

Tracking the seasons: the internal calendars of vertebrates

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Animals have evolved many season-specific behavioural and physiological adaptations that allow them to both cope with and exploit the cyclic annual environment. Two classes of endogenous annual timekeeping mechanisms enable animals to track, anticipate and prepare for the seasons: a timer that measures an interval of several months and a clock that oscillates with a period of approximately a year. Here, we discuss the basic properties and biological substrates of these timekeeping mechanisms, as well as their reliance on, and encoding of environmental cues to accurately time seasonal events. While the separate classification of interval timers and circannual clocks has elucidated important differences in their underlying properties, comparative physiological investigations, especially those regarding seasonal prolactin secretions, hint at the possibility of common substrates.

Keywords: seasonality; photoperiodism; circannual; interval timers

While the Earth remaineth, seedtime and harvest, and cold and heat, and summer and winter, and day and night shall not cease.

Genesis 8: 22, King James Version (1611)

As the Earth makes its yearly orbit around the Sun, the planet's 23.5° axial tilt leads to the cyclical environmental changes that we call the seasons. Recurrent challenges to the survival of organisms and their offspring arise with the dawning of each new season, and animals have evolved seasonally induced changes in phenotype that adapt them to these predictable events. For example, in many temperate environments, winter is generally characterized by severe decreases in ambient temperature and food availability, leading to increased energetic demands at a time when resources are diminished. Because energy requirements of female mammals typically increase markedly during lactation (Bronson 1989) and newly weaned offspring are particularly vulnerable to environmental perturbations (Hill 1992), raising offspring during this time of year is often futile. Thus, many temperate species have evolved winter-specific behaviours and physiology to conserve energy (e.g. hibernation, a more insulative pelage, huddling) or provide for escape (e.g. migration). Many species also increase the chances of offspring survival by timing their mating behaviours so that parturition occurs during energetically favourable times of year.

In this review, we highlight the mechanisms animals use to achieve seasonally appropriate adjustments. Although reference is mostly made to studies of reproduction and to particular species, the conclusions

derived probably apply to a broad spectrum of animals and to non-reproductive traits. Not covered here are remarkable recent developments in identifying some of the genes responsible for seasonal flowering in plants (Yanovsky & Kay 2003).

The simplest solution for seasonal adaptations would be a mechanism by which environmental cues directly trigger the required changes (sometimes referred to as a type 3 mechanism or rhythm; Zucker *et al.* 1991). In the absence of the external stimulus, the adaptive response would be lost. As an example, cloud forest mice, *Peromyscus nudipes*, do not give birth during the dry season in Costa Rica, although they breed year-round. Restricted food and water availability during the dry months are the stimuli that appear to prevent implantation or lead to reabsorption of the embryo (Heideman & Bronson 1992). Type 3 annual rhythms in human births have also been reported, attributable to social taboos on copulation during the yam growing season in a village in Papua New Guinea (Scaglione 1978) and to end of the year tax breaks in the United States (Dickert-Conlin & Chandra 1999).

Of course, there are limitations to a type 3 mechanism. Many seasonal changes require several weeks to complete (e.g. moult to a thicker pelage, deposition of large amounts of white adipose tissue, completion of spermatogenesis) and would occur too late if they were a direct response to an ultimate environmental factor. For example, if ground squirrels waited until the onset of winter conditions to initiate weight gain or food storage, they would have insufficient energy reserves upon entry into hibernation to survive the winter. Species often use predictive cues to forecast the coming season—primarily changing day lengths in non-equatorial regions—but even this strategy might not be sufficiently reliable under all conditions. Migrating birds experience complex,

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One contribution of 14 to a Theme Issue 'Adaptation to the annual cycle'.

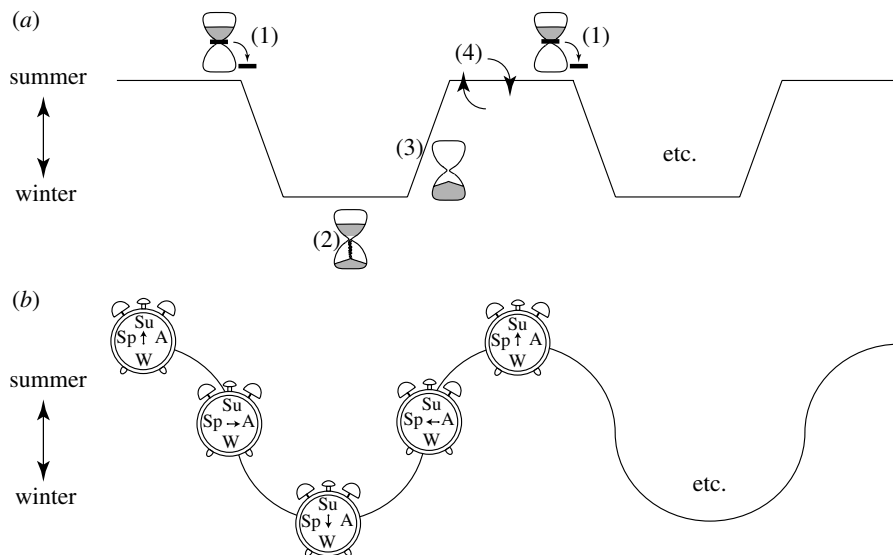


Figure 1. Annual timekeeping mechanisms. (a) Interval timer of the Siberian hamster. (1) Decreasing day lengths trigger the interval timer/induce the winter phenotype. (2) The timer runs to completion. (3) Refractoriness/spontaneous reversion to the spring phenotype. (4) Prolonged exposure to long day lengths breaks refractoriness/resets the interval timer. (b) Circannual clock of the golden-mantled ground squirrel. Successive oscillations between the summer and winter phenotypes are driven by an endogenous clock rather than exogenous factors.

dynamic environments and photoperiods, and animals that overwinter in burrows do not have access to most seasonal cues for much of the year.

An internal seasonal timekeeping mechanism, either one that measures the duration of time from an antecedent cue (like an hourglass) or one that oscillates endogenously with an annual period (like a clock), would enable animals to track, anticipate and prepare for the seasons even when predictive cues are noisy or not immediately present. Such timing mechanisms (sometimes referred to as type 1 and type 2 mechanisms or rhythms, respectively; Zucker *et al.* 1991) are widespread among seasonal species, even those with continuous access to relatively noise-free predictors (e.g. sheep, deer). Currently there is no satisfactory explanation for their prevalence in these latter species (for discussion see Gwinner 1981*a,b*).

1. ANNUAL TIMEKEEPING MECHANISMS

Both Siberian hamsters (*Phodopus sungorus*) and golden-mantled ground squirrels (*Spermophilus lateralis*) undergo seasonal cycles for several traits, including reproduction, body mass and heterothermy (Figala *et al.* 1973; Heldmaier & Steinlechner 1981; Zucker 2001). Laboratory experiments have revealed that seasonal adaptations in these two species are governed by different timing mechanisms (figure 1). Here, we illustrate this concept with reference to annual cycles of gonadal size and function, which are in breeding condition for both squirrels and hamsters during the spring and for hamsters in the summer as well (McKeever 1964; Figala *et al.* 1973). A similar argument can be made, however, using other seasonal traits of these species (figure 2; Pengelley & Fisher 1957; Pengelley & Asmundson 1974; Prendergast *et al.* 2002*b*).

(a) *Interval timers*

Siberian hamsters housed under long photoperiods (more than 13 h light per day, 13L; Hoffmann 1982*a*)

display the spring/summer phenotype of large, functional gonads indefinitely. Upon transfer to short photoperiods (less than 13L; Hoffmann 1982*a*), the gonads undergo regression, reproductive hormone concentrations decrease and gametogenesis gradually ceases over the following 6–10 weeks (Bergmann 1987). If maintained in a short photoperiod for more than 20 weeks, hamsters spontaneously revert to the reproductively competent phenotype (Hoffmann 1979). The loss of responsiveness to short day lengths (photorefractoriness) is governed by a process with hourglass properties designated an *interval timer* (Goldman 2001). This timer lacks calendar properties but adequately measures the lapse of time since the advent of short days.

