Chapter 11
Circannual Rhythms: History, Present Challenges, Future Directions

Barbara Helm and Tyler J. Stevenson

Abstract Circannual rhythms are endogenous biological oscillations that underlie a wide range of seasonal processes. Without knowledge of these underlying mechanisms, it is difficult to fully understand what drives the ways organisms change over the course of a year and to predict how they will respond to environmental conditions. The study of circannual rhythms is particularly timely given the substantial interest in seasonal processes in relationship to environmental change, and further given insights that seasonal change in human physiology and behavior is greater than previously thought. The present chapter outlines basic definitions and ideas on circannual rhythms, summarizes ground-laying work, and highlights some current developments. It then addresses challenges in this field and the opportunities that arise from the rapid development of new technologies.

Keywords Endogenous • Migration • Photoperiod • Reproduction • Seasonal

11.1 Introduction

Among the "Enigmatic Clocks" that are the subject of this book, perhaps the most enigmatic in terms of their mechanistic basis are circannual clocks. Circannual rhythms oscillate with daunting period lengths of roughly 365 days and provide the endogenous basis of long-term timing. Even today, nearly 30 years after Gwinner's (1986) authoritative assessment of the field, it is difficult to understand the biological processes that could create rhythms with such extremely long time constants. Furthermore, organisms differ greatly in the extent to which circannual rhythms are displayed in the absence of environmental cues and in the conditions under which

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these rhythms persist. Nonetheless, rhythms on this timescale are taxonomically widespread, and in some species circannual processes recur with admirable temporal precision. Circannual rhythms are typically measured as recurring biological processes over the lifetime of individuals (e.g., reproduction, migration, metabolic change). In short-lived species, rhythms may emerge on a population level, for example, by periodic recurrence of phases in which population members undergo individual developmental transitions (e.g., pupation of insects; see also the chapter by Miyazaki et al., this volume).

Increased research efforts to better understand circannual rhythms are important and timely. Interest in the seasonality and annual cycles of organisms has grown enormously over the past years. In particular, phenology (i.e., the seasonal timing of recurring biological processes; Foster and Kreitzman 2009; Visser et al. 2010) has attracted substantial scientific and public attention in view of the rapid changes in global environments. The study of phenology has benefited from methodological and analytical advances, which in turn yielded data that indicate great differences in the ways organisms modified their annual cycles in view of changing conditions. Simultaneously, evidence is increasing that seasonal changes in a range of physiological processes are more pervasive in many species, including our own species *Homo sapiens*, than previously thought (Hazlerigg et al. 2013; Helm et al. 2013; Ebling 2014; Martinez-Bakker et al. 2014; Schwartz and Andrews 2013). We are convinced that an improved understanding of the mechanisms that underlie seasonal biology, and in particular those of circannual rhythms, will contribute considerably to addressing urgent concerns in ecology, health, and global change biology.

Research during the past decades has consolidated the evidence for circannual rhythms and is inching toward tractable approaches to resolve their mechanistic basis. Several of these advances are represented by the chapters presented in this book. This introduction gives general background on circannual rhythms, discusses some difficulties, and ends with an outlook on innovative methods to resolve them.

11.2   What Are Circannual Rhythms?

The study of biological rhythms is concerned with behavioral, physiological, morphological, developmental, or molecular processes that recur with periodicities related to those of geophysical cycles (Dunlap et al. 2004). It centers on distinguishing cycles that are endogenous and persist even under constant conditions from those that are solely driven by external (environmental) factors. Formally, the definition of circannual rhythms develops along the following steps: rhythms in general are defined as regular spatial or temporal repetitions of patterns. Endogenous rhythms are temporal repetitions under conditions that provide no external information about the period they normally assume. An endogenous rhythm with a period length of approximately 1 year is called *circannual* (from *circa*, about, and *annus*, year; Gwinner 1986). Convincing evidence for an endogenous basis is provided if

the periodicities of circannual rhythms are close, but not identical, to 1 year. Because under constant conditions they then progressively drift away from the calendar year, they are termed "free running." Jointly these features specify the necessary and sufficient conditions for phenomena to be regarded as "circannual rhythms." In addition, the following features further characterize circannual rhythms as being based on *bona fide* endogenous clocks (Gwinner 1986; Dunlap et al. 2004):

1. Entrainment of the free-running rhythm to environmental cues (i.e., *Zeitgeber*). Under real life conditions, circannual rhythms are usually not free running but instead are entrained to the annual cycle. Based on experimental evidence, the most important zeitgeber is the annual change in daylength ("photoperiod"). Entrainment by other *Zeitgeber* has been shown to be possible, but evidence for their effectiveness is currently limited to proof-of-principle studies (see the chapters by Heideman, and by Goymann and Helm, this volume; Immelmann 1971; Heideman and Bronson 1994; Helm et al. 2013). Entrainment has also involved transient cycles, at least in some species (e.g., Concannon et al. 1997) (Fig. 11.1).

2. At least in some species, the free-running rhythm is temperature compensated (Gwinner 1986, p. 42ff). In contrast to the usual increase in the rate of physiological processes with increasing temperature (so-called Q_{10} properties; Rensing and Ruoff 2002), circannual period length was barely affected by experimental differences in constant ambient temperature. Nonetheless, similar to its effects on circadian rhythms, temperature had clear, and often phase-dependent, modifying effects on aspects of circannual cycles, in particular in some hibernating species (reviewed in Gwinner 1986, p. 43; Wikelski et al. 2008; Helm et al. 2013; also see the chapter by Miyazaki et al., this volume).

Although these features unambiguously characterize endogenous circannual rhythms, they have been established for only a limited number of organisms. Annual cycles are ubiquitous in most environments on earth, but such rhythmic patterns can be based on various mechanisms, including instantaneous responses to environmental fluctuations. Thus, without study under constant conditions the contribution of circannual rhythms to these cycles is unclear. Regrettably, the attribute "circannual" is nonetheless sometimes applied in the general sense of "annual cycles." To avoid confusion and to properly identify pertinent mechanisms, the use of the term "circannual" should be restricted to processes that persist under constant conditions, whereas in all other cases, the correct term is "annual" or "seasonal" cycle.

