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EDITOR INVITED REVIEW

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Gerald Lincoln: A man for all seasons

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Abstract

Gerald Anthony Lincoln died after a short illness on 15 July 2020 at the age of 75 years. Gerald was Emeritus Professor of Biological Timing at Edinburgh University and a Fellow of the Royal Society of Edinburgh. He was an outstanding scientist and naturalist who was a seminal figure in developing our understanding of the neuroendocrine mechanisms underlying seasonal rhythmicity. This review considers his life and some of his major scientific contributions to our understanding of seasonality, photoperiodism and circannual rhythmicity. It is based on a presentation at the online 2nd annual seasonality symposium (2 October 2020) that was supported financially by the *Journal of Neuroendocrinology*.

KEYWORDS

circannual, GnRH, melatonin, photoperiod, season

1 | EARLY LIFE AND CAREER

Gerald grew up on farms in Norfolk, perhaps explaining his lifelong fascination with the natural world and with conservation. As a teenager, he bought a moth trap and wrote up a project investigating how weather conditions affected moth numbers on the farm. This was awarded the Prince Philip Award for Zoology and, as an undergraduate, Gerald studied zoology at Imperial College, University of London. Gerald's work on moths came to the attention of Roger Short who was working at the University of Cambridge Veterinary School, so he was offered a PhD project studying the seasonality of reproduction in red deer on the Isle of Rum, Scotland. Rum has been a world-leading centre for research subsequent to being acquired by Nature Conservancy Council in 1958. Although much of the focus on Rum has been on behavioural ecology and population dynamics and genetics of red deer, Gerald's specific interests were to investigate how behaviour and physiology were regulated by endocrine systems.[1] He showed how the stags cast their antlers in the spring when testosterone levels are at their nadir and grow new antlers when levels remain low in the summer. As the daylength decreases in autumn, testicular synthesis of androgens increases. This facilitates rutting behaviour, and the antlers stop growing and become mineralised, resulting in hard bony weapons crucial in competitive encounters with other males.[2] When he was still a PhD student on Rum, Gerald had the rare distinction of publishing a letter anonymously in *Nature*.[3] He had been weighing his shavings daily and noted that his beard growth increased in anticipation of returning to the main land and resuming sexual activity. This was widely reported in the newspapers at the time, although it had the important message that that testosterone production could be influenced by the higher centres. When Roger Short was appointed director of the

new MRC Unit of Reproductive Biology in Edinburgh, he recruited Gerald in 1974 to study mechanisms underlying male fertility.

Arguably a major factor in Gerald's success was his decision to work with the Soay sheep as an animal model for this work. Although the laboratory rat and primates were the established animal models at the time, Gerald's work on seasonality in deer underscored the value of studying a species in which fertility changed dramatically over the course of the year, such that the underlying neuroendocrine mechanisms could be appreciated. The Soay is a small semi-domesticated breed of sheep retaining a marked seasonal cycle, which is also convenient in practical terms for collecting multiple blood samples, as well as for surgical and experimental procedures. Roger Land at the Roslin Institute provided facilities for housing Soay sheep indoors under controlled lighting environments; thus, animals could be brought into breeding conditions independently from the external time of year. Gerald also benefited from the Reproductive Biology Unit's commitment to development of radioimmunoassays; thus, hormonal profiles could for the first time be measured across multiple species in large numbers of samples, allowing accurate profiling of secretory patterns. Gerald collaborated with Alan and Judy McNeilly, who were scientists at the forefront of generating suitable antisera and protocols for radioimmunoassay.[4,5]