Growth of the testes in Siberian hamsters is not affected by the increase in day length between the winter solstice and the vernal equinox (Gorman & Zucker 1995). The regrowth process is initiated endogenously by the interval timer, all other environmental factors being held constant. Field studies of meadow voles (*Microtus pennsylvanicus*) and white-footed mice (*Peromyscus leucopus*) suggest that the interval timer governs testicular growth in the wild: spermatogenesis recommences in most males in early December in Pennsylvania (Christian 1980), when day lengths are still decreasing and short in absolute terms. Initiation of gonadal development long before the advent of stimulatory long day lengths allows animals to take advantage of favourable breeding conditions in early spring. The duration of the interval timer differs both interspecifically (e.g. Siberian and Syrian hamsters, *Mesocricetus auratus*) and between different populations of the same species (Gram *et al.* 1982); it is presumably shaped by the selection pressures of the local habitat to favour appropriately timed reproduction.

Photorefractory Siberian hamsters housed in short days do not undergo a second gonadal regression unless they are first exposed for six or more weeks to a long photoperiod (Kauffman *et al.* 2003;

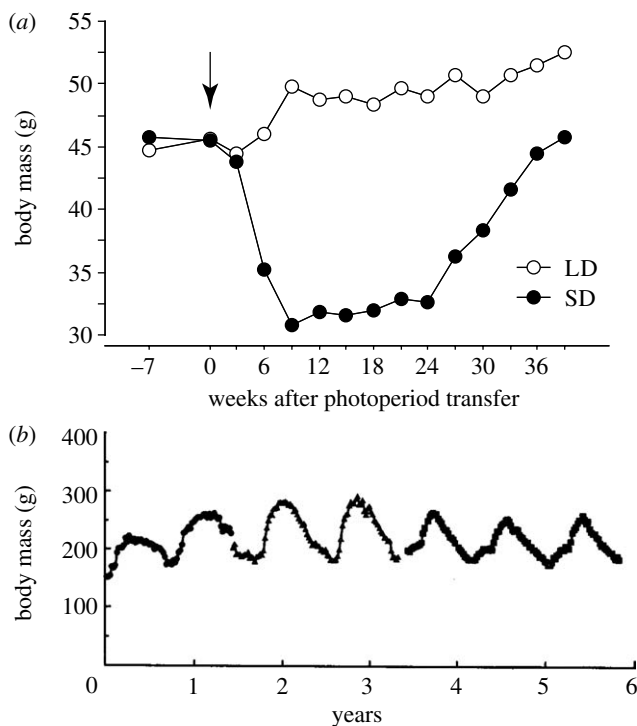


Figure 2. (a) Body mass records of two Siberian hamsters, one maintained continuously in a long day length (LD; 14 h light per day) and the other transferred to a short day length (SD; 10 h light per day) as indicated by arrow. SDs initially induce a marked decrease in body mass, but after 24 weeks body mass spontaneously reverts to LD values, even though there has been no change in environmental conditions. At this point, the hamster is unresponsive to SDs and is considered photorefractory. In contrast, maintenance in a LD results in uninterrupted body mass increases (M. J. Paul 2006, unpublished data). (b) Circannual body mass rhythm of an individual golden-mantled ground squirrel housed in a fixed photoperiod of 14 h light per day, then 12 h light per day, then constant light for the last 11 months. At year 3, the ambient temperature was changed from 23 to 6.5°C. The rhythm in body mass persists under all housing conditions (modified from Ruby *et al.* 1998).

Watson-Whitmyre & Stetson 1988). The interpolation of long days breaks refractoriness and resets the interval timer. Under simulated natural photoperiods, the decrease in day lengths in late summer initiates, and the long spring/summer day lengths reset, the interval timer resulting in successive annual cycles (Gorman & Zucker 1995).

(b) Circannual clocks

By contrast, golden-mantled ground squirrels housed under constant conditions (including static photoperiods) undergo several successive annual cycles of reproductive competence/incompetence with a period of approximately 10.5 months (Pengelley & Asmundson 1974). The largest variation in period for a given squirrel in this study was 29 days over four cycles, and in one squirrel there was only a 4-day variation in period. The generation of the ground squirrel's annual rhythm, in contrast to that of the Siberian hamster, does not require environmental input but rather is a manifestation of an endogenous circannual (approx. annual) clock. Under unchanging environmental conditions, this rhythm is said to free-run, with its period reflecting that of

the underlying oscillator. Because the free-running rhythm does not match the 12-month annual cycle, it must be adjusted via environmental cues to prevent 'out-of-season' behaviours.

How a circannual clock can run with such a long period is not understood. It does not require timed feedback from its physiological outputs (see Gwinner 1981b) and can track seasonal time even when its physiological expression is suppressed. Manipulations that either prevent the usual increase or accelerate the decrease in body mass have little or no effect on the onset or termination of the hibernation season, the period length between successive hibernation seasons or the onset of circannual weight gain in golden-mantled ground squirrels (Pengelley 1968; Heller & Poulson 1970; Pengelley & Asmundson 1974). Similar results have also been obtained in 13-lined ground squirrels (*Spermophilus tridecemlineatus*), whose energetic demands are increased by induced arousal from hibernation bouts without available food; with the return of food, the squirrels regain the proper body mass for that time of year (Mrosovsky & Fisher 1970). In this volume, Wikelski and colleagues revisit a possible role of energy turnover in circannual time-keeping mechanisms in an avian model.

(c) Timers versus clocks

It has been proposed that annual timekeeping mechanisms have multiple evolutionary origins (Farner 1985), so it is not surprising that different species have evolved distinct mechanisms for tracking seasonal time, an hourglass interval timer that needs to be reset or a self-sustaining circannual clock. Natural selection apparently has acted on different underlying substrates to solve the problem of seasonal timing. That circannual clocks are favoured by a number of long-lived species, however, argues for a functional explanation for the evolution of these two distinct classes of timekeeping mechanisms. Species that rarely live longer than a year in the wild would have no need for a mechanism that repeatedly generates annual cycles. An interval timer might also provide a selective advantage over a circannual clock in short-lived species, which tend to breed opportunistically (Bronson 1989). Anecdotally, it has been reported that out-of-season breeding is more common among interval timing than circannual species, suggesting that the timer is more easily overridden than the clock (Prendergast *et al.* 2001). A flexible annual time-keeping mechanism that can be ignored is probably a better option for species that stand to benefit from a risky breeding strategy.

Species without reliable access to noise-free environmental cues might require a circannual clock (e.g. species that migrate or overwinter in burrows). If isolation from noise-free environmental cues is sufficiently long enough, these animals would probably opt for an annual timekeeping mechanism that is less reliant on the environment. Tropical species might also lack sufficient environmental cues for interval timing. At and around the equator, changes in photoperiod are minimal at best, and other environmental cues may not occur at the correct time with respect to ultimate factors. For example, rainfall may occur too close to the

onset of available food (i.e. insects and vegetation), so this signal would not provide sufficient time for reproductive development. A circannual clock may prevent erratic environmental fluctuations from altering the seasonal rhythms in species or traits that cannot exploit small variations in seasonal onsets. For example, because gestation in sheep lasts several months, an extra month of unseasonable warmth at the end of summer would not provide an opportunity for births of additional progeny. Circannual species tend to produce but one litter a year, more or less on the same calendar date, whereas those that deploy an interval timer typically have a more extended breeding season, multiple litters and more variable times of reproduction.

2. ON THE ROLE OF ENVIRONMENTAL CUES

(a) *Photoperiod*

Without some kind of external input, interval timers would not cycle and circannual clocks would drift out of phase with the environment; both timekeeping mechanisms require environmental cues to accurately time seasonal events. Day length, the most accurate natural predictor of annual phase, is the predominant cue for timers and clocks (Gorman *et al.* 2001; Zucker 2001; Gwinner 2003). However, the functional role of photoperiod differs for the two mechanisms.