11.3 Historical Perspective on Circannual Rhythms

The expression of circannual rhythms differs between organisms and often requires specific, "permissive" conditions (Gwinner 1986). For example, in birds, rodents, and dinoflagellates, closely related taxa may differ substantially in the degree to which circannual rhythms persist under constant conditions (Anderson and Keafer 1987; Gwinner 1996; Prendergast et al. 2002). Differences in circannual
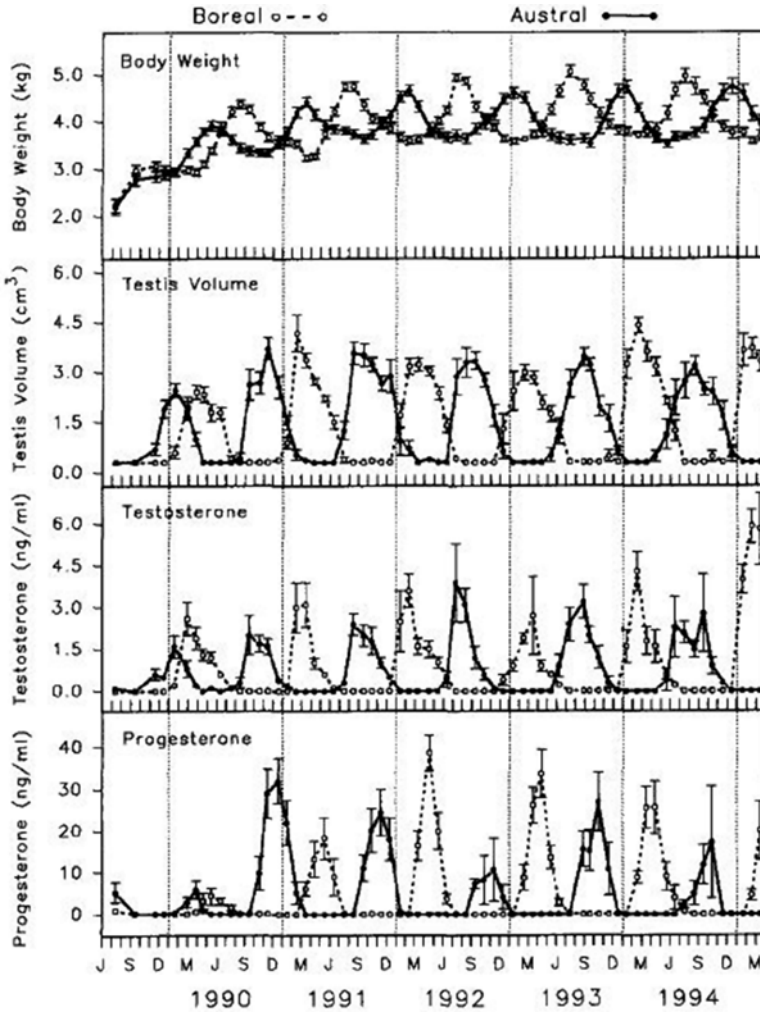
Fig. 11.1 Photoperiodic entrainment of circannual rhythms: The figure shows cycles of body mass, testis volume, testosterone, and progesterone of woodchucks *Marmota monax* in the process of phase-shifting from photoperiodic conditions of the Northern (boreal) to the Southern (austral) Hemisphere. Entrainment involved transients for at least two cycles. *Curves* show means and standard error. Animals that did not re-entrain were removed from the study. (Reprinted from Concannon et al. (1997) with friendly permission of *Biology of Reproduction*; see there for more information)

organization had been predicted from the outset of the field (Aschoff 1955, 1958) and were thought to relate to environmental seasonality and to an organism's life cycle along the following considerations. Although in most habitats on earth environmental conditions change over the course of a year, these changes differ

geographically in amplitude and year-to-year predictability (see the chapters by Heid elevated eman, and by Goymann and Helm, this volume). A high amplitude in seasonality commonly implies alternations in the availability of conditions that are conducive to growth and reproduction. Accordingly, organisms in these environments are expected to alternate between phases of growth and reproduction on the one hand, and phases of avoidance or endurance of unconducive conditions, for example, by migration or dormancy, on the other. Within a given seasonal environment, the pressure to align with the seasons will be elevated for organisms that depend on resources that are highly seasonal (e.g., in birds feeding on aerial insects compared to those feeding on seed) (Foster and Kreitzman 2009; Bradshaw and Holzapfel 2007).

If seasonal changes are predictable, organisms can anticipate them and prepare in advance, instead of simply responding to their occurrence. Classical examples for highly precise, anticipatory actions include avian long-distance migrations, in which departure dates of populations and individuals are often highly repeatable between years and occur well in advance or even in the absence of environmental deterioration (Gwinner and Helm 2003; Helm et al. 2012; Altshuler et al. 2013). In their attempt to predict in which species circannual rhythms would be the most clear cut, researchers were aware that photoperiod (annual change in daylength) usually provide information for anticipating seasonal changes (Rowan 1925, 1926; reviewed in Foster and Kreitzman 2009; Nelson et al. 2010). Therefore, they expected endogenous information to be most useful for organisms that had limited access to reliable photoperiodic or other predictive information about seasonal change. For example, Rowan (1926) pointed out that photoperiodic information alone was insufficient to explain the timely return of equatorial or transhemispheric migrants, which in their winter quarters experienced either constant or long daylengths. The plant physiologist Erwin Bünning (Bünning 1949) conducted extensive experiments with seeds that pointed in the direction of long-term rhythms but remained inconclusive because environmental influences (especially humidity) were not strictly controlled and period lengths were very close to that of the solar year.

Following the more rigorous formalization of endogenous rhythms on a circadian time scale, Jürgen Aschoff (Aschoff 1955, 1958) wrote two influential papers in which he suggested that these concepts be applied on an annual timescale. Aschoff (1955) proposed that rewarding biological systems for the study of endogenous circannual rhythms would be mammalian hibernation and avian long-distance migration. Furthermore, near the equator photoperiodic information is available, but because its annual changes are minute the information content was thought to be low. Therefore, equatorial species were also predicted to profit from clear circannual rhythmicity. Aschoff (1958) discussed possible experimental approaches to investigation and specifically recommended to keep organisms under constant light–dark (LD) cycles, which he knew were more likely to retain robust rhythmic organization than unchanging light intensities. Almost simultaneously, the first rigorous data on circannual rhythms were published. Below we introduce main study systems and also refer the reader to other sources for more complete coverage (Gwinner 1986).

11.4 Main Circannual Model Systems

Mammalian Hibernation The first unequivocal evidence that endogenous circannual rhythms were indeed involved in annual-cycle timing came from a study of hibernation in the ground squirrel *Citellus lateralis* by Pengelley and Fisher (1957). This seminal publication inspired decades of work on the regulation of seasonal processes in hibernators. Next to their formative role for research on circannual rhythms and photoperiodic entrainment (Fig. 11.1), studies of hibernating mammals were also highly relevant for understanding seasonally regulated physiology. These studies continue to reveal important information on a wide spectrum of features, including further characterization of circannual rhythms and physiological and molecular regulation of metabolism (Ebling 2014; Schwartz and Andrews 2013). For example, Kondo et al. (2006) studied circannual cycles over as long as 13 years and reported evidence for a novel protein that may be involved in the regulation of hibernation, and Olson et al. (2013) characterized circannual fluctuations in sensitivity to an agonist that induces torpor. Monecke et al. (2009) have provided detailed information on interactions of circannual rhythms and photic input in the European hamster *Cricetus cricetus*, including phase-response curves to long and short days (Fig. 11.2). Recently, they also demonstrated for this species photoperiodic entrainment independently of systemic melatonin production, which they suggest represents a specific, circannual pathway (see also Monecke et al. 2014). The chapter by Monecke and colleagues in this volume reports on these and other advances.