2 | THE GONADOTROPHIN-RELEASING HORMONE PULSE GENERATOR AND SEASONAL CONTROL OF FERTILITY

Gerald developed a protocol where male Soay sheep (rams) were maintained indoors on long days comprsing 16 hours of light and 8 hours of dark for 16 weeks, then on short days comprising 8 hours of light and 16 hours dark for 16 weeks. Many overt aspects of annual seasonality were apparent in the sheep but compressed into a 32-week cycle, including testicular diameter, inguinal skin colouration, moulting of the wool and the rate of horn growth. Collection of serial blood samples from indwelling jugular cannulae at different points in this photoperiodically driven cycle showed clearly that the cycle in testis size and function reflected changes in the pulsatile pattern of luteinising hormone (LH) secretion.[6] Specifically, the sexually inactive phase in long days reflected a low frequency of LH pulses, although those that occurred were of a relatively high amplitude. By contrast, exposure to short days induced an increase in LH pulse frequency and a consequential reduction in pulse amplitude; this was associated with an increase in plasma testosterone concentrations. Although pulsatile LH secretion had been described in a number of other mammalian species by the mid-1970s, this was clear evidence that, in the sheep at least, an increase in LH pulse frequency was the primary signal to drive steroidogenesis and, alongside increased follicle-stimulating hormone, gametogenesis.[7] The implication of this is that a change in hypothalamic function, culminating in a change in frequency of GnRH secretion, must be causing the change in the frequency of release of LH from gonadotrophs in the anterior pituitary. Gerald exploited a number of experimental strategies to confirm the relationship between gonadotrophin-releasing hormone (GnRH) and LH, as well as their role in control of the testis. For example, using small portable infusion pumps, he showed that intermittent stimulation of sexually inactive rams with synthetic GnRH at 2-hour intervals would drive testicular function[8]; thus, GnRH alone was sufficient to induce seasonal cycles in reproductive function. Conversely, he used an immunoneutralisation strategy to demonstrate that loss of GnRH led to reproductive failure.[9] The development of surgical procedures to collect blood from the portal capillaries in the median eminence of sheep confirmed the precise relationship between GnRH and LH secretion experimentally in the following decade.[10,11]

Gerald interpreted this GnRH pulse frequency-modulated seasonal control of fertility in sheep as a clear indication that the key mechanistic questions about seasonality were really about central nervous system function. An example of his creative and lateral thinking was that he had found that use of an opiate-based anaesthetic widely used in veterinary practice (Immobilon) markedly suppressed LH secretion in sheep.[12] Because the Immobilon did not impair the response to exogenous GnRH and treatment with the opiate antagonist diprenorphine rapidly restored LH secretion, he inferred that these were central effects.[13] Gerald was aware of the work of Hughes and Kosterlitz with respect to identifying enkephalin peptides as endogenous opioids,[14] and so investigated in depth whether the seasonal suppression of GnRH secretion in sheep might reflect enhanced endogenous opioid activity in the hypothalamus. This was an eminently plausible hypothesis, and was exhaustively tested using the opiate antagonist naloxone as a powerful pharmacological tool. Contrary to expectations, blockade of endogenous opioids with naloxone failed to restore suppressed gonadotrophin secretion in reproductively quiescent rams, yet it enhanced pulsatile LH secretion during the breeding season.[15] Subsequent studies confirmed a key role for opioidergic systems in mediating gonadal steroid negative feedback to the GnRH secretory system rather than a role in mediating seasonal quiescence,[16] although it is worth noting that these studies on endogenous opioids preceded the more specific identification of the kisspeptin-neurokinin B-dynorphin (KNDy) system by almost two decades.

3 | MELATONIN

The realisation that seasonal changes in testicular function and consequent changes in secondary sexual characteristics, physiology and behaviour all reflected central changes in the control of the pituitary gland directed Gerald's research direction towards how changes in photoperiod were detected and communicated to the hypothalamus. Studies in hamsters where the pineal gland had been removed implicated this structure in photoperiodic response, but, in the ruminant, the pineal gland is deep beneath the cortex on the roof of the epithalamus, and surgical access risks rupture of

