalian behavioural ecology, their mechanisms of action, and their utility for manipulating circadian rhythms in humans, remains to be more fully elaborated.

Key words: circadian rhythms, light, sleep-wake, exercise, stress, entrainment, phase shifts, masking, blindness.

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I. INTRODUCTION

Circadian clocks are assumed to enhance survival and reproductive fitness in part by promoting optimal timing of behaviour and physiology with respect to regular cycles in the environment. The rising and setting of the sun provides a precise and reliable signal for regulating the phase of the circadian clock, and it is therefore not surprising that light is a powerful, if not dominant 'zeitgeber' (entraining stimulus) for most species. However, for many species, daily changes in illumination may be secondary to what is really important, namely, the activity patterns of other denizens of the greater social community, the potential mates, competitors, predators, prey and parasites with which they must share time and space. It may therefore be hypothesized that circadian clocks in some, if not all species, have evolved a capacity for phase resetting in response to significant interactions with other organisms. There is ample evidence from field work to support the general view that animals do coordinate their behaviour in time with that of other animals, of the same or different species, but the mechanisms by which this is achieved are little studied.

The aim of this review is to assess critically the evidence for social (i.e. within-species) influences on daily rhythms in mammals and for their mechanisms of action. Conceptual pathways by which social stimuli could regulate circadian timing are first identified. A multidisciplinary literature on social influences on animal rhythms is then reviewed, organized by ontogeny, phylogeny and methodology. This approach is driven by the intuition, supported by empirical evidence, that social effects on circadian timing are likely to depend on age and species. For each keynote species, evidence is reviewed for entrainment to any nonphotic stimulus of sufficient salience to perturb behavioural state, given the possibility that social stimuli may affect circadian timing by non-specific effects on arousal. The review concludes with the evidence for social influences on the circadian system of humans. In the past 25 years, there has been a major shift in thinking about phase control of circadian rhythms in humans, from an initial emphasis on the importance of

social stimuli, to a view that light is the dominant, if not exclusive circadian zeitgeber. An objective of this review is to determine whether the available evidence is sufficient to discount social and other nonphotic factors as significant circadian zeitgebers in humans, or whether such conclusions would be premature.

II. PUTATIVE MECHANISMS: OVERVIEW

The heuristic model illustrated in Fig. 1 identifies all possible paths by which environmental stimuli could influence daily temporal programmes of behaviour in mammals. Two pathways are shown in bold print. One is from the 'sun' (or light source) to the retina and from there, via the retino-hypothalamic tract (RHT), to the master light-entrainable circadian pacemaker located in the suprachiasmatic nuclei (SCN; Klein, Moore & Reppert, 1991). A second is from 'social stimuli' to 'behavioural state' to the sun. The bold print for these pathways is intended to highlight three facts that form a framework from within which social effects on circadian rhythms must be considered. First, light is a primary zeitgeber. Second, light exposure is determined by behavioural state (e.g. opening and closing of eyes; entering or exiting dens, burrows and other houses). Third, behavioural state (and therefore light exposure) is often determined by social stimuli. These facts raise important methodological and interpretive issues (elaborated below) in evaluating whether social stimuli are true, independent zeitgebers, or whether they are simply the agents of photic zeitgebers. It is also possible that social stimuli, by effects on behavioural state, could modulate photic input to the retina (e.g. by autonomic effects on pupil size) or retinal input to circadian clock cells in the SCN (e.g. Ralph & Mrosovsky, 1992; Mistlberger & Antle, 1998). Such effects on light input would be expected to significantly influence entrainment to daily light-dark (LD) cycles, even if social stimuli have no effect on the circadian clock independent of light.

A second set of pathways identified in the model represents nonphotic inputs to the SCN pacemaker and other

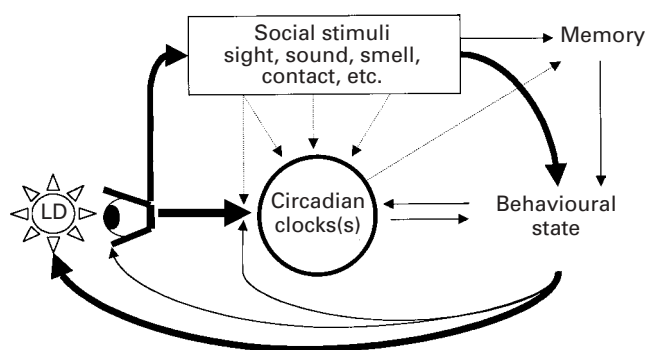


Fig. 1. Conceptual model of the mammalian circadian system identifying pathways by which social stimuli could affect circadian rhythms. Dashed lines indicate pathways for which there is as yet no evidence. LD, light-dark cycle. See text for further explanation.

oscillators at the core of the circadian clock system, and is the main focus of this review. Social stimuli that have direct effects on pacemaker phase and period (τ), sufficient to entrain daily rhythms, can be designated as zeitgebers. Social zeitgebers could access circadian clocks via sensory-specific input pathways, encoding sights, sounds, smells or tactile stimuli, or via a common input pathway encoding arousal, locomotion, stress, or some other non-specific correlate of behavioural state. Pathways encoding nonphotic information could input directly to SCN clock cells (e.g. via known neural afferents from the median raphe, thalamic intergeniculate leaflet, or cholinergic cell groups; Mrosovsky, 1996; Card, 1999; Mistlberger *et al.*, 2000), or to circadian clock cells located elsewhere in the brain or in the periphery. Non-SCN circadian oscillators of the latter sort have been formally defined by studies of behaviour (e.g. food anticipatory circadian rhythms persisting in SCN-ablated animals; Mistlberger, 1994; Stephan, 2002), and have been physically identified by analyses of clock gene expression in non-SCN tissues (e.g. the neocortex and the liver; Damiola *et al.*, 2000; Stokkan *et al.*, 2001; Cermakian & Sassoni-Corsi, 2002).

A third set of pathways in the model represents outputs from the circadian system to brain systems elsewhere that may subserve memory for time and place. Mammals, like some invertebrates (e.g. the bee *Apis mellifera*; Moore, 2001) and birds (e.g. the garden warbler *Sylvia borin*; Biebach, Falk & Krebs, 1991), may be able to use the circadian pacemaker as a continuously consulted clock to recognize circadian phase (a marker for local time in entrained animals) and remember that certain events (e.g. social encounters) recur at particular circadian phases.

Social stimuli could also influence the circadian programme by classical (Pavlovian) conditioning processes. For example, if social stimuli, such as an alarm, a radio or a spouse, reliably predict the daily occurrence of photic stimulation, such as from turning on room lights or opening window shades, the nonphotic stimulus (which in isolation may be neutral) could come to mimic photic effects on the clock by conditioning (Amir & Stewart, 1996; Amir *et al.*, 2002). A social stimulus could thereby acquire zeitgeber properties sufficient to substitute for or reinforce the actions

of light on circadian phase. Conditioning of this sort could occur via synaptic interactions between photic and nonphotic afferents within the SCN circadian pacemaker or at sites upstream.

Finally, the model must also include pathways from social stimuli to behaviour that bypass the circadian timing system, to acknowledge that social stimuli can alter the expression of daily rhythms by directly eliciting behaviours, without altering clock parameters or invoking temporal conditioning processes. When behaviours are elicited outside of the usual circadian phase of activity, the stimulus is considered to 'mask' true circadian phase (Aschoff, 1960; Mrosovsky, 1999a).

Empirical evidence for social influences on circadian rhythms in animals is evaluated next, beginning with the well-established phenomenon of maternal entrainment of foetal and neonatal circadian rhythms.

III. SOCIAL ZEITGEBERS IN ANIMALS

(1) Maternal entrainment

DeCoursey and co-workers have demonstrated that disruption of circadian rhythms by SCN ablation, under some environmental conditions, significantly increases mortality rates in wild-caught ground squirrels (*Ammospermophilus leucurus*) and chipmunks (*Tamias striatus*) reintroduced to their natural habitats (DeCoursey *et al.*, 1997; DeCoursey & Krulas, 1998; DeCoursey, Walker & Smith, 2000). This finding is consonant with our intuitions that the fidelity of daily rhythms of behaviour should have consequences for survival, and be subject to natural selection. Appropriate circadian timing of behaviour may be particularly crucial for survival during developmental stages when organisms are most vulnerable to predation and adverse environmental conditions. In at least some rodent species (e.g. the Siberian hamster, *Phodopus sungorus*), a functional, entrained circadian clock is also needed early in life to measure photoperiod, which regulates the timing of puberty (Goldman, 1989). It is therefore not surprising that in the few eutherian mammalian species that have been studied, the SCN are functional prior to birth, and are synchronized to local environmental time both *in utero* and postnatally prior to weaning (Reppert, 1995). This synchronization has been established as true entrainment, as distinct from masking. Although light can penetrate the uterus (Weaver & Reppert, 1989a), entrainment of the foetus to prevailing LD cycles is mediated exclusively by maternal signals. Maternal SCN ablation eliminates foetal synchrony to local time (Reppert & Schwartz, 1986), and shifting of maternal rhythms by restricted feeding schedules also shifts the timing of the foetal clock (Weaver & Reppert, 1989b).

The mechanisms by which maternal circadian signals entrain the foetal circadian clock include apparently redundant melatonin and dopamine inputs to SCN clock cells (Reppert, 1995; Viswanathan & Davis, 1997). Postnatally, responses of the rat SCN to melatonin and dopamine decline rapidly, and by the end of the first week of life, the SCN

switch sensitivity to photic signals, in parallel with retino-hypothalamic synaptogenesis (Reppert, 1995; Weaver & Reppert, 1995). However, some rodent species, including rats (*Rattus norvegicus*), field mice (*Apodemus sylvaticus*) and Siberian hamsters (*Phodopus sungorus*), retain a sensitivity to maternal zeitgebers that is sufficient to affect clock genes within the SCN (Ohta *et al.*, 2002) and entrain overt rhythms to the circadian cycle of a foster or natural mother up to the time of weaning (e.g. Viswanathan & Chandrashekar, 1985; Shimoda *et al.*, 1986; Takahashi *et al.*, 1989). The nature of the postnatal maternal zeitgeber in such cases is not certain. Rodent pups raised by an arrhythmic mother do not remain mutually synchronized, indicating that the mother is the primary source of entraining cues (Hiroshige, Honma & Watanabe, 1982; Reppert *et al.*, 1984). Critical maternal cues may be somatosensory, olfactory or auditory sensations, or their effects on arousal. Alternatively, maternal effects may be mediated by periodic food intake, imposed by a maternal rhythm of presence and absence from the nest.