Pupation in Carpet Beetles Blake (1958) published a first documentation of circannual rhythms of pupation in the varied carpet beetle *Anthrenus verbasci* and

Fig. 11.2 Circannual phase-response curve to short-day pulses: European hamsters *Cricetus cricetus* were kept under constant light-dark (LD) 16:8 h conditions, and during different circannual phases, were exposed to 1 month of LD 10:14. *Curves* show shifts in the timing of reproductive cycles. (Reprinted from Monecke et al. (2009) with friendly permission of *Journal of Biological Rhythms*; see there for more information)
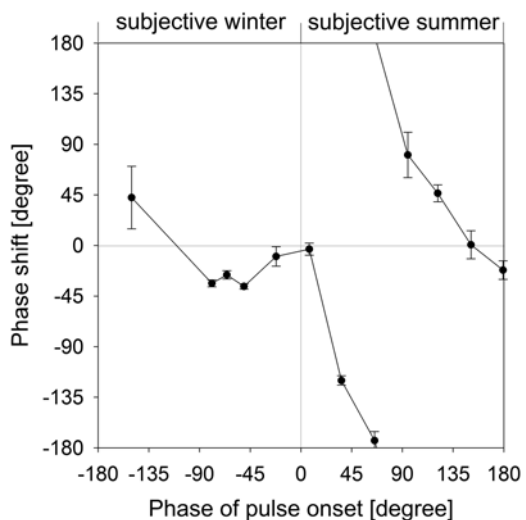
thereby initiated a tractable study system that has been used for circannual research up through the present day (see the chapter by Miyazaki et al., this volume). Carpet beetle larvae live in secluded and often light-sheltered places, from where they pupate after spending one or several years in larval stages. Under constant conditions pupation of a cohort occurs with circannual rhythmicity, so that most pupate after one, and smaller numbers after subsequent, circannual intervals. Circannual rhythms are thus measured on a population level as the number of larvae pupating at any given time. Research on this model system has contributed the most in-depth characterization of formal properties of circannual rhythms so far (Miyazaki et al. 2005, 2006, 2007), and is summarized in the chapter by Miyazaki et al. in this volume.

Avian Migration As predicted by Aschoff (1955) and earlier by Rowan (1926), long-distance migration of birds has been a rewarding system for circannual studies. The central question was what triggered the departure of equatorial and transequatorial migrants from the winter quarters in early spring to return to higher latitudes for breeding (Newton 2008). Daylengths are nearly uniform at the equator and are longer in Southern Hemisphere winter quarters than on Northern Hemisphere breeding grounds. The winter habitat clearly sustains the migrants and allows many local birds to breed at this time. Despite the absence of any obvious environmental drivers or cues, migrants nonetheless leave on time to return to the breeding grounds in spring. The groundwork for addressing this question was laid by Eberhard Gwinner, who spearheaded circannual research and was a passionate ornithologist. Since his first circannual publications in 1967 and 1968, his trademark studies involved both free-living and captive birds. Gwinner spent many months in the Republic of Congo, where he observed *Phylloscopus* warblers in the wild and in local captivity. Simultaneously, conspecifics were kept in aviaries in Southern Germany under circannual conditions (Gwinner 1967, 1968). Gwinner found that the birds developed migration-related behavior (nocturnal restlessness or *Zugunruhe*) in African and German captivity in time for their actual departure in the wild. Under constant conditions, *Zugunruhe* drifted rhythmically with circannual period lengths. These and many ensuing studies (Hamner and Stocking 1970; Gwinner 1986; Holberton and Able 1992; Berthold 2001; Newton 2008) provided rigorous evidence that in many species the signal for migratory restlessness and related processes (e.g., fat deposition) came from a circannual clock. In most songbirds, species of the order Passeriformes, periodicities were shorter than 1 year whereas in a different avian class, waders (species of the order Charadriiformes), period lengths were considerably longer (Piersma et al. 2008).

A main insight from avian studies was the wide range of processes that were under circannual regulation. For example, using laboratory testing devices for directional preference ("Emlen funnels"), researchers were able to show that birds shifted their orientation behavior based on annual and circannual programming (Emlen and Emlen 1966). With a "clock and compass" navigational system, unexperienced migrants could direct their behavior toward the winter quarters on their first journey. Another insight was that features of circannual rhythms differed greatly between
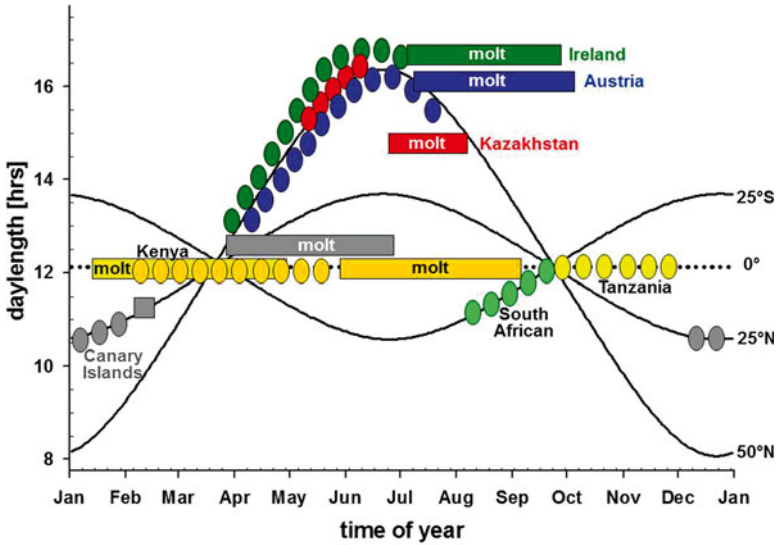
Fig. 11.3 Photoperiodic conditions under which stonechats *Saxicola torquata* breed and molt: overview of information on the timing of reproduction (*oval shapes*) and molt (*boxes*) of stonechat populations from different latitudes. Reproduction and molt are plotted on the respective daylength curves of the birds' breeding ranges; the different populations are indicated by *color-coding*. (Reproduced from Helm (2009) with friendly permission by *Integrative and Comparative Biology*; see there for details)

species and, in some cases, even local populations (Gwinner 1996; Helm et al. 2009). In flycatchers and sylvid warblers, the robustness of the rhythm and the permissive conditions under which it was expressed differed with migratory distance and daylengths normally experienced across the annual cycle (Gwinner 1988). To investigate differences between closely related taxa, Gwinner established a circannual model system using a species with an extensive north–south breeding range, the stonechat *Saxicola torquata*. This species became paradigmatic for sustained rhythms and for geographic differentiation of annual and circannual properties (Helm et al. 2009; Fig. 11.3). A succinct overview of circannual rhythms in migratory birds is given by Gwinner (1996).