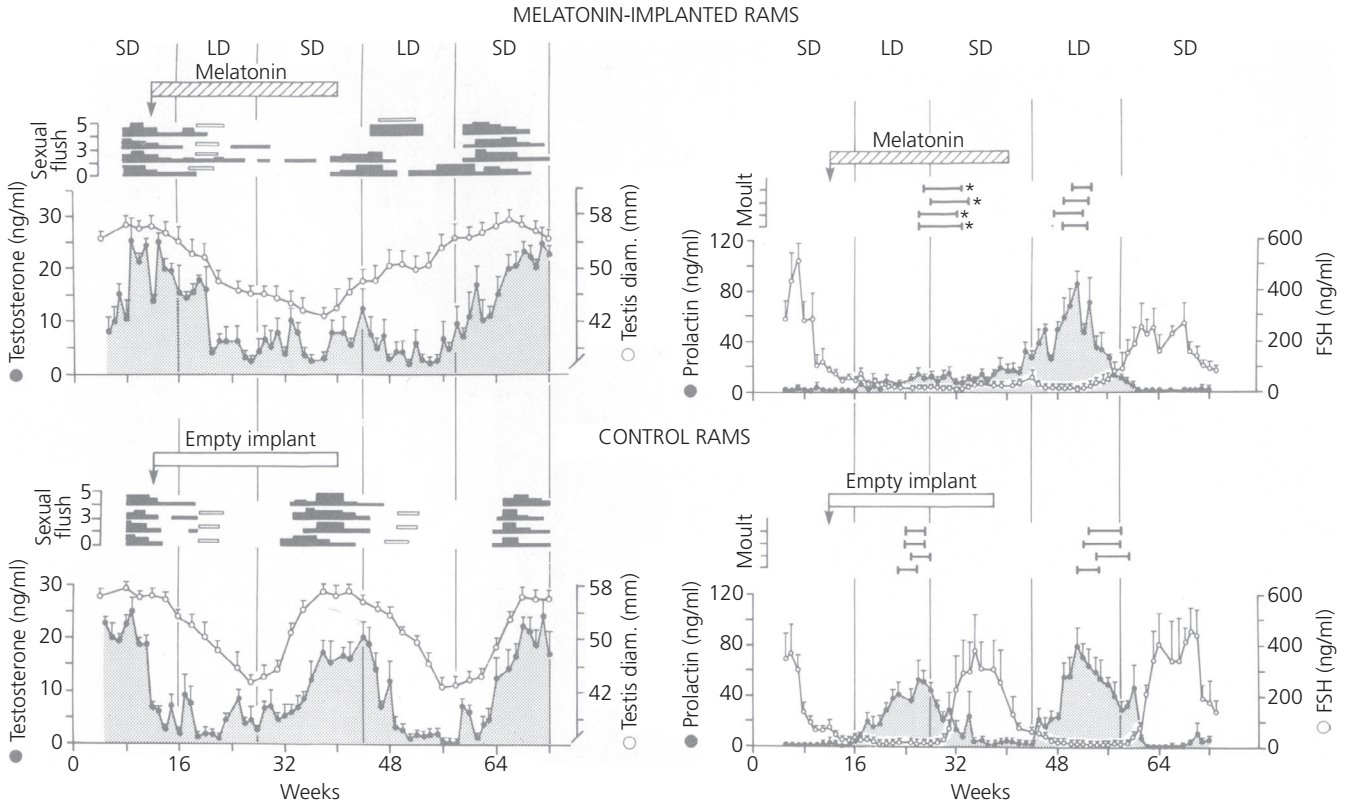

FIGURE 1 Changes in diameter of the testes (mean ± SEM), plasma concentrations of testosterone, FSH and prolactin, intensity of the sexual skin flush (individual values), the period of intense rutting behaviour (individual values, small open bars) and the timing of the moult of the wool from the scrotum (individual values in four melatonin-implanted and four control adult Soay rams, exposed to alternating 10- to 30-week periods of short days (SD) and long days (LD) for 68 weeks. The implants were introduced at week 14 during long days, and left in place throughout the remainder of the study (reproduced with permission from the *Journal of Reproduction and Fertility*[21])

the mid-saggital sinus. Gerald therefore developed an alternative surgical strategy to determine the contribution of the ovine pineal gland to the photoperiodic control of reproduction. This involved disruption of the sympathetic innervation to the face and head by removal of the superior cervical ganglion. His initial studies in just four ganglionectomised rams and four sham controls revealed that pineal function was essential for synchronisation of not just reproductive function, but also the prolactin axis to changes in artificial photoperiod.[17-19] Radioimmunoassay confirmed that ganglionectomy ablated circadian rhythmicity of melatonin secretion, although the assays still detected above baseline circulating concentrations of melatonin.[20] Later studies using subcutaneous implants that continually released melatonin (Figure 1) confirmed that melatonin was a key neurochemical signal in that this treatment disrupted the timing of reproductive and prolactin-regulated cycles in Soay rams exposed to artificial lighting regimens,[21] and also advanced the onset of reproductive activity in red deer stags maintained outside.[22]