The maternal behaviour of rabbits provides a striking example of periodic feeding of neonates. In this species, the doe visits the nest for only a few minutes each day, shortly after dusk. The pups obtain all of their daily milk during this single visit. The pups show increased activity and body temperature 1–2 h prior to feeding time, and these 'anticipatory' rhythms persist for at least three cycles in the absence of feeding visits, indicating that they are truly circadian clock-controlled (Hudson & Distal, 1989; Jilge, 1993; Jilge *et al.*, 2000). Whether this daily rhythm of anticipatory activity is mediated by the SCN or by a separate food-entrainable pacemaker, as in adult rabbits and other species, is uncertain (Jilge, 1992; Mistlberger, 1994). Nonetheless, the rabbit illustrates how social synchrony, across the lifespan, could be mediated by social influences on the timing of food intake.

Maternal entrainment ensures that in species where the neonate is not directly or regularly exposed to light, circadian rhythms at the time of weaning are nonetheless appropriately phased relative to local time. Some species are not entrained by social cues early in life. The short-tailed opossum (*Monodelphis domestica*) is a highly altricial marsupial born prior to SCN neurogenesis. In this species, the SCN, from its earliest inception as a functional circadian timer, is entrained by photic but not maternal signals (Rivkees & Reppert, 1992). As the neonates live on the mother, attached to a nipple, maternal stimuli are present continuously, rather than periodically. Moreover, as the opossum has no pouch, the neonates are fully exposed to the same photoperiod as the mother. The developmental programme of the opossum SCN reflects this early life history by proceeding directly to photic entrainment, with the maternal clock regulating only the neonate's exposure to light.

Whether sensitivity to maternal zeitgebers prior to weaning predicts sensitivity to social zeitgebers in adulthood has not been explored. However, there is no compelling reason to expect a relationship, as the potential adaptive value of social entrainment in adult animals may be unrelated to the necessity for maternal entrainment early in life in many species.

(2) Insights from behavioural ecology

A potentially rich source of evidence for social influences on circadian rhythms is the analysis of daily rhythms of mammalian behaviour in natural habitats. However, despite repeated calls for more field work on the phenomenology and adaptive significance of circadian rhythms, the circadian time dimension has been relatively neglected in behavioural ecology (Enright, 1970; Schoener, 1974; Regal & Connolly, 1980; Daan, 1981; Chandrashekar, 1982; Carothers & Jaksic, 1984; DeCoursey, 1989, 1990; Halle & Stenseth, 2000). The reasons may be primarily logistic, given the technical challenges inherent in collecting data around the clock, ideally over many consecutive days, with frequent sampling, from individual animals in social settings. Designing experiments is especially problematic, but not impossible. One elegant demonstration that social cues can serve as zeitgebers in a natural habitat is provided by the work of Marimuthu, Chandrashekar and colleagues, in their studies of nocturnal, cave-dwelling bats (*Hipposideros speoris*; Marimuthu, Subbaraj & Chandrashekar, 1978; Marimuthu, Rajan & Chandrashekar, 1981; Chandrashekar, 1982; Marimuthu & Chandrashekar, 1983). These bats roost in large colonies in true caves that provide complete darkness throughout the day. They leave the nest each dusk to forage after a period of 'light-sampling' at the cave entrance. Caged individuals prevented from seeing light nonetheless remained synchronized to local time. A bat that was caged alone in a cave for 17 days 'free-ran' with a $\tau > 24$ h (free-run refers to the state of a rhythm in the absence of an effective zeitgeber, as indicated by a progressive drift relative to local time). This and other work supports the idea that interactions among members of the same species may participate in the process of entrainment. However, most of the evidence from field work is purely descriptive, and does not illuminate mechanism. In another widely cited study, for example, beaver (*Castor canadensis*) families (2–5 individuals) over-wintering in snow-covered lodges were reported to express free-running circadian rhythms of group activity (Bovet & Oertli, 1974; Potvin & Bovet, 1975). For such a group rhythm to be detectable, individuals must be synchronously active. This finding has been interpreted as evidence for social entrainment within the group, either by mutual coupling among the multiple, oscillating animals, or by entrainment of subordinates to a dominant 'pacemaker' individual. However, from the available data, it cannot be ruled out that individual beavers were free-running independently, albeit with very similar τ , or that a dominant individual masked the true phase of the circadian clock in other group members. The same considerations apply to the evidence for circadian rhythms of group activity within colonies of blind mole rats (*Cryptomys damarensis*), a eusocial species adapted to a subterranean habitat (Lovegrove, Heldmaier & Ruf, 1993). To establish that the group circadian phase and τ are true for any individual animal, the subject must be assessed in the absence of social cues or other potential zeitgebers for at least one circadian cycle.

Many other field studies have documented daily rhythms of activity that are either in phase (synchronous), or are phase-displaced (segregated) among members of the same

species or between competitor or predator-prey species (e.g. Regal & Connolly, 1980; Kotler, Brown & Subach, 1993; Ziv *et al.*, 1993; Kotler, Ayal & Subach, 1994; Halle & Stenseth, 2000; Jones, Mandelik & Dayan, 2001). Synchronous activity within or between species has a variety of possible functions, including 'safety in numbers' from predators, protection of territory from competitors, and acquisition of mates or prey (Enright, 1970; Daan, 1981; Daan & Aschoff, 1982; Halle & Stenseth, 2000). Temporal segregation may serve to reduce competition for resources, permitting sympatric species to time-share overlapping spatial habitats (a strategy that can be effective where these resources are rapidly renewed). The extreme of temporal segregation is that between nocturnal and diurnal species, and such species may rarely interact, but there are also examples of segregation resulting from direct competition, with dominant individuals or dominant species occupying a preferred temporal niche (e.g. Skolnik, 1971; Kenagy, 1973; Greenwood, 1978; Glass & Slade, 1980; Wojcik & Wolk, 1985; Haim & Rozenfeld, 1993; Ziv *et al.*, 1993; Ziv & Smallwood, 2000; Kronfeld *et al.*, 2001). However, these studies do not reveal whether the phase of the circadian clock is truly altered, or whether synchrony and segregation reflect 'masking' effects or learning processes based on a circadian time sense. Field studies can be designed to include assessments of true circadian phase, but laboratory studies permit greater stimulus control and opportunities for analyses at the cellular and molecular levels.

(3) The Syrian hamster: non-specific arousal as mediator of social zeitgebers

In a review of circadian rhythms of animal behaviour, Rusak (1981) noted that '*If social synchronization does not represent a simple masking effect, it implies susceptibility of a central timekeeper either to social events as zeitgebers or to feedback from activity that is stimulated by social contact. Either possibility suggests a significant and largely unexplored sensitivity in the circadian system.*' These comments anticipated the description of a phase-response curve (PRC) to a social stimulus, first reported by Mrosovsky (1988) in work with the Syrian hamster (*Mesocricetus auratus*). This report was a catalyst for the current wide interest in nonphotic (behavioural) entrainment of circadian rhythms in mammals. The idea that arousal (a correlate of social interactions) might affect circadian timing was first suggested by Aschoff (1960), and given some empirical validation by evidence that an arousing behaviour, wheel running, can alter τ (Aschoff, Figala & Poppel, 1973; Yamada *et al.*, 1988), but Mrosovsky's (1988) report of entrainment and phase shifting to brief agonistic encounters between hamsters, complete with a bi-directional PRC, placed social cues on an equal footing with light as a zeitgeber. However, the phase shifts in the initial study were small, and could be mimicked by behavioural disturbances induced by non-social stimuli, e.g. changing the hamster's cage or litter. Much larger effects were soon documented (e.g. Fig. 2), but these were also induced by non-social stimulation of running activity (e.g. Reeb & Mrosovsky, 1989; Van Reeth & Turek, 1989; Wickland & Turek, 1991; Gannon & Rea, 1995) or arousal (Antle & Mistlberger, 2000). These data suggest that any

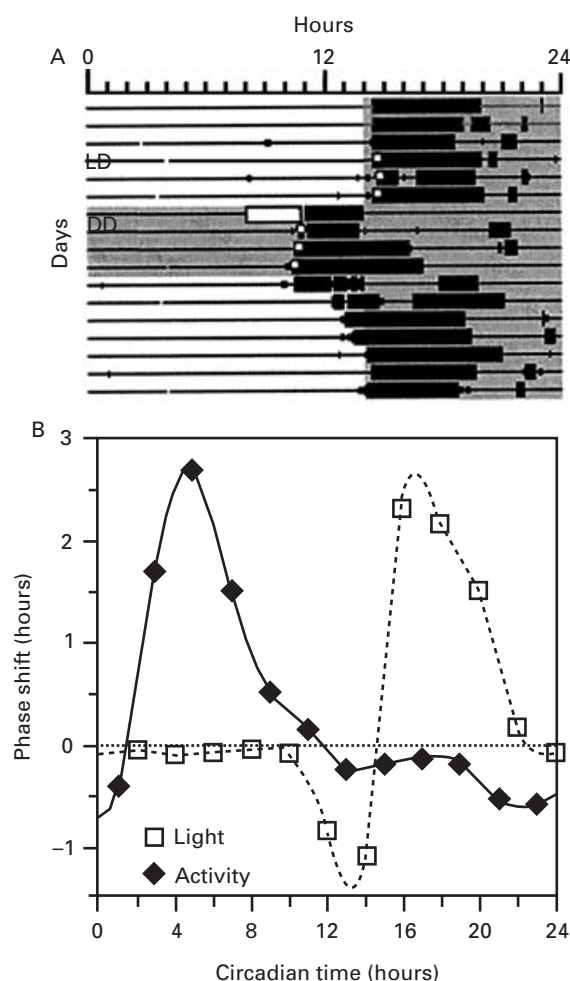


Fig. 2. (A) Wheel running activity of an 'intruder' male Syrian hamster (*Mesocricetus auratus*) illustrating a large phase advance shift induced by exposure to a 'resident' male hamster for 3 h (denoted by the open box). Each line represents 24 h, plotted in 10 min bins from left to right. Consecutive days are aligned vertically. Heavy bars indicate time bins during which wheel running occurred. Shaded areas indicate lights-off. Open squares indicate computer-detected activity onsets used for measuring phase shifts. The intruder male was physically smaller than the resident, and was scored as socially subordinate by behavioural criteria. (B) Phase response curves to light pulses (open symbols; replotted from Takahashi *et al.*, 1989) and 3-h bouts of wheel running activity (filled symbols, replotted from Mrosovsky *et al.*, 1989), illustrating the size and direction of phase shifts induced as a function of the circadian phase at which the stimuli were initiated. Circadian time (CT) in hours is referenced relative to the onset of the daily wheel-running rhythm, denoted CT12 by convention.

stimulus that is sufficiently arousing may have significance as a zeitgeber. The title of the seminal Mrosovsky (1988) paper, '*Phase response curves for social entrainment*', is thus ironic, as the data demonstrate that social interactions are entirely unnecessary to produce the nonphotic PRC.