An interval timer relies on photoperiod to both trigger and reset the hourglass mechanism. In several small rodents, the interval timer is triggered by short day lengths and reset by long day lengths (Gorman *et al.* 2001). In the majority of birds, however, long day lengths first trigger the interval timer, after which prolonged exposure results in refractoriness to long days and a reversion to the winter phenotype (Dawson *et al.* 2001). Subsequent exposure to short day lengths is then required to break refractoriness. It has been proposed that a *critical day length* exists that defines all shorter photoperiods as winter and all longer photoperiods as summer (reviewed in Gorman *et al.* 2001). Relatively sharp inflection day lengths have been reported for several species (Gaston & Menaker 1967; Elliott 1976; Hoffmann 1982a; Rhodes 1989). Although a simple critical day length model is sufficient to account for seasonal cycles of laboratory animals held in and moved between static photoperiods, it is not sufficient to explain seasonal changes of animals in the wild. Each day length, except for those at the solstices, occurs twice each year. Thus, intermediate day lengths around the equinoxes could signal either the coming winter or the coming summer depending on whether they are preceded by decreasing or increasing day lengths. The response to these 'ambiguous' day lengths must vary according to the season, whether late summer or early spring. To solve this problem, photoperiodic animals store information about preceding photoperiods that they compare to the current day length (Prendergast *et al.* 2000). Siberian hamsters transferred from 16L or 8L to the identical 14L photoperiod undergo gonadal involution or recrudescence, respectively (Hoffmann *et al.* 1986). Such experiments suggest that an animal's *photoperiodic history* allows it to track the natural changes in day length, enabling it to unambiguously predict the

upcoming season and initiate/reset the interval timer at the appropriate time of year (Gorman *et al.* 2001). Studies of Siberian hamsters in simulated natural photoperiods have revealed that both absolute day length and incremental changes in natural day lengths contribute to the timing of seasonal behaviour and physiology (Gorman & Zucker 1995; Butler *et al.* 2007).

On the other hand, a circannual clock requires photoperiod to synchronize its endogenous free-running period to the sidereal year, analogous to the photic entrainment of a circadian clock to the 24 h day by the light/dark cycle. Thus, circannual researchers have adopted the circadian terminologies of entrainment and zeitgeber (an environmental factor that shifts the phase of the endogenous oscillator; German for 'time giver'). Central to entrainment theory is the observation that the oscillator is differentially sensitive to the phase of zeitgeber presentation. This can be assessed by constructing a 'phase response curve', i.e. by plotting the phase shifts that occur in a measured rhythm when zeitgeber pulses are applied at different phase points across the free-running circadian or circannual cycle. Owing to the long time scales involved (a typical experiment lasts a minimum of 2 years), reports of complete circannual phase response curves are uncommon. The circannual body mass rhythm of golden-mantled ground squirrels exposed to a three-month block of short days (8L) in late summer is phase advanced for 2 years, whereas the identical day length manipulation has no effect when given in the spring (Zucker 2001). A pseudophase response curve has been generated for rainbow trout (*Oncorhynchus mykiss*) exposed to blocks of constant light at different phases of the circannual rhythm (Randall *et al.* 1998), but the fishes were returned to natural day lengths rather than free-running conditions after zeitgeber presentation. Only recently in the varied carpet beetle (*Anthrenus verbasci*) has a complete phase response curve to photoperiod been generated for the circannual pupation rhythm (Miyazaki *et al.* 2005). Additional data supporting the concept of a photoperiod-entrainable circannual clock include the gradual resynchronization of annual rhythmicity after artificially reversing the photoperiod (woodchucks, *Marmota monax*: Concannon *et al.* 1993; sika deer, *Cervus nippon*: Goss 1969a, 1980); and entrainment, within limits, to photoperiodic cycles that differ from 12 months (e.g. 3, 6 or 24 months; sika deer: Goss 1969a; European starlings, *Sturnus vulgaris*: Gwinner 1977; golden-mantled ground squirrels: Lee & Zucker 1991).

(b) *Other environmental factors*

In the *winter breeding* California vole (*Microtus californicus*) short photoperiods suppress and long photoperiods promote testicular growth and spermatogenesis (Nelson *et al.* 1983). Evidently some non-photoperiodic seasonal factor(s) must override the normal photoperiodic input in the wild. Food, water, ambient temperature and social cues have all been shown to alter seasonal traits (Whitsett & Lawton 1982; Desjardins & Lopez 1983; Eskes 1983; Nelson *et al.* 1983; Pearce & Oldham 1988; Schneider & Wade 1989; Wayne *et al.* 1989; Honrado & Fleming 1996; Hegstrom & Breedlove 1999; Kriegsfeld *et al.* 2000a,b; Larkin *et al.* 2001, 2002; Reynolds *et al.* 2003;

Schoech *et al.* 2004; Genin *et al.* 2005), including a single plant compound identified in newly grown vegetation that stimulates reproduction in wild montane voles (*Microtus montanus*) during the winter months (Berger *et al.* 1981).

Reliance on non-photoperiodic cues for seasonal timing appears to be highly species specific. Wingfield and colleagues (1992) have proposed a method for predicting the relative contributions of non-photoperiodic factors in seasonal timing for a given species. Their quantitative analysis is beyond the scope of this review, but in general, they argue that species with short but highly predictable seasonal events (e.g. breeding seasons) rely mostly on photoperiod because this cue should be sufficient; in fact, it might be beneficial for such species to ignore inhibitory environmental factors because the narrow seasonal window confers limited opportunities. On the other hand, non-photoperiodic cues probably provide useful information to species that inhabit seasonal environments with more year-to-year variability and a longer seasonal window. Thus, as the certainty of the seasonal event decreases, the importance of photoperiod, timers and clocks decreases, whereas that of non-photoperiodic, supplementary cues increases. These predictions have been tested in three subspecies of white-crowned sparrows (*Zonotrichia leucophrys*). *Z. l. gambelli* breed in Alaska with a short but highly predictable breeding season; *Z. l. oriantha* and *Z. l. pugetensis* breed in the temperate latitudes with longer breeding seasons of more variable onset and offset. Supporting Wingfield *et al.*'s (1992) view, ambient temperature modifies photoperiodic responses of prolactin and gonadal development in *Z. l. oriantha* and *Z. l. pugetensis* but not in *Z. l. gambelli* (Wingfield *et al.* 1996, 1997, 2003; Maney *et al.* 1999).

Tropical species also might be expected to rely more heavily on non-photoperiodic cues given the minimal changes in day length in their natural habitat. Two populations of equatorial rufous-collared sparrows (*Zonotrichia capensis*) living 25 km apart at the same latitude breed seasonally and out of phase with each other even though the amplitude of the annual day length cycle is only approximately 3 min (Moore *et al.* 2005). Few studies have investigated the non-photoperiodic cues that might regulate seasonality in the tropics, but food intake and other food-related cues are probably important (Hau *et al.* 2000; Scheuerlein & Gwinner 2002). Surprisingly, some tropical birds can respond to small changes in photoperiod in the laboratory (African stonechats, *Saxicola torquata axillaries*: Gwinner 2003; spotted antbird, *Hylophylax n. naevioides*: Hau *et al.* 1998); a 17 min increase in photoperiod is sufficient to stimulate some gonadal growth in the spotted antbird (Hau *et al.* 1998). Whether or not these species attend to day length in the wild is unknown (Gwinner 2003). Recently, it has been suggested that equatorial birds time seasonal events by tracking seasonal changes in daytime light intensity during the dry and rainy seasons; African stonechats maintained in a constant 12.5L photoperiod synchronize their reproductive and moult rhythms to 10-month cycles of light intensity (Gwinner 2003). Notably, both light intensity (Bentley *et al.* 1998b) and small changes in photoperiod (Dawson 2007) can affect the day

length perception of European starlings, a temperate avian species, indicating that these phenomena are not restricted to equatorial species.

Some individuals of photoperiodic rodent species do not express the typical winter phenotype upon transfer to short day lengths (Prendergast *et al.* 2001), but such photo-non-responders may undergo gonadal involution if short days are combined with low temperatures and/or food restriction (Desjardins & Lopez 1983; Prendergast *et al.* 2001). Thus, the reliance on non-photoperiodic cues can vary intraspecifically. In this case, it is interesting to note that these cues are necessary for the response itself rather than the timing of the response.

Most studies do not explicitly assess whether non-photoperiodic cues act by directly driving or suppressing expression of the trait ('masking') or instead by altering an underlying timekeeping mechanism; in general, the results are more in line with the former possibility. This issue has been addressed in a recent field study of African stonechats in which provision of supplemental food advanced the initial breeding season without changing the onsets of the post-nuptial moult or of the following breeding season (Scheuerlein & Gwinner 2002). This result suggests that the food-induced advance did not perturb the circannual clock, although it is possible that other uncontrolled zeitgebers (i.e. photoperiod) might have compensated for the advance prior to the onset of later seasonal changes. Although most non-photoperiodic cues probably act by masking, at least one (extended intervals of exposure to low ambient temperatures) appears to phase shift the circannual body mass and reproductive rhythms of golden-mantled ground squirrels (Mrosovsky 1980).