Equatorial Species As suggested by Aschoff (1955), equatorial species living under nearly invariable daylengths are primary candidates for showing distinct circannual rhythms. Two chapters in this volume (Heideman, and Goymann and Helm) are centrally concerned with equatorial, and more generally, tropical species. These chapters detail that many equatorial species show robust circannual rhythms in captivity, but that only a few, notably island-breeding seabirds (Chapin 1954; Reynolds et al. 2014), show free-running cycles in the wild. A main question, therefore, is the nature of the *Zeitgeber* that enable most tropical species to synchronize with the external year. The chapter by Heideman (this volume) points out bats with circannual rhythms that do not entrain to photoperiod, and the chapter by Goymann

and Helm (this volume) reports on entrainment of birds to subtle, photic cues at the equator. Both chapters also place circannual and photoperiodic timing in ecological and evolutionary context.

Algae Another environment that may be nearly constant, and thereby favor robust circannual rhythms, is the deep-sea region of oceans. Research examining different species of algae indeed established circannual rhythms in various processes, including germination, growth, and cell division (Costas and López Rodas 1991; Lüning and Kadel 1993; Matrai et al. 2005). A landmark paper by Anderson and Keafer (1987) documented the presence of circannual cycles even in the unicellular dinoflagellate *Gonyaulax tamarensis*. The mechanisms of the long biological time constants are difficult to conceive of even in multicellular organisms, let alone in unicellular organisms (see also the chapter by Lincoln and Hazlerigg, this volume). However, the relative tractability of these organisms and their unicellular organization could provide key insights into regulatory mechanisms. It would be highly desirable that work on this promising, and probably relatively tractable, circannual model system were continued.

Sheep The species introduced here have in common that their environments or life styles make photoperiodic information hard to obtain or potentially misleading, so that they would have been expected to have evolved robust circannual rhythms. However, persistent circannual rhythms can also be found in some species that live year around in temperate areas with unhindered access to photoperiodic change. Among those are breeds of sheep, for example, Soay sheep (see chapter by Lincoln and Hazlerigg, this volume). These animals have provided significant advances in our understanding of the neuroendocrine mechanisms that underlie circannual rhythms, including evidence for a circannual pacemaker located in the pituitary gland in the brain (Lincoln et al. 2006). Even after disconnecting the pituitary from neuronal input, which brought reproductive cycles to a halt, these animals showed persistent circannual cycles of the hormone prolactin secreted by lactotrophic cells in the anterior pituitary gland. These data are tantalizing and indicate that circannual timing of specific seasonal processes may reside within specific tissues in more complex species. For further background of these studies, and of the mechanistic outlook that has developed from this work, see the chapter by Lincoln and Hazlerigg (this volume).

11.5 Challenges in the Study of Circannual Rhythms

Although circannual rhythms on a whole meet the full set of criteria expected of biological oscillators, there is still some confusion in the literature about their endogenous nature and biological role (Mrosovsky 1970; Menaker 1974; Dawson et al. 2001; Dawson 2007; Newton 2008; Wikelski et al. 2008). We believe that many perceived difficulties have originated from differences in research traditions, terminologies, and choice of model species, which can ultimately be harmonized.

Circannual rhythms have sometimes been regarded as irrelevant or artefacts because under natural conditions powerful *Zeitgeber* are commonly available. This criticism is a shared legacy of endogenous rhythms in general. Good arguments for the relevance of endogenous rhythms under natural conditions include specific entrainment properties (Johnson et al. 2003) and benefits of internal representation of time and temporal coordination of physiology (Dunlap et al. 2004). For circadian rhythms, the major difficulties arising from their disruption certainly support their relevance (Fonken et al. 2013). However, for a broader appreciation of endogenous rhythms, identification of the mechanistic basis is essential. Circadian rhythms are ubiquitous in a world where photic *Zeitgeber* are available, but critics were only convinced of their existence when the formerly intractable mechanistic basis was elucidated. Today it seems hard to believe that pioneers such as Jürgen Aschoff were long accused of reporting on mere artifacts, and that the endogenous character of circadian clocks was scientifically debated at least until 1970 (Brown et al. 1970). Rhythms on other timescales, including circannual but also circatidal and circalunar rhythms, are still faced with criticism, although researchers now begin to reveal their molecular basis (see the chapter by Zantke and Tessmar, this volume; and Zhang et al. 2013).

Of the endogenous clocks, circannual rhythms are obviously the slowest to be tested (Menaker 1974). Data are still available only for some species and for relatively few circannual cycles (Gwinner 1986). Furthermore, the outcomes of these investigations were sometimes inconsistent, leading to further skepticism. For example, when several processes were studied in parallel (for example, reproductive state, body mass, and a hormone), they sometimes differed in rhythmic behavior, so that molt rhythms may have persisted although reproductive cycles became arrested (Gwinner 1986; Newton 2008). Similarly, in several but not all systems these long-term rhythms were relatively variable (Mrosovky, personal communication), and the conditions under which these rhythms persisted varied among organisms. In some species, circannual rhythms were maintained under a wide range of constant daylengths (e.g., sylvid warblers; Berthold 2001; Helm et al. 2013), including continuous light (Fig. 11.4; Rani and Kumar 2013; Holberton and Able 1992), indicating that cycling requires no alternation between light and darkness. However, in other species rhythms continued only under a limited daylength range or were not expressed at all (Dawson 2007). These observations provide challenges for circannual research, but they also point to understudied and underappreciated features of seasonal biology and photoperiodism.