Although non-specific arousal of Syrian hamsters can induce phase shifts comparable in magnitude to photic

stimuli, social cues have been reported to have weak or no phase resetting effects in several studies. In some cases, the hamsters were not in physical contact (Davis, Stice & Menaker, 1987; Gattermann & Weinandy, 1997), but even physical contact may not be sufficient if the animals become habituated to continuous or periodic exposure to the social stimuli (e.g. Honrado & Mrosovsky, 1991). Social synchrony may also require the full range of senses, as two studies that used blinded hamsters reported no entrainment to social contact that was either continuous (Refinetti, Nelson & Menaker, 1992) or periodic (Aschoff & von Goetz, 1988; but see their Fig. 1 for clear examples of phase shifts consistent with the nonphotic PRC reported by Mrosovsky, 1988).

Sensitivity of the circadian clock to non-specific arousal could serve as an adaptation for adjusting circadian timing following significant social interactions. Consistent with this idea, exposure to the sight, sound and smell of a female hamster in oestrous 4 h before the usual time of lights-off can induce small phase advances in the timing of activity onset in male hamsters entrained to LD 14:10 h (Honrado & Mrosovsky, 1991). This result is notable in demonstrating that a socio-sexual stimulus can be of sufficient strength to modify the phase angle of entrainment to LD, and such adjustments may provide a competitive advantage in acquiring a mate. However, the effect appeared to be dependent on the expression of wheel running during exposure to the female and, again, much larger effects have been reported when running was stimulated by confinement to a novel running wheel or by a triazolam injection (Turek & Losee-Olson, 1987; Mistlberger, 1991a; Mrosovsky & Janik, 1993; Sinclair & Mistlberger, 1997). Moreover, in a LD re-entrainment paradigm, hamsters confined to a novel wheel during the first hour of darkness following an 8 h advance of the LD cycle showed a greatly accelerated rate of re-entrainment, whereas hamsters provided with an oestrous female and permitted to mate rather than run did not (Honrado & Mrosovsky, 1989). These results complicate the notion that arousal-induced shifting in hamsters is an adaptation primarily for helping potential mates find each other. A successful mating episode would seem *a priori* to be the most likely type of social interaction to induce a phase shift (i.e. to 'remember' the time of a rewarding encounter by adjusting circadian pacemaker phase), and yet hamsters that mated failed to shift rapidly. Hamsters exhibit post-coital quiescence, which may limit the duration of mating-induced arousal. If the circadian clock has a high threshold for arousal-induced shifting (i.e. requiring a more sustained bout of arousal), it may be unaffected by typical bouts of mating, however rewarding these may be. Why this should be so is a puzzle, and suggests a non-social function for arousal-induced shifting, elaborated further below.

(4) Rats and mice: social hierarchies, stress and learning

Some of the earliest studies of social influences on circadian rhythms in mammals were motivated by the desire to better understand the behavioural ecology of urban pests, particularly rats and mice (e.g. Barnett, 1975; Calhoun, 1962, 1975). These and later studies, many of which utilized elaborate

semi-natural enclosures with burrow systems appropriate for semi-fossorial animals, demonstrated that daily patterns of rodent activity can be strongly influenced by social status within a resident community. In rats and mice of various strains, the activity and feeding rhythms of dominant and subordinate colony members have been observed to differ in phase and amplitude (e.g. Calhoun, 1975; Farr & Andrews, 1975). Typically, subordinates, compared to dominants, exhibited more activity and feeding during the light period, and thus had lower amplitude LD variations in behaviour. In some cases, dominants were the first to emerge from the burrow system following lights-out, whereas subordinates emerged substantially later (Farr & Andrews, 1975; Blanchard *et al.*, 1995). These effects may be contingent upon or exacerbated (e.g. loss of overt rhythms in subordinates) by overcrowding (Calhoun, 1975; Farr & Andrews, 1975), although small sample sizes and possibly inappropriate use of cosinor curve-fitting analytical techniques leave interpretation of some of these data open to question.

These ethological studies of social groups under LD cycles were not designed to elucidate mechanisms by which social interactions affect the apparent phase and amplitude of daily rhythms. However, if differences in the timing of overt rhythms in LD are due to changes in pacemaker phase, rather than simple masking, then it should be possible to phase shift or entrain rats and mice by daily schedules of social interaction in otherwise constant conditions, particularly if there is a dominant-subordinate hierarchy. If differences in the amplitude of measured rhythms reflect changes in pacemaker amplitude, then, according to limit-cycle models of circadian clocks, social interactions may also be accompanied by changes in the PRC to other stimuli (i.e. the magnitude of phase shifts to light may be altered). As social interactions may acutely alter locomotion and feeding, and may be differentially stressful for dominant and subordinate individuals (Koolhaas *et al.*, 1997), correlates of activity, food intake and stress are candidate stimuli to mediate any effects of these interactions on pacemaker phase, amplitude or τ .

Three experimental strategies have been used to examine mechanisms by which social interactions affect rhythms in rats and mice; cohabitation (i.e. two or more subjects in a single cage, to test for mutual entrainment), repeated daily interactions at the same phase (to test for entrainment to a periodic social stimulus), and a single interaction at a pre-determined phase (to test for phase shifts to an acute stimulus). Cohabitation experiments using pairs or small groups of preweaned or adult rats have generally produced little evidence for inter-individual synchronization of free-running activity rhythms. Three studies used blinded rats (Takahashi *et al.*, 1978; Hiroshige *et al.*, 1982; Reppert *et al.*, 1984), and one used sighted rats in constant dark (DD) (Richter, 1970). The latter study is notable as the subjects were male-female dyads that failed to entrain mutually despite successfully mating when their active periods overlapped. Positive evidence for social synchrony is provided by one study showing that single groups of rats or mice entrained to LD retain a normal-amplitude group activity rhythm for at least five days in LL (Stupfel *et al.*, 1981), and a second study showing the gradual emergence of a group circadian rhythm of

metabolism from two groups of rats housed together in DD, following entrainment to LD cycles in antiphase (Stupfel *et al.*, 1989). Evidence for a group rhythm in DD or LL implies synchronous activity of individuals, but whether apparent synchrony was due to mutual entrainment or masking from dominant individuals cannot be determined from these data.

Mice appear to be more likely to show synchronous activity rhythms in cohabitation experiments, but the database is modest in size. In one experiment, pairs of deer mice (*Peromyscus maniculatus*) with different free-running periods exhibited synchronous activity when cohoused, with a compromise τ closest to that of the dominant animal (Crowley & Bovet, 1980). In a few of these cases, masking could be ruled out because the phase from which the animals free-ran when separated was greatly displaced from that predicted from the phase prior to cohousing. There is an earlier report that single-housed blind mice in a colony room showed rhythms in synchrony with LD if sighted mice were housed in adjacent cages (Halberg *et al.*, 1954), but it is unclear whether this was true entrainment or masking.

A number of experiments have examined the effects of a single social interaction on circadian rhythms, using the resident-intruder paradigm as a model of psychosocial stress (social defeat of a subordinate intruder by a dominant resident is a potent stressor; Koolhaas *et al.*, 1997). The most thorough evaluation was carried out by Meerlo and colleagues, in studies of rats. Single episodes of social defeat in LD or DD attenuate the amplitude of overt circadian locomotor and body temperature rhythms (Meerlo *et al.*, 1996, 1999; Meerlo, Overkamp & Koolhaas, 1997a). However, this is not accompanied by a change in the magnitude of phase shifts to light, suggesting that the effect is not due to a change in the amplitude of the circadian pacemaker (Meerlo *et al.*, 1997b). Moreover, in DD, single or double bouts of social stress in the mid-rest or mid-active phase altered neither the phase nor the τ of free-running rhythms (Meerlo *et al.*, 1997b; Meerlo & Daan, 1998). The latter of these two studies included a sociosexual stimulus condition (acute exposure of male rat to an oestrous female), which also did not induce phase or τ changes. No studies have attempted to entrain rats to scheduled daily bouts of social stress. As only a few circadian phases have been tested in the phase shift studies, the PRC to social defeat is not sufficiently complete to make predictions about the likelihood of entrainment. Comparable PRC studies of acute psychosocial stress in mice are lacking. Syrian hamsters, by contrast, can be markedly phase shifted by 3 h exposure to dominant resident or subordinate intruder hamsters (Mistlberger *et al.*, 2003), and some exhibit small shifts to intra-peritoneal saline injections that induce a cortisol response (Mead *et al.*, 1992). However, Syrian hamsters do not exhibit phase shifts in response to other stressful procedures, such as physical restraint (Van Reeth *et al.*, 1991; Mistlberger *et al.*, 2003) or confinement to a platform over water (Mistlberger *et al.*, 2003), or to single injections or daily infusions of glucocorticoid agonists (Albers *et al.*, 1985; Janik, Nest & Janiga, 2001), or the anxiogenic α_2 antagonist yohimbine (I. Webb & R. Mistlberger, unpublished observations, 2002). Stressful stimuli and adrenal or sympathetic autonomic responses

thus do not appear to cause phase shifts, and may actually impede shifting if hamsters have limited opportunity to be active when stressed.

Other studies have used noxious non-social stimuli to assess stress effects on circadian rhythms in rats. However, only one of these was conducted in DD (Barrington *et al.*, 1993). This study reported entrainment in only 10 % of rats subjected to a daily 30 min bout of immobilization or novelty, or to a minute or two of handling. Stable entrainment in these few cases occurred when the daily manipulations overlapped with the transition from the active to the rest portion of the daily rest-activity cycle, i.e. circadian phases that have not been tested in the social stress phase shift studies.