Jacobs & Wingfield (2000) have proposed a 'finite state machine' model to predict the impact of environmental signals and their dependence on the state of the organism, determined by a finite number of inputs and outputs. The model emphasizes that individual cues such as day length may be sufficient in some circumstances, but in others they combine with temperature and food availability signals to affect seasonally appropriate responses. Laboratory-based scientists would do well to take seriously their caution that 'isolating a single cue and presenting it to the organism may result in responses not normally expressed in the field' (p. 45).

Wild animals almost certainly attend to multiple environmental cues. At sites with considerable year-to-year variability in the onset of seasonally favourable conditions, cues such as food availability and soil temperature can fine-tune annual rhythms. Perhaps photoperiod acts to grossly time seasonal changes by triggering, resetting and entraining interval timers and circannual clocks, while other environmental cues adjust precise rhythm onsets each year by a masking mechanism.

3. PHOTOPERIODIC TIME MEASUREMENT

(a) Models

In 1936, Erwin Bünning suggested that plants use the circadian timekeeping system to measure day length (for review see Saunders 2005). He proposed the

existence of a circadian-controlled photo-inducible phase; a sufficiently long day length would illuminate this phase and trigger a long-day response. In this scheme, light both entrains and illuminates the photo-inducible phase for *photoperiodic time measurement* (PTM). Colin Pittendrigh later extended this 'external coincidence' PTM model and proposed an alternative 'internal coincidence' or dual oscillator model. The latter postulates two circadian oscillators: one accelerated by light and synchronized to dawn (morning oscillator, M), and the other decelerated by light and synchronized to dusk (evening oscillator, E). As day length changes, the changing phase relation between the two oscillators encodes seasonal time. Several variations of these models have been developed more recently to account for findings in insects (see Vaz Nunes & Saunders 1999).

Several unnatural photoperiod treatments have been used to test the circadian basis for PTM. Animals housed in a short photoperiod but given a brief light pulse during the dark portion of the light/dark cycle (scotophase) respond as though they were housed in a long photoperiod, even though the total duration of light provided falls far below the critical day length (Follett & Sharp 1969; Hoffmann 1982b; Underwood & Hyde 1990). In Syrian hamsters, two 1 s light pulses administered daily 14 h apart maintain the reproductive system in its long day mode (Earnest & Turek 1983), whereas 11 h of continuous light exposure sustains the short-day reproductive phenotype (Elliott 1976). Thus, PTM in these cases is not a simple quantitative measure of the hours of light, hours of darkness or the ratio of light to darkness.

While the skeleton photoperiods described above suggest that the circadian system is used for PTM, they do not rule out the use of other non-circadian timing mechanisms. Nanda-Hamner, Bunsow and bi-stability experiments provide the best evidence for circadian involvement in PTM (Vaz Nunes & Saunders 1999). The Nanda-Hamner protocol, also referred to as resonance photocycles, has been used extensively (see also Elliott 1976). In such studies, groups of animals are exposed to photocycles with the same duration photophase (e.g. 6L) followed by varying durations of darkness (e.g. 18, 30, 42 and 54 h). Animals display a short-day response if the period of the total photocycle ($T = \text{light plus darkness}$) is a multiple of 24 h, whereas those in non-24 h T cycles display a long-day response. These results are compatible with a circadian mechanism in which light in the non-24 h photocycles falls during the postulated photo-inductive phase every few cycles or alters the phase relation between morning and evening circadian oscillators. Circadian involvement in PTM has been implicated in insects (Vaz Nunes & Saunders 1999), fishes (Baggerman 1972; Bromage *et al.* 1990), reptiles (Underwood & Hyde 1990), birds (Hamner 1963, 1964; Follett & Sharp 1969) and mammals (Elliott *et al.* 1972; Almeida & Lincoln 1982; Nelson *et al.* 1982) and is believed to be ubiquitous among birds and mammals. In insects, reliance on the circadian system for PTM is more variable, with some species using an hourglass mechanism (Vaz Nunes & Saunders 1999). Evidence in other insects is conflicting and depends on the type

of test given or even the ambient temperature during the test. Nonetheless, with notable exceptions, the circadian system is implicated in PTM in the majority of insects tested.

Recent experiments in European starlings have questioned the validity of the external coincidence model. Starlings maintained in 18L photophases of different light intensities do not exhibit the same photoperiodic response; lower light intensities are interpreted as a less stimulatory photoperiod (less than 18L, but greater than the critical day length) as determined by the rate of photostimulation of testicular development and onset of photorefractoriness (Bentley *et al.* 1998b). This appears to contradict the external coincidence model of PTM; if detectable light illuminates the same proportion of the photo-inductive phase, then the same long-day response should ensue. Yet as the authors point out, differing light intensities differentially affect the underlying circadian oscillator, which could alter timing of the photo-inducible phase. Thus, even though all birds were maintained in 18L, the lower light intensities may have resulted in a later photo-inductive phase and thus less overlap with light. Similarly, differing light intensities could affect the phase relation between morning and evening oscillators of an internal coincidence model via differing entrainment strengths.

(b) Melatonin

Only in mammals has the physiological basis for PTM been elucidated. An intact pineal gland is necessary for seasonal responses to photoperiod; pinealectomy prevents seasonal responses in most interval-timing species and in the majority of cases results in a persistent expression of the long-day phenotype (Goldman 2001). The indolamine, melatonin, is produced in the pineal during the night by the rhythmic activity of the rate-limiting enzyme *N*-acetyltransferase (NAT); this rhythm is controlled by a light-entrainable circadian pacemaker in the hypothalamus, the suprachiasmatic nucleus (SCN; Schwartz *et al.* 2001). A multi-synaptic pathway from the SCN communicates lighting information to the pineal gland (Moore 1996; Perreau-Lenz *et al.* 2003); the paraventricular nucleus (PVN) of the hypothalamus receives extensive SCN projections, and PVN efferents, including some to pre-ganglionic neurons of the sympathetic nervous system, relay to post-ganglionic neurons that ultimately innervate the pinealocytes. The SCN exhibits endogenous circadian rhythms that are photoperiod dependent in pinealectomized animals (Sumová & Illnerová 1996; Jacob *et al.* 1997). In the Syrian hamster and rat SCN, rhythms of photosensitivity (Sumová *et al.* 1995; Vuillez *et al.* 1996), electrical activity (Mrugala *et al.* 2000; Schaap *et al.* 2003) and gene expression (see Schwartz *et al.* 2001 and de la Iglesia *et al.* 2004 for references) display intervals of high activity that expand and contract in concert with changes in the ambient photophase and scotophase. Light, by both entraining the circadian pacemaker in the SCN and suppressing NAT activity in the pineal, restricts melatonin secretion to the scotophase. The contraction of the melatonin signal during short summer nights and its expansion in long winter nights provides an accurate endocrine

representation of night length. Indeed, exogenous administration of short and long *duration* melatonin infusions to pinealectomized mammals induces the summer and winter phenotypes, respectively (Bittman *et al.* 1983; Carter & Goldman 1983*a,b*). The circadian basis for PTM is thus realized by its role in the generation of a hormonal signal proportional to night length. The induction of the summer/winter phenotype by exotic lighting schedules (resonance and night-interruption protocols) can now be referred to their effects on melatonin secretion (Illnerová 1991).

Although the duration of nightly melatonin is sufficient to mimic photoperiodic responses, gonadal development can be attenuated in pinealectomized Siberian hamsters infused with melatonin for only 1 h per day, provided the hormone is administered just before or at the onset of the scotophase (Gunduz & Stetson 2001*a,b*). This raises the possibility that long duration melatonin infusions induce short-day responses because they overlap with a phase of target tissue sensitivity to melatonin. This view is compatible with the contention that the phase of melatonin sensitivity is entrained by the pattern of endogenous melatonin secretion (Stetson & Watson-Whitmyre 1986; Pitrosky & Pévet 1997). However, these studies infused supraphysiological doses of melatonin and the effects on the reproductive axis were less robust than those obtained with long duration melatonin infusions within the physiological range. Importantly, the putative phase of melatonin sensitivity in pinealectomized hamsters (around the onset of the scotophase) would correspond to a time of low endogenous melatonin secretion (Shaw & Goldman 1995; Goldman *et al.* 1984). At present, the evidence is insufficient to invalidate the current melatonin duration hypothesis for PTM.