In retrospect, we can appreciate that the constant release of supraphysiological concentrations of melatonin served to 'blindfold' the animals to the ambient photoperiod, although these dramatic actions of melatonin in ruminants underpinned later elegant studies using timed infusions to identify the precise characteristics of the nocturnal melatonin signal that is communicated to the neuroendocrine system.[23] Gerald and other research groups exploited a miniaturised version of this continuous-release melatonin implant strategy to identify potential target sites of melatonin.[24,25] Microimplants placed in the mediobasal hypothalamus but not in the preoptic area significantly accelerated the onset of testicular regrowth[24] and initiated a rapid decline in prolactin secretion.[26] Control studies using radiolabelled melatonin revealed that the hormone diffused quite a distance away from the implant site, so precise location of melatonin target cells was not feasible. Autoradiographical analysis of radiolabelled melatonin binding identified widespread melatonin receptor distribution in the sheep brain,[27,28] and so these microimplant studies certainly helped to focus interest on melatonin regulating classical neuroendocrine regions in sheep, whereas, in many other mammalian species, the distribution of melatonin receptors was far more limited and, in some mustelids, restricted to the pituitary gland rather than the brain itself,[29] raising the issue of how the mediobasal implant experiments should be interpreted.

4 | THE PARS TUBERALIS

Even in sheep, the pituitary stalk (pars tuberalis) was found to be the most dense region of melatonin binding,[30] and Gerald followed up

his central implant studies by showing that implants placed in the pars tuberalis but not the pars distalis could alter seasonal cycles in reproductive endocrinology and in prolactin secretion,[31] further supporting the pars tuberalis as a direct melatonin target. Arguably Gerald's greatest contribution to this debate was the development with Iain Clarke of the hypothalamo-pituitary disconnected (HPD) Soay ram model. This was a complex surgical approach where, via a transsphenoidal approach, tissue from the *tuber cinereum* was removed and an aluminium barrier inserted, retaining a sufficient pituitary blood supply to maintain viability of the pars tuberalis and pars distalis.[32] The rationale for this complex approach is that, if the effects of melatonin in sheep are exclusively within the hypothalamus, then no seasonal cyclicity or photoperiodic responsiveness will be seen in HPD sheep because communication between the hypothalamus and the pituitary gland has been abolished. If, however, the pars tuberalis is an important melatonin target site, then because communication between the pars tuberalis and pars distalis is still intact, cyclicity in some neuroendocrine axes should still be observed. Of course the HPD disrupts the delivery of GnRH to the pituitary, and so HPD sheep have hypogonadotrophic hypogonadism; thus, the reproductive axis cannot be used as a test of the hypothesis. However, because prolactin secretion is under predominantly inhibitory control by hypothalamic dopamine, this can be used as an index of seasonality. Gerald placed HPD sheep and sham-operated controls under alternating 16 week periods of long and short days and found that the prolactin cycles and wool growth remained perfectly in synchrony with the photoperiodic regime (Figure 2 [32]). In confirmation of the loss of central input, prolactin concentrations never fell to the undetectable levels seen in sham-operated rams in short days, presumably reflecting the loss of the hypothalamic dopamine signal. Correspondingly, acute induction of stress caused a short-term rise in prolactin in the sham animals but was ineffective in the HPD animals, and the centrally acting glutamate agonist NMDA suppressed prolactin secretion in sham animals but not in the HPD sheep, with both findings comprising lines of evidence that the loss of central communication was complete in the HPD animals.[32] Follow-up studies confirmed that secretagogues such as thyrotrophin-releasing hormone could elicit prolactin secretion in HPD sheep and dopamine agonists could suppress prolactin, whereas dopamine antagonists were without effect.[33] Moreover, the HPD sheep responded to peripheral melatonin implants with an initial suppression but eventual increase in prolactin secretion, similar to the sham controls.[34] This brilliant series of experiments provided the most compelling evidence of a direct action of melatonin on the pars tuberalis, at least with respect to the control of prolactin secretion.