Dissociation of Processes The observation that, under circannual conditions, physiological processes can dissociate, is a powerful indication that their fixed sequence results from synchronization by light. Thus, although hormones mediate the transitions between life history stages (Jacobs and Wingfield 2000), the underlying processes are physiologically sufficiently independent to become uncoupled (see also the chapter by Lincoln and Hazlerigg, this volume). Under natural conditions, the wide range of variation in the sequence of life history stages gives further testimony to a principally modular, flexible composition of the annual cycle.
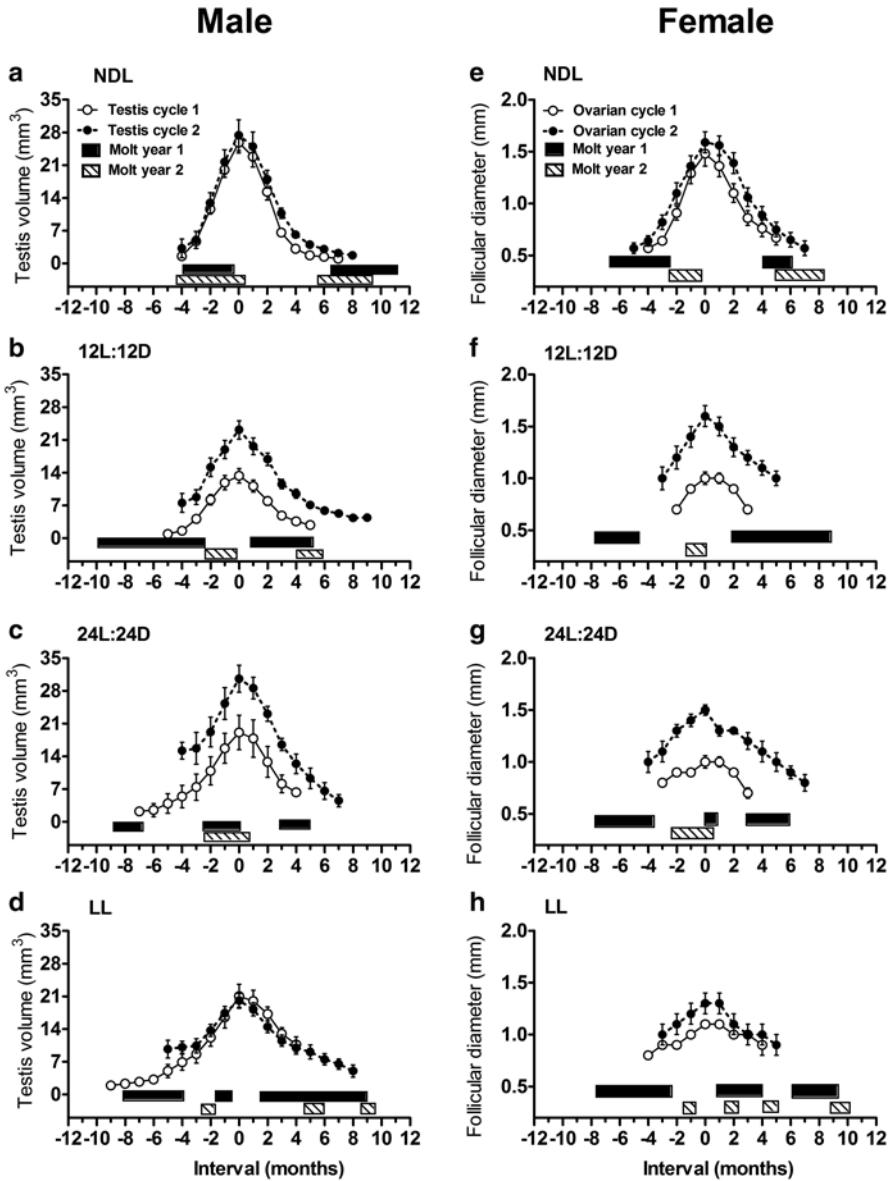
Fig. 11.4 Persistence of avian circannual rhythms under different light conditions: reproductive (*curves*) and molt (*bars*) cycles of male and female spotted munia (*Lonchura punctulata*) kept under different light conditions. In all cases, data are shown for two cycles (first year, *white circles*; second year, *black circles*). Male (**a–d**) and female (**e–h**) birds were kept under natural (*NDL*) and artificial lighting conditions (12 L:12D, 24 L:24D and LL; L=22±2 lux, D=0 lux). On the *x*-axis, zero indicates the timing of maximal gonadal size in a given year. The preceding and following months are plotted from −12 to +12. (Reproduced from Rani and Kumar (2013), with friendly permission by *General and Comparative Endocrinology*; see there for details)
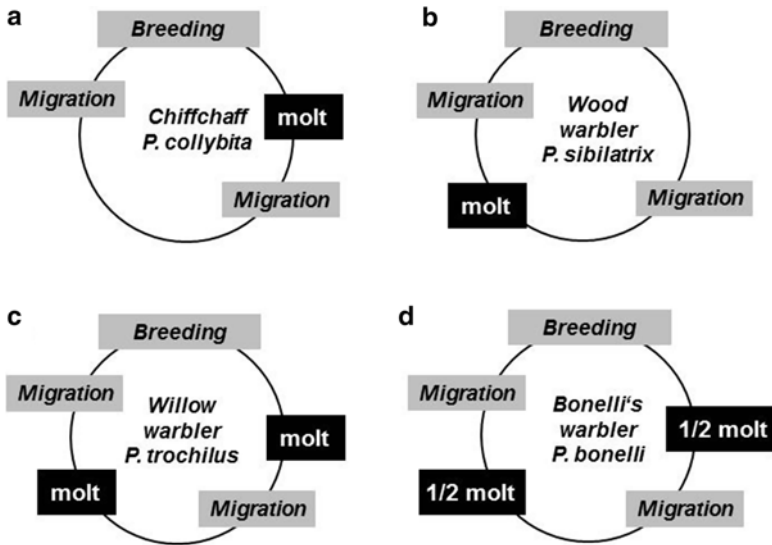
Fig. 11.5 Variable position of molt within the annual cycle: schematic shows timing of molt in four sympatrically breeding species of *Phylloscopus* warblers. In these migratory songbirds, molt occurs either (**a**) solely after breeding, or (**b**) solely in the winter quarters, or (**c**) is fully completed twice per year, or (**d**) is split between the winter and breeding quarters. These patterns are thought to relate to migration strategy. (Based on summary in Newton 2008)

For example, warblers of the genus *Phylloscopus* are similar in appearance but differ in the extent of their migrations, as well as in their annual cycles (Newton 2008). Figure 11.5 shows schematically the position of molt with respect to breeding and migration. Four closely related species molt either directly after reproduction, or in winter after autumn migration, or partially at both times, or undergo two complete molts (Newton 2008). This plasticity in nature and in the experimental studies should inspire fresh mechanistic thinking. Circannual rhythms were sometimes seen to arise as sequences of connected stages with sequential negative feedback, adding up to roughly 1 year (Mrosovsky 1970; Wikelski et al. 2008). For example, reproductive activation could activate pelage or molt, which would inhibit reproduction. After molt completion, inhibition could be lifted, and reproductive activation could recapitulate. The continuation of circannual cycles in some but not all traits, and the plasticity of sequences in wild organisms, makes this explanation unlikely and calls for other ideas. Menaker (1974) correctly considered the discussion of whether circannual rhythms were really rhythms or merely a series of sequential steps to be unproductive, and explained: "Of course, both circannual and circadian rhythms must consist of sequences of interdependent steps, the productive question in both fields (but perhaps more easily studied in circannual rhythms) is at what level of organization do the crucial steps occur and can they be identified and their interactions analyzed." The chapter by Lincoln and Hazlerigg in this volume outlines how we are beginning, 40 years later, to distinguish different levels of

organization on which sequential steps can occur. The annual cycle may be composed of modular, circannual processes, such as reproductive state, molt, metabolic state, and migration, which may be integrated through photoperiodic synchronization and be mediated by endocrine control (see the chapters by Monecke et al., and by Heideman, this volume).