Because light pulses independently phase shift the evening onset and morning offset of pineal NAT activity, the search for the dual M and E oscillators of the 'internal coincidence' model has focused on the SCN. There is some evidence to suggest that the SCN is composed of two oscillating components differentially affected by changes in the antecedent photoperiod (Sumová & Illnerová 1998; Jagota *et al.* 2000; Hazlerigg *et al.* 2005) and independently shifted by zeitgebers in a phase-dependent manner (Jagota *et al.* 2000). Several authors have proposed that M and E might be represented by the differently phased transcription of SCN 'clock' genes, the cyclic expression of which are thought to underlie the autoregulatory feedback loops that constitute the core of the circadian oscillatory machinery (Daan *et al.* 2001; see also Hastings & Herzog 2004 for a current review of circadian clock genes). Data on *Period 1* (*Per1*) and *Per2* expression patterns of mutant mice in different photoperiods suggest that the two genes might be anchored to morning and evening, respectively (Steinlechner *et al.* 2002). It is not known if photoperiodic effects are a property of individual SCN cells, with their activities compressed and decompressed, or instead emerge from intercellular interactions, with the cells assuming variable phase relations as a function of day length. Recent analyses

hint that the latter may be the case (Schaap *et al.* 2003; Rohling *et al.* 2006).

The duration of nocturnal melatonin secretion also entrains circannual clocks. In both golden-mantled ground squirrels and Suffolk sheep (*Ovis aries*), pinealectomy prevents entrainment to annual photoperiodic regimens (Woodfill *et al.* 1991; Hiebert *et al.* 2000), and melatonin administration phase shifts and entrains circannual reproductive rhythms in pinealectomized ground squirrels (Zucker 2001) and sheep (Woodfill *et al.* 1991), respectively. In sheep, long duration infusions during the summer result in the most reliable entrainment compared to melatonin profiles mimicking other seasons, and winter infusions are ineffective (Woodfill *et al.* 1994; Barrell *et al.* 2000). The winter melatonin profile, although neither necessary nor sufficient for entrainment of circannual rhythms of reproduction in ewes, is probably the short-day physiological signal that regulates the duration of the breeding season (Malpaux *et al.* 1988; Malpaux & Karsch 1990).

(c) *Physiological basis of PTM in non-mammalian vertebrates*

Much of the research into PTM in non-mammalian vertebrates has focused on whether the roles of the pineal gland and melatonin elaborated for mammals are also characteristic of other vertebrates, but the results obtained often differ depending upon the species tested (see Mayer *et al.* 1997). The pineal gland of many non-mammalian vertebrates contains both photoreceptors and a circadian pacemaker (Underwood & Goldman 1987); it thereby has direct access to day length and circadian information, placing it in an ideal position for PTM. As in mammals, the daily pineal and/or plasma melatonin profile of reptiles and birds is entrained by the light/dark cycle with peak values occurring during the scotophase, and in some species, changes in day length have been shown to alter the waveform (duration, amplitude or phase; Underwood & Goldman 1987; Mayer *et al.* 1997 and references therein). Cultured pineal glands from house sparrows (*Passer domesticus*) housed in either long or short day lengths maintain their differing durations of melatonin secretion for several cycles under constant darkness (Brandstätter *et al.* 2000), indicating that the house sparrow pineal itself is capable of storing a photoperiodic 'memory', at least for a few cycles.

The pineal gland and melatonin play a significant role in regulating the reproductive axis of at least some snakes and lizards. In the chequered water snake (*Natrix piscator*), pinealectomy is antagonistic during the autumn testicular recrudescence phase, but progonadal during the winter and spring regression and inactive phases, respectively (Haldar & Pandey 1989). Constant release melatonin implants, as well as both morning and evening melatonin injections, administered to pineal-intact water snakes decrease testicular size at all phases of the annual reproductive cycle except when testes are already fully regressed (Haldar & Pandey 1988). In the iguanid lizard (*Anolis carolinensis*), pinealectomy stimulates gonadal growth at certain times of year, and subcutaneous melatonin implants block these progonadal effects (Underwood 1985*a*).

It is not known if these effects of melatonin involve the transduction of photoperiodic cues. Although melatonin secretion in non-mammalian vertebrates is restricted to the night, there is some question whether melatonin duration conveys day length information. In *Anolis*, the phase, rather than the duration or amplitude, of the melatonin signal correlates with seasonal responses in various nightbreak, T cycle and resonance photocycles (Hyde & Underwood 1993). Whether phase differences mediate seasonal changes have not been tested. In the ruin lizard (*Podarcis sicula*), the amplitude of the melatonin signal differs in long and short days, but again, a causal relation between the amplitude of melatonin secretion and seasonal characteristics has not been established (Bertolucci *et al.* 2002; Bertolucci *et al.* 2003).

In some ectothermic species, temperature alters the amplitude of the daily melatonin rhythm (iguanaid lizard: Menaker & Wisner 1983; diamondback water snake, *Nerodia rhombifera*: Tilden & Hutchinson 1993; box turtle, *Terrapene carolina triunguis*: Vivien-Roels *et al.* 1988) suggesting that the daily rhythm in circulating melatonin may also integrate seasonal temperature cues (Vivien-Roels 1985). In the iguanid lizard, temperature cycles (approx. 9 h at 20°C, approx. 15 h at 32°C in constant dim light) entrain the daily pineal melatonin rhythm, with peak concentrations occurring during the cold phase (Underwood 1985b). In fact, when these lizards are exposed to 'cold days' and 'warm nights' (20°C during photophase, 32°C during scotophase), the melatonin profile entrains to the temperature cycle with peak values occurring in the light. Post-hibernation courtship behaviours of male red-sided garter snakes (*Thamnophis sirtalis parietalis*) are thought to be regulated by the characteristic environmental temperature changes of winter and spring (Hawley & Aleksyuk 1975; Crews 1990). Pinealectomy in the autumn, but not spring, eliminates courtship behaviours in the majority of males (Mendonca *et al.* 1996a,b). Pinealectomized males that do not court females exhibit a disrupted daily melatonin profile, whereas those that continue to court have normal daily melatonin rhythms (Mendonca *et al.* 1996a,b). These correlative data suggest that a normal daily rhythm of melatonin in the autumn is necessary to trigger springtime courtship behaviours; in some individuals, however, extra-pineal sources of melatonin may be sufficient to maintain this daily rhythm.

In birds, the effects of pinealectomy and melatonin administration are more varied, in part because tissues other than the pineal, mainly the eyes, contribute to melatonin concentrations in the general circulation (Underwood & Goldman 1987). Results in a few species, however, have led to the view that neither the pineal gland nor circulating melatonin plays a role in photoperiodic regulation of the reproductive axis. Blinded and pinealectomized American tree sparrows (*Spizella arborea*) continue to display seasonal gonadal cycles in response to changes in photoperiod (Wilson 1991). In the Japanese quail (*Coturnix coturnix japonica*), melatonin injections that extend the nocturnal melatonin profile do not mimic short-day suppressive effects on gonadal growth (Juss *et al.* 1993). A recent investigation, however, has revived a possible role for melatonin in photoperiodic regulation of

reproduction in Japanese quail via control of gonadotrophin-inhibitory hormone (GnIH; Ubuka *et al.* 2005), a hypothalamic peptide known to suppress pituitary luteinizing hormone (LH) secretion (Tsutsui *et al.* 2000; Osugi *et al.* 2004) and male gonadal development (Ubuka *et al.* 2006) when administered exogenously. GnIH mRNA and protein content in the diencephalon of Japanese quail increase after three weeks of short-day exposure (Ubuka *et al.* 2005). Pinealectomy combined with bilateral ocular enucleation, which markedly decreases plasma and neural melatonin, decreases GnIH mRNA and protein content, whereas melatonin implants restore these levels in a dose-dependent fashion. The results of Juss *et al.* (1993), however, suggest that altered melatonin secretion alone is insufficient to drive seasonal alterations of gonadal function in Japanese quail. It also remains possible that the effects of melatonin on GnIH represent pharmacological actions with a role for endogenous melatonin yet to be demonstrated.