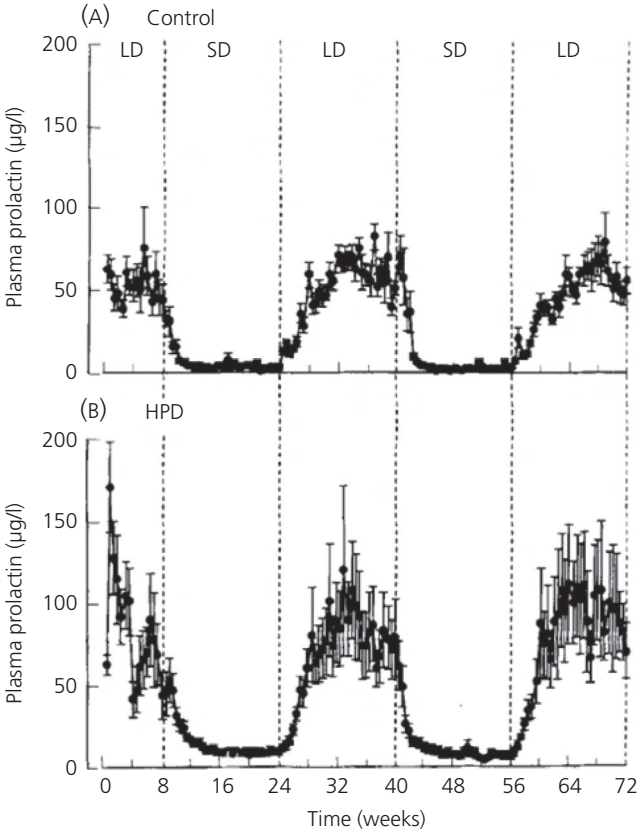

FIGURE 2 Long-term changes in the blood plasma concentrations of prolactin in groups of (A) control and (B) hypothalamo-pituitary disconnected (HPD) Soay rams housed indoors under an artificial lighting regimen of alternating 16-weekly periods of long days (16L:8D, LD) and short days (8L:16D, SD) for 72 weeks. The HPD and sham-operations (half control group) were performed in experimental week 1 (8 weeks into a 16-weekly period of long days). The values are mean ± SEM, $n = 8$, based on blood samples collected twice weekly (reproduced with permission from the *Journal of Neuroendocrinology*[32])

It may appear to be counter-intuitive that the pars tuberalis would signal in a retrograde manner to the hypothalamus to regulate

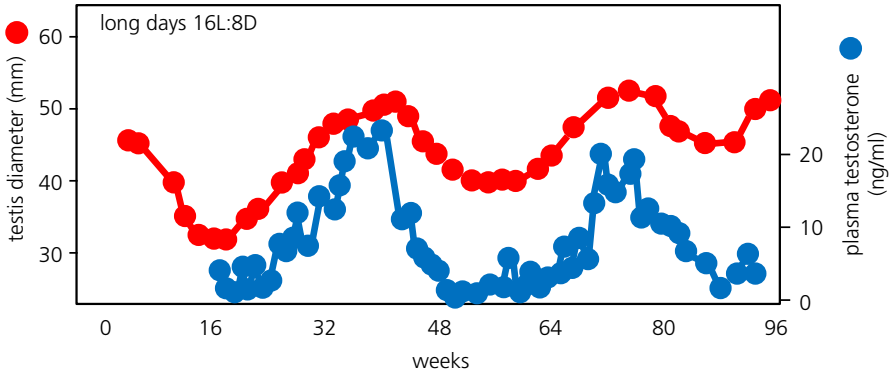

FIGURE 3 Changes in diameter of the testes and the blood plasma levels of testosterone (mean ± SEM) in adult Soay rams exposed to long days (16L:8D) for 94 weeks following pre-treatment with short days (8L:16D) for 16 weeks (data redrawn from *Biology of Reproduction*[47])

other neuroendocrine axes, although there is now compelling evidence that this is the case. Studies by many research groups including Yoshimura in quail[35] and Hazlerigg[36] in sheep identified the beta subunit of the thyroid-stimulating hormone (βTSH) as a major paracrine factor from the pars tuberalis that acts on TSH receptors in hypothalamic tanycyte cells to regulate thyroid hormone processing and, ultimately, seasonal reproductive function.[37] Gerald focussed his attention on the mechanisms by which the photoperiodically regulated change in nocturnal duration of melatonin might be decoded by thyrotrophs in the pars tuberalis. Given the cloning of multiple mammalian 'clock' genes in the 1990s, as well as the hypothesis that the circadian phase at which melatonin was present might determine how a long and short duration of melatonin could elicit different seasonal responses, understanding the effects of melatonin on clock gene expression in the pars tuberalis was a natural step forward. Not only were many clock genes highly and rhythmically expressed in the pars tuberalis, but the phasing of the period family (*per1*, *per2*) and the cryptochrome family (*cry1*, *cry2*) differed in long and short photoperiods.[38] In sheep maintained in constant light to suppress endogenous melatonin production, infusion of melatonin was found to acutely induce *cry1* expression and suppress other clock genes, indicating a causal link,[39] and in vitro analyses also identified the immediate early gene *egr1* as a potential mediator of the effects of melatonin.[40] Subsequent transcriptomic analysis of sheep pars tuberalis identified a large number of genes that had altered phasing in long vs short photoperiods,[41] and *bmal2*, *eya3* and *TAC1* have all emerged as pathway candidates in transducing the melatonin signal into a seasonal drive from the pars tuberalis.[42-44] However, somewhat unexpectedly, sheep maintained for a prolonged time on long days showed clock gene phasing in the pars tuberalis that corresponded to the ambient melatonin phasing, yet downstream seasonal physiology reversed from the initial photoperiodic state.[45] Gerald considered this as important evidence for the existence of intrinsic circannual mechanisms that were independent of melatonin-regulated timers.[45]