Circannual Rhythms and Photoperiodism Research on photoperiodism and circannual rhythms, respectively, has not always been sufficiently integrated, which has sometimes led to the false perception of noncompatible mechanisms. From a circannual perspective, it is entirely clear that in the real world, circannual rhythms normally are entrained by photoperiod as its main *Zeitgeber*, much as circadian rhythms are normally entrained by the daily light cycle. Recent findings from several circannual study systems have underpinned this basic insight by elaborating phase-response curves, which closely resemble those of circadian rhythms (Fig. 11.2, Monecke et al. 2009; see also the chapter by Miyazaki et al., this volume). These curves detail how the response of the organism to a given daylength depends on the phase of the circannual cycle, underpinning the realization that photoperiodic sensing is mechanistically distinct from the underlying long-term timer (Johnston et al. 2003; Lincoln et al. 2005). Correspondingly, from a photoperiodic perspective there is ample evidence that responses to daylength depend on the phase of the annual cycle (Bradshaw and Holzapfel 2007). In view of these convergent findings, the remaining difference is in an emphasis on endogenous cycles and an associated *Zeitgeber* role of photoperiod, or on photoperiod as the driver of the cycle via long-term timing mechanisms, respectively.

Harmonizing these perspectives is made complicated by terminology used by many researchers to describe photoperiodic regulation and circannual rhythmicity, respectively, and by the choice of study organisms and photoperiodic conditions (Butler et al. 2010). Circannual studies have mainly focused on systems on the extreme end of sustained rhythmicity, selecting species with robust cycles and constant daylengths that optimized rhythmicity. Photoperiodic studies, in turn, have focused on species whose cycles are highly responsive to or completely dependent on photoperiod, and have chosen daylength conditions that efficiently switch between life history stages or arrest rhythmicity (Gwinner and Wozniak 1982). The definitions that are central to the two approaches reflect these respective focal interests. For photoperiodism, the main interest was in robust reproductive responses to relatively short-term changes in photoperiod. Birds such as the European starling *Sturnus vulgaris* maintained on short daylengths (e.g., <12 h) showed a prepubertal-like state and were then often referred to as being *photosensitive* (Nicholls et al. 1988; Dawson et al. 2001). Exposure of these birds to long daylengths initiates a cascade of events that results in a state referred to as *photostimulated*, characterized by gonadal development and reproductive competence. However, long days also lead to the generation of a state referred to as *photorefractory*, in which these birds experience complete involution in reproductive physiology. Recent comparative work has highlighted that the term "photorefractoriness" stands for a host of forms of temporary or permanent inhibition of the advance of the annual cycle under particular photoperiodic conditions

(Nicholls et al. 1988; Hahn et al. 1997; Hahn and MacDougall-Shackleton 2008; MacDougall-Shackleton et al. 2009). Detailing these forms and relating them to the progress or dampening of circannual rhythms is beyond the scope of this introduction but is certainly worth further exploration. The experimental data and the associated characterization of the neuroendocrine light input pathway hold considerable potential for identifying circannual mechanisms. Unfortunately, the polarization between photoperiodic and circannual perspectives has slowed the much-needed progress in understanding long-term timing processes.

Highly flexible interactions between circannual rhythms and photoperiodism are supported by the wide range of avian breeding and molt cycles under natural conditions. For example, many species or even local populations breed on short and even declining photoperiods. Figure 11.3 shows that breeding cycles of closely related stonechats from different geographic regions are spread out across the year (Helm 2009). The respective daylengths under which these processes occur underpin their photoperiodic flexibility. For avian populations inhabiting arid and hot environments, breeding in winter is common, even if conspecifics in different environments breed in summer. We consider it unlikely that such populations would use a markedly different mechanism than their summer-breeding conspecifics to time reproduction and molt. Correspondingly, migratory species show highly diverse responses to the daylength conditions they experience in winter. For example, from a photoperiodic point of view, transequatorial migrants such as bobolinks (*Dolichonyx oryzivorus*) would be expected to breed in winter when austral daylengths are long (Hamner and Stocking 1970; Gwinner 1988). Instead, these species display greatly extended relative photorefractoriness, which however eventually dissipates under these long days, allowing migrants to reactivate their reproductive system in preparation of breeding. When tested under constant circannual photoperiods, species such as the garden warbler *Sylvia borin* (Berthold et al. 1972), and also the white-crowned sparrow *Zonotrichia leucophrys* (Wingfield 1993), reactivated their reproductive system under long days (16–18 h of light). Clearly, therefore, birds appear to be relatively flexible in the adjustment of their response to components of the photoperiodic cycle. Evolutionary shifts seem to be compatible with the idea of an underlying circannual rhythm (Helm et al. 2009). Changes in the timing of events, such as winter breeding of stonechats or winter molt of *Phylloscopus* warblers (Fig. 11.5; Newton 2008), would thereby arise from adjustments of the phase relationship of components of the circannual cycle to components of the photoperiodic cycle. Such adjustments could be effected by shifts of the molecular mechanisms that regulate the neuroendocrine control of reproduction (e.g., neuropeptides), permitting reproduction under daylengths that better predict local environmental conditions favorable to breeding (Perfito et al. 2012).

The chapters in this book provide valuable information for linking the diversity of annual cycles to differences in photoperiodic responses and underlying mechanisms. Phase-response curves (Miyazaki et al., and Monecke et al., this volume) pinpoint phase-specific responses of the circannual system, and the physiological underpinnings of variation in photoperiodic responses are discussed in depth for mammals (see Heideman, this volume).