A few studies have examined the effects of forced treadmill running on circadian rhythms in rats and mice. It is not certain that this procedure constitutes a stress stimulus, as rats and mice are avid runners and are likely to habituate to any stress effects over the several weeks of daily testing. Rats can be entrained to 3 h daily treadmill sessions but only when τ is very close to 24 h, suggesting that forced running is a weak zeitgeber at best in this species (Mistlberger, 1991b; Strijkstra, Meerlo & Beersma, 1999). This conclusion is reinforced by studies of restricted daily feeding schedules in constant light (LL) or DD, which result in an intense bout of food-anticipatory wheel running beginning 1–3 h prior to the daily mealtime, but which rarely entrain the free-running (light-entrainable) circadian rhythm of activity (Mistlberger, 1994; Stephan, 2002). Mice are more readily entrained to daily schedules of forced treadmill running (Edgar & Dement, 1991; Marchant & Mistlberger, 1996), but entrainment is gradual (only small daily phase adjustments are evident), and clear phase shifts in response to a single bout of forced or voluntary running, at any circadian phase, are rarely observed in blind or sighted mice in DD (Marchant & Mistlberger, 1996). Thus, in both rats and mice, forced running appears to be a weaker zeitgeber by comparison with stimulated running in hamsters. Nonetheless, the effect is sufficiently robust that social stimuli or non-social stressors could potentially entrain circadian rhythms in these species by stimulating activity.

There are numerous studies of acute social or non-social stressors (handling, shock, restraint) applied to rats at the same circadian phase over successive days in LD. Rats fail to learn to avoid a shock presented at a fixed time each day (Bolles *et al.*, 1974), but may show changes in circadian rhythms suggesting that they do anticipate the shock. The most common effect is a change in general activity, body temperature or other autonomic variables just prior to, or at the usual time of the stress test (e.g. Imada, Kondo & Imada, 1985; Eikelboom, 1986; Ottenweller, Pitman & Natelson, 1987; Ottenweller *et al.*, 1989; Tornatzky, Cole & Miczek, 1998). These changes may persist over many extinction days. This apparent 'memory' for circadian phase could reflect a 'time-stamping' process (also referred to as 'time-sense', or *zeitgedächtnis*), whereby any arbitrary circadian phase can be discriminated and stored in memory in association with the stress event memory. Alternatively, it could reflect a classical conditioning process, whereby circadian phase has by association become a conditioned

stimulus for a conditioned autonomic response. A third possibility is that the daily stress test may displace or stimulate feeding, which may engage the food-entrainable pacemaker, and produce anticipatory behavioural and autonomic responses that are coincidental with the usual time of stress induction. The possibility that effects of stress on circadian rhythms are secondary to changes in feeding has not been evaluated, to our knowledge.

(5) The case for species-specific auditory or olfactory zeitgebers

Studies with hamsters, rats and mice suggests that entrainment and phase shifts to social stimuli, to the extent that they occur, are likely to be mediated by neural and/or endocrine correlates of non-specific arousal or associated locomotor activities. A similar non-specific arousal mechanism may underlie social synchrony observed within groups of cohabiting bats, beavers and eusocial mole rats (discussed above). According to this view, any social stimulus capable of arousing an animal could mediate social entrainment. This does not rule out the possibility that in some species, the social zeitgeber function is limited to only certain sensory modalities. For example, there is one report that, unlike *Hipposideros speoris* bats (noted above), bats of the species *Taphozous nudiventris kachhensis* confined to a dark cave with 400 unrestrained *Hipposideros speoris* bats do not entrain to local time, despite the raucous auditory, visual and somato-sensory (air disturbance) stimuli that herald the daily mass exit to forage at dusk and mass return to roost at dawn (Chandrashekar, 1982; Marimuthu & Chandrashekar, 1983). These two species emit ultrasonics at different frequencies, which invited speculation that ultrasonics may have a species-specific social function in synchronizing daily rhythms. However, it was not shown that *Taphozous nudiventris kachhensis* bats entrain even to their own species, which is a necessary first step to evaluate the role of species-specific auditory cues as agents of social entrainment. Auditory stimuli can entrain circadian rhythms in birds (Gwinner, 1966; Menaker & Eskin, 1966), but sounds do not have to be from the same species (Lohmann & Enright, 1967; Reeb, 1989), which is consistent with a non-specific arousal mechanism for social entrainment.

A recent report of social effects on circadian rhythms in fruit flies (*Drosophila melanogaster*) suggests that olfactory signals can function as zeitgebers in that invertebrate species (Levine *et al.*, 2002). Olfactory cues (possibly pheromonal) have also been implicated as zeitgebers in a mammalian species, the degu (*Octodon degus*). The degu is a diurnal rodent that lives communally in small colonies of extended families that include female and male adults and offspring, and is thus an interesting model species by which to explore social effects on daily rhythms. Female but not male adults have been reported to re-entrain more rapidly to a 6 h phase advance or delay of LD if they are housed in a cage with a female or male already entrained to the new LD cycle (Goel & Lee, 1995a,b, 1996; Goel *et al.*, 2000). Females showed some phase and τ changes when co-housed in DD with females that were either entrained to a daily 1 h light pulse delivered in a separate room (thus having $\tau = 24$ h), or were

also free-running (Goel & Lee, 1997). Females also showed accelerated re-entrainment to a LD shift by continuous exposure to the odour of a group of five females, and were entrained or showed 'partial entrainment' to a daily schedule of odour exposure (Governale & Lee, 2001). The sex difference appears to be mediated by testosterone, as social facilitation of re-entrainment was evident in adult males after castration and was absent in adult females after testosterone treatment (Jechura, Walsh & Lee, 2003).

Although these effects have been interpreted as evidence that conspecific odours can serve a weak zeitgeber function in female degus, the data and their interpretation are in some respects not compelling. Degus have relatively imprecise daily activity rhythms, thus objective measurement of phase in these animals is problematic, and some of the reported effects are indeed difficult to see in the published activity charts. In cases where degus free-running in DD were exposed to a social odour for a limited time each day, only one example of stable synchrony has been provided (Fig. 1 in Governale & Lee, 2001). This animal clearly had a 24 h activity rhythm that matched the period (T) of the daily odour stimulus, but for this to qualify as entrainment, i.e. to rule out the possibility that τ was by coincidence 24 h, a non-24 h free-run must be established in the absence of the daily social stimulus. Alternatively, it must be shown that this animal's rhythm remains synchronized to the daily cycle of odour exposure if T is lengthened or shortened, and free-runs from that phase when the odour cycle is removed.

In other cases, daily exposure of free-running degus to conspecific odours was reported to induce 'temporary entrainment'. However, entrainment is by definition phase and τ control, yet 'temporary entrainment' as reported occurred across a wide range of phase angles, both within and across animals (Governale & Lee, 2001). Moreover, there was no significant relationship between the phase angle of temporary entrainment and τ . Given that episodes of temporary, or 'partial' entrainment, were often quite short (approximately 50% were 3–7 days in duration), it is conceivable that many of these reflect spontaneous variations in phase or τ , rather than phase control by social cues. The data are thus, at best, only weak evidence that social cues can serve as a zeitgeber in degus. More robust effects might be evident if the animals could interact physically as they would in a natural colony.

Despite the weak evidence for a zeitgeber action of social stimuli in degus housed without LD cycles, several studies reported that social odours could facilitate reentrainment to a shifted LD cycle. In these experiments procedures to rule out masking (e.g. Mrosovsky, 1989) were not always employed. This reservation aside, the mechanism by which odours from conspecifics might facilitate re-entrainment is unclear. Circadian gating of odour emission or reception was not demonstrated, thus it is unknown whether the hypothetical stimulus was constant (thus containing no timing information) or periodic. One possibility is that odour emission and reception were constant, but that the presence of the odours, on the first cycle of the LD shift, promoted arousal when the lights were on, thereby increasing light exposure or light input to the retina (e.g. by autonomic effects on pupil size). Even small changes in light input could

have a significant effect on re-entrainment rate. Similar effects on light input could explain why exposure of rats to a neutral odour (cedar chips) can enhance light-induced phase shifts and expression of c-fos within the SCN, while the odour alone has no effect on either variable (Amir *et al.*, 1999). Note, however, that in hamsters and mice, arousal induced by wheel running or sleep deprivation procedures attenuates rather than potentiates light-induced phase shifts (Ralph & Mrosovsky, 1992; Mistlberger, Landry & Marchant, 1997; Mistlberger & Antle, 1998; Mistlberger & Holmes, 1999; Challet *et al.*, 2001). It remains to be seen whether the different effects on light-induced clock shifting reported in these studies are related to the different species, experimental procedures or stimuli. In any case, these data indicate that stimuli with neither social significance nor zeitgeber action can modulate responses to photic zeitgebers and potentially influence rates of re-entrainment.

(6) Primates and the nonphotic PRC in diurnal mammals

Many primates live in organized social groups but surprisingly little work has been done to explore whether and how social interactions might affect circadian timing in individual group members. There are reports that the rest-activity cycles of rhesus (*Macaca mulatta*) and macaque (*Macaca macaca*) monkeys in the laboratory can be synchronized by social stimulation, but these studies did not use procedures to rule out masking effects (Rohles & Osbaldiston, 1969; Rohles, 1971; Yellon & Hauty, 1971; Fuselier, 1973). One study reported that a squirrel monkey (*Saimiri sciureus*, gender not reported) housed alone in LL failed to entrain to 8 h daily exposure to the sight and sound of a female squirrel monkey entrained to LD (Sulzman, Fuller & Moore-Ede, 1977). This result is often cited in the social entrainment literature, but it is worth emphasizing that it is a case study, that only a limited range of phase relations were examined, and that free-running τ was > 25 h, which may have been out of the range of entrainment. Also, there was no physical contact between the two subjects. Sulzman *et al.* (1977) also reported that a larger sample of monkeys caged individually in isolation boxes in LL did not entrain to the sounds of other colony monkeys entrained to LD.