In addition to being species specific, a photoperiodic role for the avian melatonin rhythm may be trait specific. Pinealectomy prevents the long day-induced increase in nesting behaviour of male ring doves (*Streptopelia risoria*; McDonald 1982). In castrated European starlings, constant release melatonin implants prevent photorefractory-induced changes in the immune system (Bentley *et al.* 1998a) and long day-induced increases in the high vocal centre (HVC), a brain nucleus important for birdsong (Bentley *et al.* 1999). Again, these effects may be of pharmacological rather than physiological significance. To our knowledge, long-term melatonin infusions that mimic the endogenous secretory profile have not yet been conducted in either birds or reptiles.

A pineal- and melatonin-independent mechanism of PTM and its subsequent transduction has been proposed for Japanese quail, via local regulation of thyroid hormone in the medial basal hypothalamus (MBH; Yasuo *et al.* 2006). The MBH has long been proposed to regulate photoperiodic responses of the reproductive system. Immediate early gene expression is induced within this area after exposure to a single long day (Meddle & Follett 1995, 1997). Lesions within the MBH block photoperiodic responses of Japanese quail (Sharp & Follett 1969), and electrical stimulation induces LH secretion (Konishi *et al.* 1987) and testicular growth (Ohta *et al.* 1984). Photoperiodic cues may act directly on the MBH via deep brain photoreceptors within the infundibular nucleus (Oliver & Bayle 1982; Silver *et al.* 1988). Selective daily illumination of the MBH for 16 h per day stimulates gonadal growth in quail housed under 10L conditions (Ohta *et al.* 1984). Type 2 iodothyronine deiodinase gene expression in the MBH is elevated under long compared to short day lengths (Yoshimura *et al.* 2003). This enzyme, which converts thyroxine (T₄) to 3,5,3'-triiodothyronine (T₃), implicates local changes in thyroid hormone concentrations in the photoperiodic stimulation of the testes. Lending support to this idea, intracerebroventricular (ICV) infusions of T₃ induce gonadal growth in quail housed in a short day length, whereas infusions of iopanoic acid, a type 2 iodothyronine deiodinase inhibitor, attenuate gonadal growth in long day lengths (Yoshimura *et al.* 2003). Interestingly, MBH mRNA

levels of type 3 iodothyronine deiodinase, an enzyme that degrades both T₃ and T₄, are decreased under long compared with short day lengths, a photoperiodic pattern opposite to that of type 2 iodothyronine deiodinase (Yasuo *et al.* 2005).

Thyroid hormones (Vriend 1985; Dawson 1998; Wilson & Reinert 2000; Watanabe *et al.* 2004; Revel *et al.* 2006b; Freeman *et al.* 2007) and the MBH/premammillary bodies (Maywood & Hastings 1995; Malpoux *et al.* 1998; Lewis *et al.* 2002) have also been implicated in the transduction of day length information in several other birds and mammals, and melatonin has been shown to regulate MBH type 2 iodothyronine deiodinase expression in several rodents (Watanabe *et al.* 2004; Revel *et al.* 2006b; Yasuo *et al.* 2007). Thus, a role for thyroid hormones within the MBH may be an evolutionarily conserved photoperiodic mechanism in birds and mammals, directly regulated by light impinging on deep brain and possibly retinal photoreceptors in the former and indirectly by light affecting the duration of nocturnal melatonin secretion in the latter.

It is important to note that the precise role for thyroid hormones in seasonality remains uncertain. In some species, the hormones appear to act downstream of photoperiodic transduction. Thyroidectomy prevents the development of refractoriness to unchanging photoperiods in sheep (Moenter *et al.* 1991; Parkinson & Follett 1994) and the transition from the breeding to the non-breeding condition in red deer (*Cervus elaphus*) maintained in natural day lengths (Shi & Barrell 1992). In sheep, the effect of thyroid hormones on refractoriness also appears to be mediated in the MBH/premammillary region (Anderson *et al.* 2003). In European starlings, different experimental procedures have shown that thyroidectomy can prevent both the photoperiodic responses (Dawson 1993) and the development of refractoriness (Goldsmith & Nicholls 1984). The full suite of seasonal responses (photoinduction and photorefractoriness) can be restored in thyroidectomized American tree sparrows by icv infusions of thyroid hormones (Wilson & Reinert 2000). At least in starlings, thyroid hormones appear to act permissively (Bentley *et al.* 1997a), involving changes in hypothalamic GnRH synthesis and/or secretion (Dawson *et al.* 2001, 2002), possibly mediated by nerve growth factor (Bentley *et al.* 1997b). The direction of thyroid hormone action on photorefractoriness, however, may not be consistent across all species; thyroidectomy hastens the onset of gonadal recrudescence in short day-housed Siberian hamsters (Prendergast *et al.* 2002a; see also Dawson & Thapliyal 2001).

(d) Other factors implicated in photoperiodic transduction

Thyroid hormones are not the only hypothalamically controlled factors involved in phenotypic changes to photoperiod. In Japanese quail, transforming growth factor α has been implicated in photoperiodic stimulation of the reproductive axis and appears to act through a separate signalling mechanism from that of type 2 iodothyronine deiodinase (Takagi *et al.* 2007). The search for additional neural substrates involved in the transduction of day length information is underway

and recent investigations have uncovered novel hypothalamic candidates.

The recently discovered hypothalamic peptide, kisspeptin, which stimulates gonadotrophin secretion, is regulated by photoperiod in the arcuate and anteroventral periventricular nuclei of Siberian hamsters and in the arcuate nucleus of Syrian hamsters (Revel *et al.* 2006a; Greives *et al.* 2007). In sheep, the levels of kisspeptin expression in the arcuate nucleus are altered according to season (Smith *et al.* 2007). Photoperiodic differences in hypothalamic kisspeptin expression in male Syrian hamsters persist in short-day hamsters given testosterone implants, but are blocked by pinealectomy, indicating that these effects are not the result of changes in gonadal hormone secretion but more likely reflect changes in the duration of nocturnal melatonin secretion (Revel *et al.* 2006a). Exogenous administration of kisspeptin stimulates LH secretion in short-day-housed Siberian hamsters and testosterone secretion and testis growth in short-day-housed Syrian hamsters (Revel *et al.* 2006a; Greives *et al.* 2007), probably by direct actions on GnRH neurons (for reviews see Navarro *et al.* 2007; Smith & Clarke 2007). Kisspeptin also appears to convey feeding-related information to the reproductive axis (Castellano *et al.* 2005), suggesting that this peptide integrates reproductive inputs from various environmental stimuli.

Other studies point to the dorsal medial posterior arcuate nucleus and the ependymal layer as candidate sites involved in photoperiodic regulation of body mass and/or reproduction in Siberian hamsters. Transcription of several genes within the dorsal medial posterior arcuate nucleus (VGF, histamine H3 receptor and several retinoic acid related genes) and the ependymal layer (cellular retinoic acid-binding protein 1, G-protein-coupled orphan receptor 50, nestin, type 2 iodothyronine deiodinase and type 3 iodothyronine deiodinase) is regulated by photoperiod (Barrett *et al.* 2005, 2006; Watanabe *et al.* 2004, 2007; Ross *et al.* 2005). Changes in the expression of VGF, histamine H3 receptor and cellular retinoic acid-binding protein 2 within the dorsal medial posterior arcuate nucleus occur before any detectable changes in body mass or gonadal size, raising the possibility that these genes play a role in the induction of photoperiodic changes in behaviour and physiology (Ross *et al.* 2005).

4. ON THE LOCATION OF INTERVAL TIMERS AND CIRCANNAL CLOCKS

The neural circuitry that mediates different seasonal traits remains largely unspecified. The search for biological substrates of annual timekeeping mechanisms has been largely restricted to mammals and focused on neural structures that might logically function as targets of melatonin action. In fact, the distribution of tissues that exhibit melatonin binding and receptor expression is highly species specific; the pars tuberalis (PT) of the pituitary gland is thought to be the only melatonin target tissue common to all mammals (Bittman 1993; Morgan *et al.* 1994). Melatonin implants directed at various targets (including the anterior hypothalamus, SCN, nucleus reuniens, paraventricular nucleus of the thalamus or MBH) in sheep, Siberian hamsters or

white-footed mice induce seasonal changes in various traits (Glass & Lynch 1982; Dowell & Lynch 1987; Badura & Goldman 1992; Lincoln & Maeda 1992; Malpoux *et al.* 1998; Freeman & Zucker 2001). Although these studies provide evidence that melatonin can act at multiple structures to effect seasonal changes, they do not specify the precise role of the hormone at each site.