11.6 Opportunities and Perspectives for Unraveling Circannual Mechanisms

Despite the many challenges facing the circannual biologist, these are exciting times. Pioneering nucleic acid sequencing conducted by Edward Sanger had been considered the gold standard for molecular biology, especially DNA sequencing, for the latter part of the twentieth century (Sanger et al. 1977). His advances were essential for the direct sequencing of target genes, such as insulin, and his work resulted in being awarded the Nobel Prize in Chemistry in 1980. Recent developments of second-generation Sanger sequencing methods, also known as next-generation sequencing (NGS), have permitted massive high-throughput sequencing that has allowed an entire genome to be sequenced in less than 1 day. These new methods are quite ingenious: instead of sequencing a single nucleic acid region, NGS technologies simultaneously sequence millions of nucleic acids at a time (Metzker 2010). Truly, our ability to provide whole genomes has provided immense molecular information at an unprecedented rate. The availability of NGS technologies will undoubtedly provide significant advances for our understanding of the molecular mechanisms that generate the immense range of weird and wonderful rhythms described in this book.

The ability to sequence entire genomes will be an extremely valuable tool for the identification of evolutionarily conserved sequences that facilitate or dampen oscillations in physiology and behavior. Functional genome comparisons are currently hampered by the lack of genomes from nontraditional species. With the advent of NGS methods, it is now possible to obtain large bits of genomic information from simple organisms such as the dinoflagellates (see the chapter by Lincoln and Hazlerigg, this volume), to more complex organisms such as beetles, stonechats, European hamsters, and ground squirrels (see the chapters by Myazaki et al., Heideman, Monecke et al. and Goymann and Helm, this volume). Full genome-wide comparisons of circannual species with those that exhibit less pronounced oscillations (e.g., humans, mice) will yield valuable fundamental knowledge that will in turn allow for a better understanding of naturally occurring annual or possibly circannual rhythms in humans (Foster and Roenneberg 2008; Martinez-Bakker et al. 2014).

The application of NGS has also permitted the broad analyses of other molecular levels, such as RNA expression and genome-wide profiling of epigenetic markers and chromatin structure. Emerging techniques that permit these large-scale analyses of molecular processes include RNA-sequencing (RNA-seq); methylation-sequencing (methyl-seq), and chromatin precipitation assays (ChIP). RNA-seq consists of sequencing all RNA pieces within a cell or tissue and ultimately provides a snapshot of the RNA that is expressed at a single point (Metzker 2010). Using this technique an ambitious chronobiologist could unravel the seasonal "transcriptome" and ultimately map all genes that are transcribed during the circannual cycle. Furthermore, RNA-seq will also result in the discovery of substantial changes in noncoding (nc)RNA. ncRNAs range in size from small or microRNA (<50 bp) to longer

ncRNA (>200 bp). It is widely believed that ncRNA serve to permit genetic flexibility, and we suggest that the phenotypic plasticity associated with circannual rhythms may, in part, be regulated by these ncRNA (Cech and Steitz 2014). Our understanding of the role these ncRNAs play for regulating circannual rhythms is in its infancy. During the next few decades, delineating how ncRNA participate in the generation and regulation of circannual rhythms will undoubtedly identify novel agents for orchestrating the large changes in seasonal genomic, physiological, and behavioral plasticity.

Epigenetic modifications, including DNA methylation and histone acetylation and their enzymatic effectors, are becoming major players in the molecular regulation of biological timing (Fig. 11.6). Methyl-seq involves the sequencing of the genome with a specific focus on the location of DNA methylation, resulting in the creation of a "methylome." DNA methylation is an important molecular biological event, consisting of the addition of a methyl (CH_3) group to cytosine nucleotides in the genome sequence. Increased levels of methylation serve to prevent the ability of transcription factors from binding to the DNA template, effectively inhibiting gene transcription and reducing RNA expression. Given the recent identification of seasonal changes in enzyme expression involved in methylation (Stevenson and Prendergast 2013; Fig. 11.6b), it is likely that several genomic regions will exhibit seasonal variation in methylation levels (Fig. 11.6c); these epigenetic modifications most likely contribute to the extensive genetic plasticity identified in various microarray studies (Ross et al. 2004; Nakao et al. 2008; Mukai et al. 2009; Stevenson et al. 2012a). Furthermore, given the observation of heritable variation in neuroendocrine traits associated with circannual timing of reproduction, epigenetic modifications such as DNA methylation provide a strong candidate mechanism involved in the selection underlying this phenotypic plasticity (Avigdor et al. 2005; see the chapter by Heideman, this volume). For example, DNA methylation of key genomic regions in parents provides a molecular level at which selection can act to regulate the probability of gene expression, either by permitting or inhibiting, and thereby regulate circannual or annual timing that is subsequently passed on to the next generation. By employing methyl-seq approaches, it now has become possible to identify specific genomic targets that may facilitate the divergence in circannual physiological and behavioral processes despite the lack of genomic changes.

Advances in proteomics are another exciting technological advancement that will have significant impacts for the circannual biologist. The proteome consists of the entire set of proteins present in a cell, tissue, or organism. Our understanding of annual or seasonal changes in protein expression has primarily focused on select