By contrast, strong evidence for social entrainment of circadian rhythms has been obtained from studies of the common marmoset (*Callithrix jacchus*; Wechselberger, 1994). Marmosets housed alone responded to auditory stimuli from other marmosets in the colony room, but these stimuli failed to entrain free-running rhythms (Erkert, Nagel & Stephani, 1986). However, when mating pairs were co-housed in LL, they showed extended periods of synchronous activity (Erkert & Schardt, 1991). When housed together after several weeks apart, their rhythms quickly synchronized, in at least one case by a large acute phase shift. When separated again, they free-ran from the same phase, but with different periods. In some cases, pairs of individuals became synchronized with other pairs that were in both auditory and visual contact. Synchrony between pairs that were only in auditory contact was evident only when the individuals were

closely related (e.g. a mating pair and their twin offspring). These data reinforce the evidence from work with other species that physical contact (or at least the sharing of physical space) is a primary determinant of social entrainment. In the absence of physical contact, cognitive factors (e.g. familiarity) may give sufficient meaning to vocalizations for these to serve as zeitgebers.

Most recently it has been demonstrated that isolated marmosets free-running in DD can be phase shifted or entrained by a 1 h daily arousing disturbance by cage agitation and the occasional squirt from a water pistol (Glass *et al.*, 2001). This finding suggests that social influences on circadian rhythms in marmosets are likely to be mediated by non-specific arousal. Notably, the nonphotic PRC obtained by this procedure is consistent with the nonphotic PRC of the nocturnal Syrian hamster (Fig. 2B). A similar nonphotic PRC in diurnal European ground squirrels (*Spermophilus citellus*) has been inferred based on the phase angle at which the squirrels entrain to a 3 h daily bout of stimulated running (Hut, Mrosovsky & Daan, 1999). Another diurnal rodent, the palm squirrel (*Funambulus pennanti*), exhibits mutual entrainment between pairs housed in LL, such that their rest-activity cycles are in phase, as inferred from the phase at which they free-run after being separated (Rajaratnam & Redman, 1999). This is the same phase relation that nocturnal rodents assume in cases of mutual entrainment between individuals co-housed in DD or LL (e.g. Crowley & Bovet, 1980). Thus, it appears that among mammals, the circadian pacemaker's intrinsic rhythm of sensitivity to nonphotic zeitgebers, like its sensitivity to photic input, is the same in diurnal and nocturnal species.

(7) Social influences in animals: what remains to be discovered

The study of social influences on circadian rhythms in animals has a relatively short history, and only a few species have been examined in any detail. Additional work is needed on several fundamental issues.

Foremost among these is the functional significance of nonphotic zeitgebers for animals in their natural habitats. These functions may well differ across species. In the case of nocturnal, cave-dwelling bats, for example, it appears that social cues can substitute for photic cues to maintain synchrony with local time. A PRC for social stimuli is not available for the bat, but this could be of either the classic photic type (phase delays to evening and advances to morning stimuli) or the nonphotic type (advances to early evening and delays to morning stimuli). In either case, social cues in this species appear to serve as a surrogate or reinforcement for photic entrainment. Adult Syrian hamsters, by contrast, live solitary lifestyles. Social cues are therefore likely to be sporadic, and presumably do not serve to reinforce photic entrainment. Rather, they may compete with light to fine-tune the phase of entrainment to LD in accordance with recent social experience. In species that do live in social groups, particularly those that are not regularly exposed to light (e.g. subterranean mole rats or non-hibernating rodents over-wintering under snow pack), the nonphotic PRC would promote synchronous activity among members

of the colony, which may have adaptive value, e.g. by ensuring synchronous thermoregulatory huddling during the sleep period, or promoting more consolidated (and functionally restorative) sleep bouts.

It remains perplexing that something as social and as salient as mating is not sufficient to facilitate rapid phase shifts in hamsters, in a paradigm where arousal by running is effective (Honrado & Mrosovsky, 1989). This begs for an additional, non-social interpretation of behavioural influences on the clock. In mice, a high concentration of spontaneous locomotor activity early in the active period is associated with a shorter τ in DD (Edgar, Martin & Dement, 1991) and an advanced phase of activity onset in LD (Mistlberger & Holmes, 2000), and physical restraint at this time induces small phase delay shifts (Van Reeth *et al.*, 1991). These results suggest that locomotor activity at the transition from subjective day to subjective night has a small phase advancing effect on the clock. Social interactions early in the evening thus have the potential to advance the phase of entrainment by stimulating activity or arousal. Evening light exposure, by contrast, delays the clock. The opposing effects of nonphotic and photic stimuli at dusk may play a role in keeping activity onset close to some preferred phase of entrainment (e.g. tracking dusk). Thus, an additional function of social, nonphotic inputs to the clock, at least at certain phases, may be to enhance the precision of photic entrainment.

A second broad question to resolve concerns the neural or metabolic pathways by which social stimulation affects pacemaker phase or τ . Behavioural studies suggest that social influences may be mediated entirely via neural representations of non-specific arousal. Pacemaker resetting by non-specific arousal has the economical feature of endowing the circadian system with a sensitivity to interactions with members of the same or different species. However, the possibility that in some species, some species-specific stimuli (e.g. sounds or smells) have privileged access to the circadian system cannot be ruled out, particularly given recent suggestions that olfactory stimuli can modulate cellular responses to light in the rodent SCN (Amir *et al.*, 1999). The SCN receives many inputs that presumably encode nonphotic information, but so far only the geniculohypothalamic tract, arising from the thalamic intergeniculate leaflet, has been identified in more than one species as necessary for phase resetting or τ changes in response to behavioural activity (Janik & Mrosovsky, 1994; Maywood *et al.*, 1997; Marchant, Watson & Mistlberger, 1997). The information coded by geniculohypothalamic inputs to the SCN remains uncertain (these neurons are also retinorecipient; Harrington, 1997). The possibility that social synchrony in some species could be mediated by direct effects of body temperature (regulated by social huddling) or metabolic fuels (regulated by socially scheduled feeding) on circadian clock cells has yet to be evaluated, but is given credence by evidence that both temperature and metabolism can affect and may entrain circadian clocks even in mammals (Rensing & Ruoff, 2002; Rutter, Reick & McKnight, 2002; Herzog & Huckfeldt, 2003).

A third question of importance concerns the role of moderator variables in determining nonphotic clock

resetting. Among these include age, gender, reproductive state, and social status. The nature of individual differences also needs explanation; in hamsters, for example, most but not all individuals exhibit phase shifts to stimulated arousal or social interactions (e.g. Mrosovsky, 1988; Antle & Mistlberger, 2000). Whether this is related to individual variability in stress reactivity, arousal or circadian clock parameters (e.g. τ and amplitude) is unknown.

Finally, little is yet known about the role of learning and memory in social effects on circadian timing. Rats appear to be capable of remembering the circadian phase at which food or escape routes are available (Boulos & Logothetis, 1990; Mistlberger *et al.*, 1996; Aragona *et al.*, 2002; Lukoyanov *et al.*, 2002; Pizzo & Crystal, 2002), but whether associative or computational learning processes mediate temporal synchrony or segregation between members of a species is unknown. Also, whether social stimuli can become conditioned stimuli for photic-like clock resetting has yet to be explored (see de Groot & Rusak, 2000; Daan, 2000; and Arvanitogiannis, Stewart & Amir, 2000, for discussion of difficulties establishing classical conditioning of circadian rhythms in rats to a non-photic, non-social stimulus).

IV. SOCIAL ZEITGEBERS IN HUMANS

Circadian rhythms in humans exhibit formal properties of free-run and phase-dependent resetting by photic stimuli that are entirely consistent with those of other mammals (Wever, 1986; Czeisler & Dijk, 2001). Thus it seems reasonable to hypothesize that the human circadian pacemaker might also be amenable to resetting by nonphotic stimuli, such as daily variations in arousal associated with social interactions. The efficacy and relative importance of light and social stimuli as circadian zeitgebers in humans has historically been a matter of contention (see reviews by Wever, 1979, 1989; Campbell *et al.*, 1995b; Czeisler, 1995). Influential studies by Aschoff, Wever and colleagues (Poppel, 1968; Wever, 1970, 1975; Aschoff *et al.*, 1971) suggested that artificial light (i.e. of typical indoor intensity) was a relatively weak zeitgeber and that social cues were both necessary and sufficient to maintain entrainment to local time. As recently as 1989, Wever concluded that '*the most relevant zeitgeber in humans is of social or behavioural nature*' (Wever, 1989). However, numerous studies have now demonstrated that light of sufficient intensity (e.g. approximately 1500–10 000 lx) can affect circadian τ , phase or amplitude (e.g. Wever, Polasek & Wildgruber, 1983; Czeisler *et al.*, 1986, 1989; Hoban *et al.*, 1989; Wever, 1989; Minors, Waterhouse & Wirz-Justice, 1991; Jewett, Kronauer & Czeisler, 1991, 1994; Honma *et al.*, 1995; Czeisler, 1995), and dose-response studies have revealed phase resetting effects of light at typical indoor intensities (e.g. 180 lx; Boivin *et al.*, 1996). By contrast, control procedures involving shifted sleep-wake and social interaction schedules without bright light stimulation produced little evidence for clock shifting (e.g. Duffy *et al.*, 1996; but see below for critique). Consequently, the initial proposition that social stimuli play

a major role in human circadian entrainment was revised to the extent that light acquired the status of dominant zeitgeber, while variations in sleep-wake and social cues were viewed as having negligible, if not zero direct drive on the pacemaker (Duffy, Kronauer & Czeisler, 1996). Is the human circadian system truly insensitive to social or other nonphotic stimuli, perhaps uniquely among mammals studied to date?