(a) Multiple sites for timers and clocks

Long duration daily melatonin infusions via microdialysis to the SCN, paraventricular nucleus of the thalamus or the nucleus reuniens prevents gonadal development of juvenile hamsters housed in constant light (Badura & Goldman 1992). Melatonin implants directed at these same structures of adult pinealectomized Siberian hamsters each first induced gonadal regression, followed some weeks later by gonadal recrudescence indicative of refractoriness to melatonin (Freeman & Zucker 2001). Even though each of these individual tissues was rendered refractory to melatonin, subsequent subcutaneous long duration melatonin infusions induced a second testicular regression. This result establishes that the induction of refractoriness in a single tissue is not associated with refractoriness in all other melatonin targets. The interval timing mechanism that culminates in refractoriness to melatonin may be a feature common to multiple melatonin target tissues. These results and those of Badura & Goldman (1992) point to a highly redundant system for seasonal control of gonadal function. Alternatively, these brain nuclei may regulate different aspects of the melatonin-based photoperiodic reproductive response (Teubner & Freeman 2007). Melatonin signalling to the nucleus reuniens in Siberian hamsters appears to be critical for photostimulation by long day lengths and development of a photoperiodic history. Interrupting the melatonin signal in the SCN, however, only affects the photoperiodic history response, whereas the same treatment in the paraventricular nucleus of the thalamus has no effect on photostimulation or photoperiodic history.

Whether seasonal rhythms in several different seasonal traits (e.g. food intake, sex behaviour, aggressive encounters, body mass) are selectively regulated by one or more melatonin targets are presently unknown. Separation of function and multiple seasonal mechanisms is inferred from a study of garden warblers (*Sylvia borin*), in which at least two circannual clocks control the annual rhythms of gonadal function and moulting; under constant conditions, free-running circannual rhythms of testis size and moult dissociate and oscillate with different periods (Gwinner & Dorka 1976). Analogously, T3 injections delay the onset of gonadal, but not somatic, recrudescence in Siberian hamsters (Freeman *et al.* 2007). In hamsters and sheep, melatonin differentially controls seasonal variations in prolactin and gonadotrophin secretion through its actions on the PT and MBH, respectively. In the Syrian hamster, MBH lesions that block photoperiodic responses in gonadal function do not compromise short day-induced decreases in prolactin secretion (Maywood & Hastings

1995; Maywood *et al.* 1996; Lewis *et al.* 2002). Hypothalamo–pituitary surgical disconnection in Soay rams disrupts photoperiodic changes in food intake, body weight and metabolic hormones, but seasonal changes in prolactin secretion persist (Lincoln & Clarke 1994; Lincoln *et al.* 2001). Thus, an annual timekeeping mechanism that suffices to control prolactin is critically dependent on the pituitary, whereas other seasonal traits are mediated by neural tissues, probably within the hypothalamus and thalamus (Lincoln & Clarke 1997).

The PT, situated on the pituitary stalk between the median eminence of the hypothalamus and the pars distalis of the pituitary gland, is currently the best understood annual timekeeping tissue and probably contains an interval timer (in hamsters) and a circannual clock (in sheep) that regulates seasonal prolactin secretion. Soay rams whose pituitary is surgically isolated from direct hypothalamic inputs continue to show long-term seasonal changes (i.e. refractoriness) and circannual cycles of prolactin secretion under constant photoperiod exposure (Lincoln & Clarke 1997, 2000; Lincoln *et al.* 2003a, 2006). This tissue provides a powerful model system for elucidating the melatonin decoding and annual timekeeping mechanisms that contribute to the seasonal regulation of prolactin secretion.

Melatonin is believed to act directly on PT cells to regulate photoperiodic changes in prolactin secretion (Lincoln & Clarke 1994); high melatonin receptor binding is seen in the PT of several species, whereas little to no binding is found in the pars distalis of adult sheep, Siberian hamsters, Syrian hamsters, rats and mice (Bittman & Weaver 1990; Morgan *et al.* 1994). Current evidence suggests that melatonin-sensitive cells in the PT secrete a prolactin releasing factor ('tuberalin') that acts in a paracrine fashion to stimulate lactotrophs in the pars distalis (reviewed in Johnston 2004). Melatonin binds to melatonin 1a (MT₁) receptors coupled to the G_i class of G proteins in PT cells, inhibiting adenylyl cyclase activity and cyclic AMP production and somehow altering the synthesis and/or release of tuberalin. The chemical identity of tuberalin remains unknown.

Prolactin mRNA and protein content of the pars distalis decrease in short-day-housed hamsters but rebound to approximate long-day levels in short-day refractory animals, indicating neuroendocrine refractory state of these cells (Bockers *et al.* 1997; Johnston *et al.* 2003). The endocrine cells of the PT of Soay sheep and Siberian hamsters also become refractory as assessed by the α -glycoprotein hormone subunit (Bockers *et al.* 1997; Lincoln *et al.* 2005). In PT cells from refractory Siberian hamsters, melatonin receptor kinetics and the cAMP response to melatonin continue to reflect the photosensitive phenotype (Weaver *et al.* 1991), indicating that the substrate of the refractory state must lie downstream from melatonin signal transduction. On the other hand, PT cell cultures from refractory Syrian hamsters can induce long-day release of prolactin from pars distalis co-cultures, so the refractory state in PT must lie upstream of tuberalin secretion (Johnston *et al.* 2003).

(b) Circadian substrates beyond PTM

Several investigations have questioned whether the circadian system might be a part of the annual time-keeping mechanism, in addition to and downstream from its well-known role in PTM. At least in the golden-mantled ground squirrel, the data indicate that the circadian pacemaker in the SCN is not the location of the circannual clock. SCN lesions that induce circadian arrhythmicity of wheel-running behaviour do not disrupt circannual rhythms in body mass, hibernation and reproduction in the majority of squirrels (Zucker *et al.* 1983; Ruby *et al.* 1998). Circannual rhythms were disrupted in a subset of squirrels, but this effect did not correlate with lesion size or location (Zucker *et al.* 1983; Dark *et al.* 1985; Ruby *et al.* 1998). Interestingly, when lesioned animals were housed in the cold, a significant number hibernated indefinitely, displaying torpor bouts throughout the 2.5 year experiment, in contrast to the normal hibernation season in this species, which is approximately five to six months (Ruby *et al.* 1996). Thus the SCN, which remains functional at low ambient temperatures (Kilduff *et al.* 1990; Ruby & Heller 1996), may play a role in regulating the duration of the hibernation season, but it is not the site of an indispensable circannual clock.

Additional data argue against a role for the circadian system in setting the duration of the interval timer or the oscillation of the circannual clock. Circannual timing is not achieved by 'counting' circadian cycles, the so-called frequency-demultiplication model (Gwinner 1973). According to this hypothesis, animals entrained to light dark cycles of various circadian periods (T cycles) should have different circannual periods with respect to real time; animals housed in short T cycles (e.g. 23 h) will experience a greater number of circadian cycles in a given interval and should have shorter circannual cycles than those housed in longer T cycles. Yet the circannual periods of golden-mantled ground squirrels and European starlings entrained to different T cycles (squirrels T=23, 24 or 25 h; starlings T=22 or 24 h) are indistinguishable (Gwinner 1981b; Carmichael & Zucker 1986). The frequency demultiplication hypothesis also failed to gain support in Syrian hamsters, an interval-timing species. In the free-running *tau* mutant Syrian hamster, the shortened circadian period (20 h in homozygotes) does not alter the duration of the seasonal interval timer relative to that of free-running wild-type hamsters with approximately a 24 h circadian period (Lucas *et al.* 2000).