Fig. 11.6 (continued) and circannual rhythmicity, exhibit light-dependent changes in expression. When hamsters are in the summer breeding condition (*green bars*), there is an increase in enzyme expression compared to the winter nonbreeding condition (*red bars*). **c** *dnmt3b* expression in immune cells (i.e., peripheral leukocytes) also changes in a seasonally dependent manner. (Data from Stevenson and Prendergast 2013; Stevenson et al. 2014, with friendly permission by the publishers)
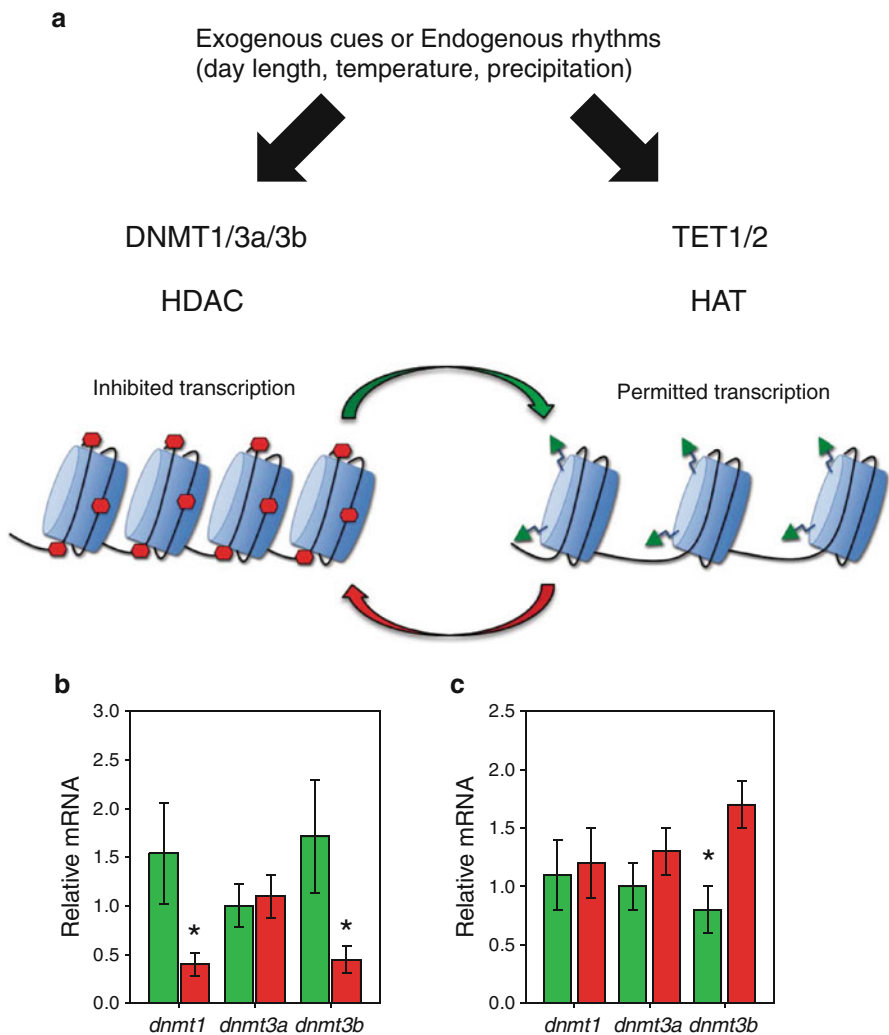
Fig. 11.6 Epigenetic modifications and the regulation of circannual or seasonal rhythms. **a** Endogenous circannual rhythms or exogenous environmental cues act to regulate gene transcription by regulating enzymes involved in epigenetic modifications. Two epigenetic events, DNA methylation and histone acetylation, can act independently or together, leading to the inhibition or enhancement of gene transcription. Epigenetic enzymes can be divided into those involved in DNA methylation or histone acetylation. DNA methyltransferase enzymes (isoforms 1, 3a and 3b; DNMT) are critical for adding methyl groups (indicated by *red hexagons*) onto the DNA. Another family of enzymes referred to as ten–eleven translocator (TET1 and TET2) are important for initiating the removal of methyl from the DNA, permitting the ability of genes to be transcribed. Another class of enzymes has been identified to increase or decrease the levels of acetyl molecules (indicated by *green arrows*) on histone proteins. Histone deacetylase (HDAC) and histone acetylase (HAT) enzymes are the primary effectors that remove or attach, respectively, acetyl to histones. **b** Recent work in the seasonally breeding Siberian hamster has found that *dnmt1* and *dnmt3b* enzyme expression in the hypothalamus, a key brain region implicated in the control of seasonal

neuropeptides, for example, gonadotropin-releasing hormone (GnRH; Stevenson et al. 2012b), neuropeptide VF precursor [NPVF; also known as gonadotropin inhibitory hormone (GnIH) Tsutsui et al. 2013], and KiSS metastasis suppressor (KISS; Revel et al. 2007). Annual or seasonal changes in these neuropeptides are well documented and provide a strong indicator of different seasonal reproductive states in a wide range of vertebrate species. Indeed, there are several other proteins that also exhibit changes over circannual timescales. Given that protein activity is the ultimate biological effector, a comprehensive understanding of genomic and proteomic plasticity will be important for future research in circannual rhythmicity at molecular and cellular levels.

Finally, there is growing evidence that circannual changes in histogenesis occur in many key brain and peripheral tissues (Hazlerigg and Lincoln 2011; see the chapter by Lincoln and Hazlerigg, this volume). Studies that have examined the neural distribution of bromodeoxyuridine (BrdU), a marker of newborn neurons, indicated that cortical, hypothalamic, and pituitary tissues are targets for neurogenesis. The origin of these new neurons appears to derive from stem cell niches located in the subventricular zone along the third ventricle (Hazlerigg and Lincoln 2011). Cyclical changes in neurogenesis are well established in seasonal species (Tramontin and Brenowitz 2000), however, the challenge is linking the variation in new cells with a functional outcome. Recent work that attempted to resolve this issue employed double-labeled histochemistry and revealed that approximately 10 % of BrdU cells coexpress CD-45, a pan-leukocytic marker (Hazlerigg et al. 2013). These data suggest that seasonal changes in neurogenesis may be involved in neuroimmune mechanisms. Given the large number of other BrdU cells expressed in the hypothalamus, it is likely that annual changes in histogenesis will have pleiotropic effects. Unraveling the relative contribution of cyclical histogenesis and epigenetic modifications for the generation of circannual rhythmicity will be one hurdle facing the next generation of circannual biologists. The next several years will undoubtedly provide exciting and innovative findings.

Conclusions

In the field of circannual rhythms, the decades invested in laying the foundations, by collecting hard-won whole-organism data over many years, may soon provide the basis for understanding the underlying mechanisms. Model systems are principally in place, and the major recent advancements in circannual biology are intriguing and highly innovative. The benefits of understanding seasonal processes are becoming evident for many applications, including ecology, climate change biology, health, and well-being. Given the timeliness, it should be feasible to master perhaps the most difficult of all hurdles: convincing funding agencies to support long-term research on circannual clocks.

For those daring enough to tackle the challenges and rewards in circannual research, they might find solace in an old advertisement posted by the great British

explorer Sir Ernest Shackleton: "Men wanted for hazardous journey, small wages, bitter cold, long months of complete darkness, constant danger, safe return doubtful, honor and recognition in case of success." For today's explorers, men and women alike, the reward may lie in a much deeper understanding of the genuinely rhythmic life on earth. The wide taxonomic spread of circannual rhythms, down to the level of unicells, and the findings of their phase-specific interaction with photoperiod, suggest the possibility of a fundamental, endogenous basis to organismal seasonality. The appreciation of such a mechanism may have been obscured in the past by conceptual problems (Paul et al. 2008: "The rigid classification of timing mechanisms as either timers or clocks may be physiologically misleading despite its heuristic value") and by particular photoperiodic experimental settings (Butler et al. 2010: "Distinctions between photoperiodic and circannual seasonal organization erode with the incorporation in the laboratory of ecologically relevant day length conditions"). Moving beyond these difficulties will clear our vision for the relevance of circannual rhythms. The circannual system drives seasonal transitions, provides temporal coordination of physiology, and, importantly, regulates a seasonally changing suite of flexible, species-specific responses to environmental input. The potential importance of this function of circannual rhythms was outlined in an unpublished note left to us by the late Eberhard Gwinner: "Idea: To study only the photoperiodic part of photoperiodism is like studying hormones without considering hormone receptors".

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