(1) Methodological issues: dim light sensitivity and near 24 h circadian period (τ)

To interpret the effects of social and other nonphotic manipulations on human circadian rhythms, associated changes in light exposure must be carefully considered. The most unambiguous method of testing social zeitgebers in sighted people would be to study them in DD. However, this is not a practical design for long-term studies. In 1980, Lewy and colleagues reported that light of 1500 lx, but not 500 lx, suppresses nocturnal melatonin synthesis (Lewy *et al.*, 1980), a response that is mediated by the retino-hypothalamic tract. This finding suggested that the human circadian pacemaker might be insensitive to light of less than approximately 1500 lx (i.e. indoor levels), a result that was consistent with the failure of human subjects to entrain to 24 h LD cycles in laboratory studies employing artificial light (e.g. Wever, 1970). If true, then typical indoor light should not represent a potential confound in tests of phase shifting or entrainment to social stimuli. However, subsequent work demonstrated significant suppression of melatonin by as little as 100 lx of light (Brainard, Rollag & Hanifin, 1997), significant clock resetting by even a few 10 s of lx or less (Boivin *et al.*, 1996; Kronauer, Forger & Jewett, 1999; Zeitzer *et al.*, 2000; Wright *et al.*, 2001), and evidence that sensitivity to light is increased following exposure to reduced levels of light (e.g. in quail, Meyer & Millam, 1991; in humans, Hebert *et al.*, 2002). Moreover, it is now accepted that the Aschoff-Wever protocol of self-selected light exposure in free-running subjects tends to lengthen τ , by differential stimulation of the phase delay and advance zones of the photic PRC (Klerman *et al.*, 1996). When this differential exposure is controlled using 'forced desynchrony' protocols, the average endogenous period is approximately 24.2 h (Czeisler, 1995; Hiddinga, Beersma & van den Hoofdakker, 1997; Czeisler *et al.*, 1999), rather than approximately 25 h as previously thought. Thus, any reports that humans can be synchronized to 24 h social or sleep-wake schedules must be considered in view of the evidence that the circadian clock is sensitive to very dim light and may have a free-running τ very close to 24 h. The recent demonstration that dark blue monochromatic light (maximum wavelength $\lambda_{\max}$ 456 nm) of low photopic intensity (3.3 lx) can suppress nocturnal melatonin production whereas red light ($\lambda_{\max}$ 548 nm) of 50 lx does not (Thapan, Arendt & Skene, 2001) adds the further complication that both the spectral composition of the light source and its photon flux must be controlled to rule out light as a confounding variable following manipulations of nonphotic stimuli or behaviour (Brainard *et al.*, 2001; Thapan *et al.*, 2001).

(2) Humans cohabiting

One intuitively powerful test of social entrainment is to house two or more people together in a time-free environment. Humans co-housed under such conditions in the laboratory have been reported to free-run in synchrony (Wever, 1975, 1979). However, these early studies permitted auxiliary light access, raising the possibility that the circadian rhythms of one subject were entrained or masked by the self-selected lighting schedule of the other. By contrast, Middleton, Arendt & Stone (1996) and Middleton, Stone & Arendt (2002) showed that neither social contact nor knowledge of clock time were sufficient to maintain synchrony among volunteers co-housed in 'dim' light (<8 lx). There are numerous other reports that humans in social contact may free-run independently in environments lacking regular LD cycles (e.g. Verniko-Danellis & Winget, 1979; Kennaway & Van Dorp, 1991; Steel *et al.*, 1995; Sorokin *et al.*, 1996). The absence of mutual synchrony in these cases indicates that social effects on the circadian clock, unlike photic effects, are weak and are probably gated by volition, i.e. humans can choose to attend to or to ignore periodic social cues, and the mere availability of such cues is not sufficient to ensure entrainment. The nature of individual differences in susceptibility (e.g. due to differences in τ , age, gender or other variables) to mutual synchrony has not been systematically explored.

(3) Manipulations of the sleep-wake cycle

For many people, social obligations, and proximate social cues (e.g. clock radios, spouses, parents or children), directly influence sleep and wake times. Thus, if these cues serve as zeitgebers, independently of their obvious role in determining light exposure, it is reasonable to consider the possibility that they would do so by their effects on behavioural state. According to this hypothesis, manipulations of the sleep-wake cycle, with or without social contact, should be capable of controlling the phase of the human circadian clock.

Field studies consistently show that the circadian rhythms of shift workers rotating from day to night shifts adapt slowly and incompletely or not at all despite large forced advances or delays of the sleep-wake cycle (Akerstedt, 1985; Rosa *et al.*, 1990; Eastman, 1991; Eastman *et al.*, 1995). Lack of adaptation is even observed in permanent night shift workers. Continued exposure to natural light appears to play a major role in impeding clock resetting to the night-shift (Czeisler *et al.*, 1990; Eastman *et al.*, 1994; Mitchell *et al.*, 1997). Thus, in conflict, photic inputs may dominate any nonphotic influences on circadian clock phase. Control of lighting is therefore crucial to evaluate experimentally possible zeitgeber actions of the sleep-wake cycle.

Unfortunately, most laboratory studies of clock resetting by manipulations of sleep-wake are complicated by corresponding changes in light exposure. Early studies reporting entrainment to daily auditory signals (for scheduling behavioural tests or physiological samples; Wever, 1970; Aschoff *et al.*, 1975) or a 4 h 'anchor' sleep (Minors & Waterhouse, 1981) in otherwise 'constant' conditions did not attempt to control light exposure. Subsequent studies have incorporated various procedures to separate photic and nonphotic effects.

One group of studies has shown that evening or morning bright light can phase shift circadian rhythms even if the normal nocturnal sleep period is held fixed (Czeisler *et al.*, 1986; Broadway, Arendt & Folkard, 1987; Lewy *et al.*, 1987; Dijk *et al.*, 1989; Drennan, Kripke & Gillin, 1989). Three studies have employed the reverse approach of shifting sleep-wake by a few hours within fixed evening and morning buffer zones of 'dim' light, with natural light exposure at other times of day. In two cases, the background dim light was reported as <10 lx, and sleep-wake displacement of 2 or 3 h failed to significantly phase shift the core body temperature rhythm [(Hoban *et al.*, 1991; Gordijn *et al.*, 1999; note that in Gordijn *et al.*, 1999 some shifting of the melatonin rhythm was observed, but the author's preferred explanation was that this did not reflect clock shifting)]. Another study with a similar design employed 'dim' light of <200 lx, and did report significant shifts following 3 h sleep-wake displacement (Jelinkova-Vondrasova, Hajek & Illnerova, 1999). However, the direction of the shifts was consistent with what would be predicted by manipulation of light exposure, i.e. advances when sleep was terminated early (resulting in more dim light exposure in the phase advance portion of the photic PRC), and delays when sleep was terminated late (resulting in less dim light exposure in advance portion of the PRC).

Others studies employing larger shifts of sleep time may be interpreted similarly. In these studies, a bout of sleep (at least 6 h bedtime), with lights off, was scheduled during the usual wake period, simulating either a nap, or a delayed or advanced sleep-wake schedule at least 6 h out of phase with the usual nocturnal sleep time (e.g. Honma *et al.*, 1995; Goichot *et al.*, 1998; Van Cauter *et al.*, 1998; Buxton *et al.*, 2000; Horowitz *et al.*, 2001; Sharkey & Eastman, 2002). Maximal background 'dim' lighting ranged from 37 to 500 lx across studies. Significant phase shifts were observed in each study, but again the direction of the shifts was consistent with a photic manipulation, i.e. delays or advances when dim light was absent during either the early morning (advance phase of PRC) or late evening (delay phase), respectively. Given the evidence that the human circadian pacemaker has at least a weak sensitivity to light throughout the day (Jewett *et al.*, 1997), a role for light in these observed phase shifts cannot be ruled out.

Displaced sleep/dark bouts have also been employed in phase- and dose-response studies of light-induced phase shifting. One protocol required subjects to remain awake through their subjective night, when the circadian clock is maximally sensitive to light, and to sleep during their usual subjective day (e.g. Czeisler *et al.*, 1989; Boivin *et al.*, 1994; Duffy *et al.*, 1996). Dim light of <10 – 15 lx was employed as a background during scheduled waking. Bright light (5 h) at 'night' was compared with 5 h of darkness during which the subjects were not permitted to sleep. Large shifts were induced by the bright light, and no shifts by the dark 'control' procedure, despite the social interactions used to keep subjects awake. This was interpreted as evidence that scheduled sleep-wake, and attendant social stimulation, have negligible drive on pacemaker phase. However, the control condition in these experiments creates a dim light 'skeleton' photoperiod, consisting of two periods of dim

light exposure each day, separating one 8 h dark period for sleep in the usual daytime from one 5 h dark period in the middle of the forced wake period at night (Fig. 3B). Two daily periods of light exposure can prevent clock shifting in animals (e.g. Pittendrigh & Daan, 1976; Sinclair & Mistlberger, 1997), and may impede a phase shifting effect of sleep-wake inversion in humans. While these experiments do not eliminate light as a confounding variable in interpreting the effects of scheduled sleep-wake on circadian phase, they do permit the substantive conclusion that inversion of the sleep-wake cycle, if it has any zeitgeber action, is weaker than a dim skeleton photoperiod.

In another group of experiments, subjects are required to maintain a sleep-wake schedule of some fixed period (T). If T is set at 18, 20 or 28 h, circadian rhythms of body temperature, melatonin and other variables free-run (forced desynchrony; e.g. Aschoff & Wever, 1976; Wever, 1986; Kelly *et al.*, 1999). Clearly, such schedules are well out of the range of entrainment of the circadian system, regardless of multiple photic and nonphotic cues. Another study in which subjects were exposed to natural zeitgebers under field conditions reported that two out of four subjects entrained to a 26 h sleep-wake cycle (Eastman, 1987). However, the relative contributions of photic and nonphotic stimuli could not be assessed. In laboratory studies, subjects have failed to entrain to sleep-wake schedules of 23.5, 23.66 and 24.6 h (Nakamura, 1996; Miyazaki *et al.*, 2001; Wright *et al.*, 2001). However, three studies have reported that humans can entrain to a 24 h sleep-wake schedule. Two of the studies are difficult to interpret, either because of exposure to relatively high background light (up to 200 lx) during the wake period (Nakamura, 1996), or because the schedule was maintained for only four days, with no procedures to rule out masking (Aschoff *et al.*, 1971). Given the evidence that human τ is very close to 24 h, more than four days is needed to assess entrainment with any confidence. In a third study, five of six subjects did entrain to a 24 h sleep-wake schedule maintained for up to 55 days (Wright *et al.*, 2001). Notably, in this study ambient lighting during scheduled waking was only approximately 1.5 lx in the angle of gaze (described as like dim candlelight). There is one additional, recent report that circadian rhythms can be advanced by a daily sleep-wake schedule of 23.66 h, with background lighting of <0.2 lx (Danilenko, Cajochen & Wirz-Justice, 2003). Phase lag of the melatonin and temperature rhythms relative to sleep-wake in these subjects suggest that this is at the lower limit of entrainment. The very low level of light employed in these latter two studies is suggestive that the critical zeitgeber was nonphotic. Nonetheless, if sensitivity to light increases sufficiently with prolonged exposure to dim light, then even candlelight may be adequate to mediate synchrony to a 24 h sleep-wake schedule.