Whereas the circadian system does not appear to underlie the annual timekeeping mechanism of timers and clocks, the data regarding its role in decoding melatonin duration are conflicting. On one hand are studies in pinealectomized Syrian hamsters that do not support this possibility; melatonin infusions in such animals are effective at all phases of the circadian cycle (Maywood *et al.* 1990) and at frequencies outside the limits of entrainment of the circadian locomotor activity rhythm (once every 20 h; Grosse *et al.* 1993). Infusions provided once every 16 or 28 h do not result in the winter phenotype, demonstrating the limits to non-circadian intervals that are effective (Grosse *et al.* 1993). Lesions of the

SCN have been reported to prevent photoperiodic responses to melatonin infusions in Siberian hamsters (Bartness *et al.* 1991), but similar findings have not been obtained in SCN-ablated mink (*Mustela vison*), spotted skunks (*Spilogale putorius latifrons*) or Syrian hamsters (Bittman *et al.* 1979; Berria *et al.* 1988; Bonnefond *et al.* 1990; Maywood *et al.* 1990). Curiously, the SCN may play some role in decoding a series of melatonin signals in Syrian hamsters; SCN-intact, but not SCN-ablated, pinealectomized Syrian hamsters are capable of responding to long duration melatonin infusions presented in a random fashion (Grosse & Hastings 1996). The relevance of such random infusions for understanding normal function is not clear.

On the other hand, a few studies of *tau* mutant Syrian hamsters hint at a possible circadian involvement in decoding melatonin signal duration. Melatonin infusions presented to this mutant at 16 h (but not at 24 h) intervals induce the short day phenotype (Stirland *et al.* 1996). This 4 h shift in the range of effective melatonin frequencies from that of wild-type hamsters correlates well with the shortened circadian period of the *tau* mutant. *Tau* mutant hamsters also have shorter critical day lengths and more robust short-day responses to an intermediate duration melatonin infusion (6.67 h) than do wild-type hamsters; this circadian mutation does affect the threshold duration of day length and melatonin required for short-day responses (Stirland *et al.* 1995; Shimomura *et al.* 1997). Perhaps decoding the melatonin signal, while not using a circadian mechanism, must resonate temporally with underlying daily physiological processes that are regulated by the circadian system. Alternatively, reading the melatonin signal may involve extra-SCN circadian oscillators within the target tissues.

(c) Circadian 'clock' genes and the seasons

Whereas prior investigations had suggested that extra-SCN circadian oscillators might exist, only recently have a variety of cultured brain regions (Abe *et al.* 2002), peripheral tissues (including the pituitary gland: Yamazaki *et al.* 2000; Abe *et al.* 2002) and even immortalized fibroblasts (Balsalobre *et al.* 1998) been shown to exhibit circadian oscillations in the expression of circadian clock genes. These *in vitro* oscillations are sustained (Granados-Fuentes *et al.* 2004; Yoo *et al.* 2004), although overall amplitude may dampen as the rhythms of individual cells desynchronize (Nagoshi *et al.* 2004; Welsh *et al.* 2004). The physiological significance of the cycling of such genes in extra-SCN tissues is not known, but they may be autonomous 'slave' oscillators whose phase is set by the 'master' oscillator within the SCN. Conceivably, such a multi-site circadian network could allow for the independent adjustment of multiple rhythm phases to each other and to the ambient photoperiod; hypothetically, extra-SCN tissues might co-opt the expression of circadian clock genes for a 'calendar' mechanism that decodes melatonin signal duration (Lincoln *et al.* 2003b).

Such genes are rhythmically expressed in the PT (Lincoln *et al.* 2002) and at least the *Per1* rhythm is

melatonin dependent. The rhythm is absent in pinealectomized Syrian hamsters (Messenger *et al.* 2001), as well as in inbred strains of mice that do not synthesize melatonin (Sun *et al.* 1997) or lack functional melatonin 1a receptors (von Gall *et al.* 2002). Peaks of *Per1* and *Per2* mRNA in the early photophase appear phase-locked to the suppression of melatonin secretion by light onset at dawn. Acute melatonin administration inhibits *Per1* mRNA expression while chronic treatments appear to sensitize it to some other stimulatory factor in the PT (Morgan *et al.* 1998; Messenger *et al.* 1999, 2000; von Gall *et al.* 2002). In contrast, melatonin stimulates *Cryptochrome 1* (*Cry1*) mRNA expression (Dardente *et al.* 2003; Johnston *et al.* 2006), and peaks of *Cry1* and *Cry2* mRNA in the early scotophase appear phase locked to the activation of melatonin synthesis by light offset at dusk. Thus, a differential phase relation between *Per* and *Cry* levels in the PT could act to transduce day length and melatonin duration into seasonal changes in prolactin secretion (see Lincoln *et al.* 2003b). However, immunoreactive PER and CRY protein levels have yet to be measured and a causal link between clock gene expression and tuberalin activity has not been demonstrated.

Researchers have also questioned whether clock gene expression contributes to the annual timekeeping mechanism itself, specifically whether their phase relations in refractory animals would no longer reflect the ambient photoperiod. Yet mRNA rhythms of such genes continue to faithfully represent the ambient photoperiod and melatonin profile in short-day refractory Syrian hamsters and long-day refractory sheep (Johnston *et al.* 2003; Lincoln *et al.* 2005).

5. A POSSIBLE SYNTHESIS: ARE CIRCANNUAL CLOCKS CONSTRUCTED FROM INTERVAL TIMERS?

Seasonal regulation of prolactin secretion appears to be an ancient system (Lincoln 2000) highly conserved between species using either an interval timer (hamsters) or circannual clock (sheep; Lincoln *et al.* 2003a). Goldman *et al.* (2004) proposed that the circannual clock is an interval timer whose refractoriness is spontaneously broken, i.e. the stimulus for resetting the interval timer in a circannual species is endogenous and no longer relies on the environment. Interval timing species such as the Siberian hamster only display successive cycles when exposed to alternating short and long photoperiods because they require short days to trigger the timer and long days to reset it. Circannual species may have evolved a completely endogenous mechanism for triggering and resetting the interval timer.

This concept may help account for species that express endogenous annual cycles but only under a specific set of photoperiodic conditions ('permissive photoperiods'). European starlings (and possibly European hamsters, *Cricetus cricetus*; see Canguilhem *et al.* 1988a,b; Canguilhem 1989) display circannual cycles when housed in 12L, but not in other photoperiods (Schwab 1976; Dawson 2007). In sika deer, 12L is the only photoperiod in which the

circannual rhythm in antler growth is not expressed (Goss 1969b; Goss 1984). Rams exhibit a robust circannual rhythm of prolactin secretion under long photoperiods, but rhythmicity is weak or absent in short photoperiods (Howles *et al.* 1982; Langford *et al.* 1987; Lincoln & Clarke 2000). In contrast, obligate circannual species such as the golden-mantled ground squirrel display circannual cycles under all photoperiodic conditions tested, including constant light and constant darkness (Pengelley & Asmundson 1970; Zucker & Boshes 1982; Zucker *et al.* 1983). Permissive photoperiods may reveal the sequential activation of interval timers that is otherwise suppressed. Circannual cycles in European starlings and European hamsters might result from sequential interpretation of 12L first as a long day and then as a short day (Gwinner 2003), thereby triggering and resetting the interval timer. Turkish hamsters (*Mesocricetus brandti*) could provide an interesting opportunity to demonstrate circannual cycles in a species traditionally considered to use an interval timer. Because a 20L photoperiod can both initiate seasonal gonadal regression and break refractoriness to short day lengths in Turkish hamsters (Hong *et al.* 1986; Hong & Stetson 1988), circannual rhythmicity might be predicted in 20L if the interval timer is both triggered and reset by this day length.

In theory, there are many ways in which seasonally appropriate adjustments can be assured, but the limited data available have been interpreted as evidence for just two conceptual mechanisms, despite the probable independent evolution of seasonality several times (Farner 1985) and the assertion that natural selection selects for outcomes, not mechanisms (Mayr 1982). The rigid classification of timing mechanisms as either timers or clocks may be physiologically misleading despite its heuristic value. It seems probable that the timekeeping mechanism of the 'circannual' golden-mantled ground squirrel is more similar to that of the 'interval-timing' Syrian hamster than to that of 'circannual' birds or even ungulates. In addition to the existence of true timers and clocks in some animals, other species may rely on mechanisms that lie on a continuum between timer-like and clock-like classifications.

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