In aggregate, although the most recent studies of sighted people in very dim light are suggestive, it remains uncertain whether entrainment to near 24 h sleep-wake schedules is due to photic or nonphotic inputs to the circadian clock. If scheduled sleep-wake is the zeitgeber, then by necessity the PRC to this complex behavioural stimulus must be roughly similar to that for light, with advances induced by early (dawn) waking, and delays by late (dusk) sleep onset. If

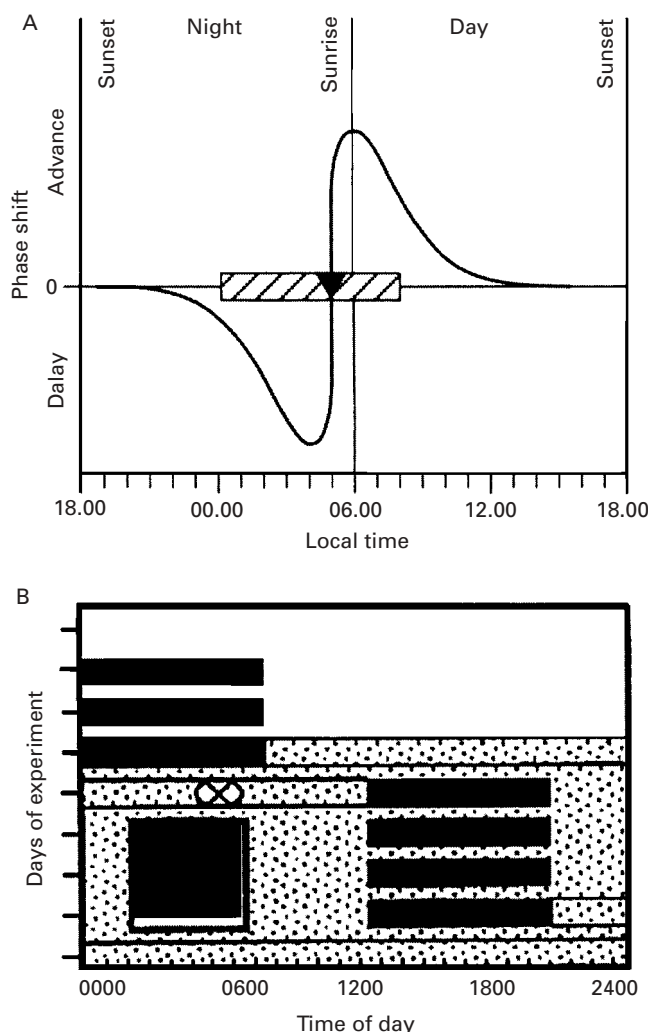


Fig. 3. (A) Schematic phase-response curve illustrating the relationship between the time of day (circadian phase) of light exposure and the expected direction and relative magnitude of the resulting phase shifts in humans (adapted from Eastman & Martin, 1999). The hatched bar represents the usual sleep time, and the arrowhead the usual time of the body temperature minimum (a standard marker for circadian phase). Light exposure prior to the body temperature minimum induces phase delay shifts, whereas light after the minimum induces advance shifts. Light during the day has small but detectable effects (Jewett *et al.*, 1997). (B) Schematic of the protocol of an experiment in which sleep time with lights off (denoted by the heavy black bars) was shifted back (phase delayed) by 12 h (adapted from Duffy *et al.*, 1996). Consecutive days are aligned vertically. Beginning on the day after the sleep/dark shift, subjects were also required to lie awake in the dark for 5 h (indicated by black box) up to the predicted time of the temperature minimum (indicated by the oval marked X) as determined during the constant routine prior to sleep schedule inversion. Research staff (i.e. social stimuli) were present to ensure that subjects stayed awake. During the remainder of the day subjects were exposed to continuous dim illumination (10–15 lx). This procedure resulted in no significant shifting of the circadian phase marker, suggesting that inversion of the sleep-wake schedule, and attendant social cues, has little effect on the

the PRC is bidirectional, then it should also be possible to entrain subjects to sleep-wake schedules slightly longer than endogenous τ . Parametric studies are needed to determine how the duration and timing of waking interact to determine entrainment. Ultimately, however, the only way truly to eliminate light as a confounding variable is to study either sighted people in total darkness, or blind people.

(4) Blind people

If light exposure is the true cause of entrainment to fixed sleep-wake schedules in sighted people, then blind people should be incapable of entraining to a 24 h day. This appears to be true for blind subjects who have been bilaterally enucleated. To our knowledge, all bilaterally enucleated subjects that have been studied in detail exhibited free-running circadian rhythms despite strong social and other nonphotic time cues (Lockley *et al.*, 1997; Skene *et al.*, 1999a,b). A significant percentage of totally blind people with intact eyes also free-run relative to the 24 h day (Lewy & Newsome, 1983; Sack *et al.*, 1992; Lockley *et al.*, 1997; Klerman *et al.*, 1998; Skene, Lockley & Arendt, 1999a). However, other individuals with no conscious light perception (approximately 35–60% across studies) appear to be entrained to 24 h (Sack *et al.*, 1992; Lockley *et al.*, 1997; Klerman *et al.*, 1998; Skene *et al.*, 1999a,b). A number of possible explanations for this phenomenon have been proposed (Klerman *et al.*, 1998): (1) photic entrainment occurring via an intact retino-hypothalamic pathway; (2) a free-running τ very close to 24 h; (3) circadian entrainment via extraocular photoreception; (4) nonphotic entrainment.

In a few totally blind subjects with intact eyes, bright light has been shown to suppress pineal melatonin synthesis acutely and phase shift its circadian rhythm (Czeisler, 1995; Klerman *et al.*, 2002). Suppression of nocturnal melatonin synthesis by light suggests that the circadian system in these people is not 'blind'. In these cases, there must be an intact retinal input to the circadian pacemaker, sufficient to mediate phase shifting and entrainment to a 24 h day. This input may originate from the recently discovered network of photosensitive, melanopsin-containing retinal ganglion cells that project to the SCN (reviewed by Hannibal & Fahrenkrug, 2002; Menaker, 2003). Nonetheless, other totally blind subjects with intact eyes have been identified that appear entrained to the 24 h day and yet do not exhibit melatonin suppression in response to light (Klerman *et al.*, 1998; Skene *et al.*, 1999a,b). In two of these subjects, an intense light stimulus (8 h, approximately 10 000 lx, for three days) also failed to induce phase shifts of their melatonin and core body temperature rhythms (Klerman *et al.*, 1998). In these cases, entrainment of the circadian clock by ocular photoreception is highly unlikely.

The possibility of entrainment by extraocular photoreception was raised following a report by Campbell & Murphy (1998). In later studies, however, extraocular light failed to suppress nocturnal melatonin levels (Lockley *et al.*,

pacemaker. However, shifting to nonphotic cues may be impeded by competition with the periods of light exposure that separate the two daily dark periods.

1998; Hebert, Martin & Eastman, 1999; Lindblom *et al.*, 2000*a*) or produce phase shifts (Eastman, Martin & Hebert, 2000; Lindblom *et al.*, 2000*b*; Wright & Czeisler, 2002) making it an unlikely explanation for entrained circadian rhythms in totally blind people.

Thus, it appears that, in at least some blind people, nonphotic cues associated with the 24 h day are sufficient to entrain the circadian pacemaker. Entrainment may fail in some individuals because of a relatively long τ , which may be out of the range of entrainment for weak nonphotic zeitgebers. Consistent with this idea, the group mean τ of blind subjects with free running rhythms is approximately 24.5 h (Sack *et al.*, 1992; Lockley *et al.*, 1997, 2000; Klerman *et al.*, 1998; Skene *et al.*, 1999*c*), significantly longer than the most recent estimates of τ in sighted subjects (Czeisler, 1995; Middleton *et al.*, 1996; Hiddinga *et al.*, 1997; Czeisler *et al.*, 1999). At least three explanations for this apparent difference in τ are possible. First, it could reflect aftereffects of photic entrainment and light history in the sighted subjects. For example, in animals released from LD entrainment into constant conditions, it may take weeks to months before a steady state of the free-running rhythm is reached (Aschoff, 1979). Second, τ in blind humans under field conditions could be lengthened by feedback from behavioural variables, analogous to shortening of τ by spontaneous wheel running in nocturnal rodents (Yamada *et al.*, 1988; Edgar *et al.*, 1991; Mrosovsky, 1999*b*). In sighted people, τ is usually measured under more sedentary laboratory conditions; similar laboratory studies of totally blind people are therefore needed to assess this possibility. Third, the longer τ in free-running blind people could reflect sampling bias, because it does not include those that appear entrained to the 24 h day. These individuals may have an endogenous τ close to 24 h, and within the range of weak 24 h nonphotic zeitgebers. Indeed, the possibility that some of these apparently entrained subjects have a free-running τ of 24 h cannot be ruled out. Again, laboratory studies are needed to compare τ in apparently entrained and free-running blind people in temporal isolation.

(5) Can exercise help?

The best evidence for nonphotic entrainment in a human may be the case study of a totally blind person by Klerman *et al.* (1998). Circadian rhythms in this subject, whose endogenous τ was estimated as 24.1 h, entrained to a 23.8 h sleep-wake schedule by phase advance. This subject did have an intact eye, but did not exhibit phase shifts or melatonin suppression to bright light, making it unlikely that entrainment was secondary to behaviourally determined variations in dim light exposure. Assuming that extraocular photoreception was also not involved, entrainment can be attributed exclusively to nonphotic stimuli, although which stimuli remain unspecified. The protocol in that experiment included a daily bout of exercise on a stationary bike. The evidence that circadian rhythms in animals can be shifted or entrained by bouts of forced or voluntary exercise raises the possibility that exercise could increase the strength of sleep-wake schedules as circadian zeitgebers. Consistent with this idea, Miyazaki *et al.* (2001) showed that phase advances

in response to a 23.66 h sleep-wake cycle in <10 lx were greater in subjects that were required to exercise for 2 h twice during each wake period (beginning 3 h and 7 h after wake-up). As light levels were identical in the exercise and sedentary conditions, light cannot explain this effect of exercise, unless exercise somehow potentiates light input (e.g. by dilating the pupils or altering the PRC to light, which normally predicts minimal response to light during the mid-subjective day).

Exercise has also been tested as a procedure to enhance the rate at which circadian rhythms can be reset following acute shifts of sleep-wake and LD schedules. Two studies reported that exercise potentiates the rate of resynchronization following eastward jet travel, but neither controlled light exposure (Klein & Wegmann, 1974; Shiota, Sudou & Ohshima, 1996). Two studies reported either a small beneficial effect (Eastman *et al.*, 1995) or no effect (Baehr, Fogg & Eastman, 1999) of nocturnal exercise following rotation to a night shift, but in both cases exercise was distributed across the night. A similar procedure was used in a forced desynchrony protocol that employed a 20 h sleep-wake cycle with 30 min bouts of exercise at 2 h intervals during each 10 h wake period (Beersma & Hiddinga, 1998). Exercise did not promote entrainment to this schedule, which was far outside the expected range of entrainment, but neither did it affect free-running τ , suggesting that it had no effect on pacemaker motion. However, such a design can reveal little about the sensitivity of the human pacemaker to exercise, because exercise was distributed across a very large portion of each circadian cycle, and the range of phases stimulated was shifted by 4 h each day. Exercise may have induced no shifts, or it may have induced delays at some phases that, within the same or the next cycle, were offset by exercise-induced advances at other phases.

Studies of single bouts of exercise (1–3 h at various intensities) demonstrate that the timing of exercise does matter. Exercise during most of the subjective night induces phase delay shifts (Van Reeth *et al.*, 1994; Buxton *et al.*, 1997, 2003), whereas exercise in the late subjective day can induce advances (Buxton *et al.*, 2003). The PRC inferred from these studies is consistent with the bi-directional exercise PRC obtained in work with other diurnal and nocturnal mammals. The timing of this PRC is sufficiently different from the photic PRC to rule out light as a confounding variable. However, circadian phase in these studies was evaluated during constant routine for only one or two cycles after the exercise stimulus, so there remains the possibility that apparent shifts reflect transient changes in rhythm waveform, rather than a real change in pacemaker phase (e.g. Buxton *et al.*, 2003). Assuming that these apparent shifts are real, then it would appear that in humans sleep-wake manipulations and exercise manipulations induce different kinds of shifts, the former consistent with light, and the latter consistent with the nonphotic PRC defined by activity studies in animals.

(6) Melatonin and pharmacological effects

The issue of pharmacological effects on circadian rhythms is a large topic and beyond the scope of this review. However,

it is worth noting that drugs that alter behavioural state could affect circadian timing by modulating photic or non-photic input pathways to the circadian system. A case in point is exogenous melatonin, which is often cited as a nonphotic chronobiotic due to its demonstrated ability to phase shift or entrain free-running rhythms in at least some blind and sighted people with circadian entrainment disorders (e.g. Skene *et al.*, 1999c; Lockley *et al.*, 2000; Sack *et al.*, 2000). The PRC describing its phase-resetting effects is distinct from that to light, and more similar to other nonphotic PRCs (Lewy *et al.*, 1992; Burgess, Sharkey & Eastman, 2002). Exogenous melatonin is also a soporific in humans (Wirz-Justice & Armstrong, 1996), raising the possibility that its entraining effects are at least in part due to its ability to promote an early sleep onset. For additional discussion of behavioural mediation of pharmacological effects on circadian rhythms see Mrosovsky (1997).

(7) Social influences in humans: what remains to be discovered

We were motivated to write this review by someone who wished to know if having conjugal relations would phase shift his clock. A not unreasonable response to this question is that it depends on whether the lights are on or off. In humans, social stimuli participate in the entrainment process at least to the extent that they affect daily patterns of light exposure. The evidence that a few totally blind people can entrain to a 24 h day, and that sighted people can entrain to near-24 h sleep-wake schedules in very dim light, and can be phase shifted by discrete bouts of exercise, suggests that nonphotic stimuli may also function as weak zeitgebers independently of light. Numerous questions remain.

More data are needed on the ability of fixed sleep-wake cycles and discrete bouts of exercise to entrain or produce phase shifts in sighted and blind people, using protocols that eliminate potential photic confounds (e.g. in constant dark, or bilaterally enucleated blind subjects). Are the PRCs for these manipulations truly distinct? If so, then exercise within a fixed sleep-wake schedule may be a more powerful zeitgeber than either alone, but only if timed appropriately.

Apart from studies of exercise, few attempts have been made to isolate specific behavioural correlates of the sleep-wake states that may be involved in nonphotic entrainment. Social habits and sleep-wake schedules control the timing of food intake in humans, and timed food intake is a potent zeitgeber in many animals (Mistlberger, 1994; Stephan, 2002), but research programmes to examine thoroughly the effects of meal timing and nutrient content on the human pacemaker are just beginning (e.g. Iraki *et al.*, 1997; Bogdan, Bouchareb & Touitou, 2001; Krauchi *et al.*, 2002). Also to be considered is the possibility that wake-onset, by repeated temporal pairing with light exposure in the morning (phase advance portion of the photic PRC), may acquire the ability to mimic light via a classical conditioning process (Amir *et al.*, 2002; this obviously would not explain entrainment to non-photic stimuli in blind people). Conversely, humans are physiologically aroused by light at night (Campbell *et al.*, 1995a); does this arousal contribute in any way to photic

resetting, e.g. via activation of non-retinal inputs to the clock that mimic or potentiate photic inputs?

The nature of individual differences in entrainment to nonphotic stimuli also needs study. Why do some but not all totally blind people, and some sighted people, fail to entrain to 24 h local time in their natural environment (e.g. as manifest by non-24 h sleep-wake disorder and other circadian rhythm sleep disorders; reviewed by Dagan, 2002)? To what extent is this related to individual differences in τ , as opposed to differences in sensitivity to nonphotic cues (or to light, in sighted people)? To what extent might individual differences in physical fitness determine phase shift responses to scheduled exercise? Psychological variables may also be important, as individual differences in personality may determine the degree of exposure to social cues in natural environments and the physiological response to these cues. There have been no formal studies of this in sighted people. In one sample of 17 free-running blind people, more than half of the subjects were employed and lived with their families and thus had regular social interactions (Lockley *et al.*, 1997), but personality variables have not been assessed.

What role if any do nonphotic cues (e.g. social contact, feeding, arousal) play in the development of circadian rhythmicity in human infants? Could those blind from birth develop a greater sensitivity to nonphotic zeitgebers? Does sensitivity to nonphotic cues change across the lifespan? Animals may lose sensitivity to maternal cues prior to weaning (e.g. Ohta *et al.*, 2002), but retain or acquire a sensitivity to other social or behavioural cues in adulthood. Animal studies have produced mixed evidence that ageing attenuates phase shifts to activity-inducing procedures (Van Reeth *et al.*, 1992; Mrosovsky & Biello, 1994; Duncan & Deveraux, 2000) whereas the one available study of humans detected no effect of age on phase shifts to nocturnal exercise (Baehr *et al.*, 2003).

Finally, how do light and nonphotic cues interact in humans? Animal studies show that light and behavioural arousal have opposite effects on circadian clock genes and cellular activity within the SCN pacemaker, and, in some temporal combinations, are mutually inhibitory (e.g. Ralph & Mrosovsky, 1992; Mistlberger & Antle, 1998; Maywood *et al.*, 1999; Antle & Mistlberger, 2000; Schaap & Meijer, 2001). Initial studies have not detected an effect of nocturnal exercise on phase shifts to light in humans (Baehr *et al.*, 1999; Youngstedt, Kripke & Elliot, 2002), but additional parametric studies of photic and nonphotic stimuli in combination are needed. The possibility that nonphotic manipulations, appropriately timed, could be used in conjunction with light to improve adaptation of circadian rhythms following transmeridian jet travel, shift rotations, or in people with circadian rhythm sleep disorders make this a worthwhile area to research.

V. SUMMARY AND CONCLUSIONS

(1) LD cycles are recognized as a dominant zeitgeber for entraining circadian rhythms in mammals. Social stimuli are also widely cited as important zeitgebers, but there is often

a lack of critical analyses aimed at determining whether social stimuli can affect circadian timing independently of their role in regulating light exposure. In cases where social stimuli do have entraining actions independent of light, there have been few studies to identify the components and consequences of social interactions that are necessary and sufficient for effects on circadian timing.

(2) The most convincing case for entrainment of mammalian circadian rhythms to social stimuli is from studies of maternal coordination of the circadian clock in utero and postnatally prior to weaning. The circadian clock in the foetus is entrained by melatonin and dopamine signals, but signals mediating entrainment postnatally have not yet been identified. In some species, it is likely that maternal entrainment postnatally is mediated by maternally-imposed daily cycles of food intake. Whether entrainment to maternal feeding cycles is mediated by the SCN light-entrainable circadian pacemaker or by a specialized food-entrainable pacemaker is not yet known.

(3) Analysis of phase shifting or entrainment to social interactions in Syrian hamsters indicates that these effects can be explained by social stimulation of arousal and activity. The circadian phase-dependence of arousal-induced shifts is very different from that of light-induced shifts, indicating that these shifts are truly independent and are mediated by separate photic and nonphotic input pathways to the circadian system. Nonspecific arousal also appears to mediate social entrainment in the marmoset, a diurnal primate, and may mediate social effects on circadian timing in the degus, a diurnal rodent. Stressful stimuli, although obviously arousing, do not have strong effects on circadian timing, and may induce shifts only if at least low levels of activity are permitted. It is not known whether this is because activity *per se* is necessary or because activity attenuates an inhibitory effect of stress on clock resetting. The neural bases for differential phase shifting effects of arousing stimuli remain to be elucidated.

(4) The adaptive significance of phase shifting or entrainment to social stimuli in neonates is transparent, but in adult organisms is less clear. Effects of social stimuli on circadian phase may serve to coordinate the activity patterns of potential mates, but this conception is weakened by evidence that successful bouts of mating may be ineffective in species such as the Syrian hamster in which aversive interactions can induce shifts. An alternative conception is that social effects on arousal and activity serve to enhance the precision of entrainment to LD cycles, but this needs further empirical validation.

(5) Humans cannot be studied for prolonged durations in constant dark, thus social effects on light exposure are an important methodological consideration in evaluating the empirical literature. Early studies suggested a necessary and sufficient role for social cues as circadian zeitgebers independent of light, but subsequent work has reversed the emphasis, such that light is now viewed as the primary, if not exclusive circadian zeitgeber. There is limited evidence that socially determined sleep-wake schedules can entrain circadian rhythms within narrow limits, and that bouts of exercise can shift the clock. Much more work is needed to determine those features of social interactions and physical

activity that may mediate entrainment to local time in blind people, and that might be exploited to help adjust circadian timing in shift workers and jet travelers.

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