5 | CIRCANNUAL RHYTHMICITY

Throughout his career, Gerald had appreciated the contribution of endogenous circannual rhythmicity to the generation of seasonal cycles in behaviour and physiology, recognising that seasonality not only resulted from responses to changing ambient photoperiod, but also reflected innate long-term timing processes with a periodicity of approximately 1 year. This appreciation may have arisen from his fieldwork in tropical habitats, where annual rhythmicities in reproductive cycles exist in many species despite relatively small changes in daylength and, in some cases, these are out of synchrony in a population, although individuals retain quite precise annual timing.[46] In a very long-term study with his PhD student Osborne Almeida (Figure 3), it was observed that innate cyclicity in reproductive activity occurred in Soay rams maintained under constant photoperiod for 96 weeks.[47] However, this rhythmicity persisted under constant

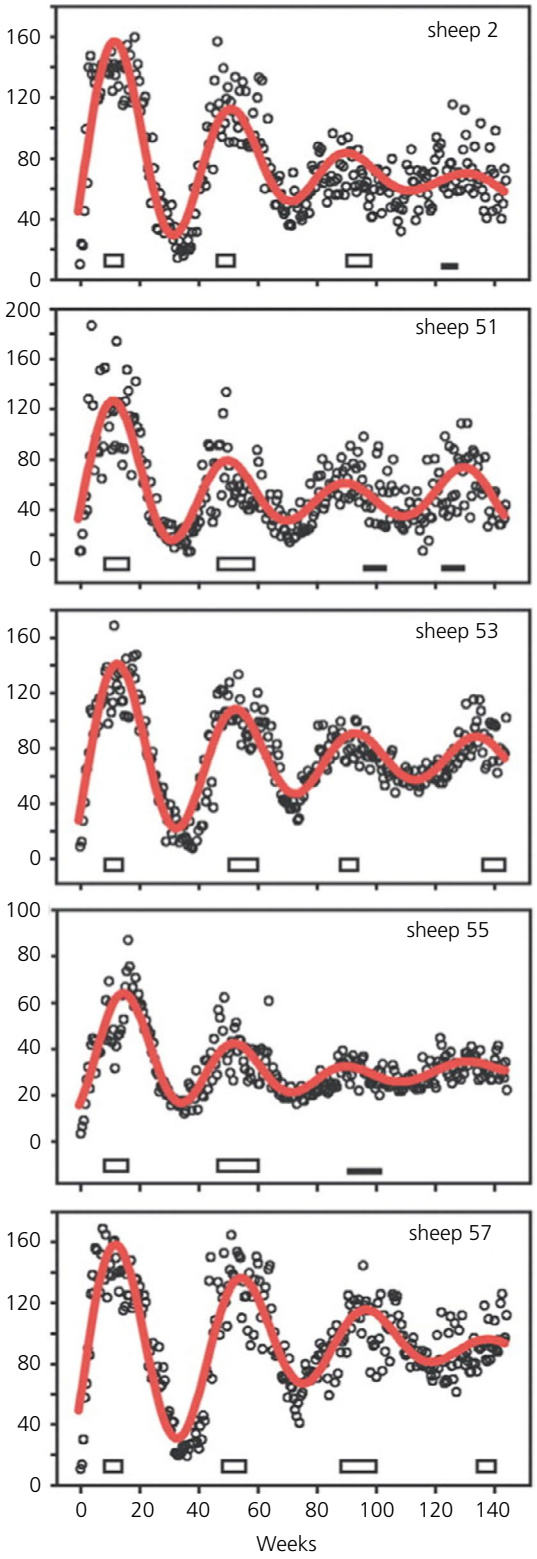

FIGURE 4 Examples of free-running circannual prolactin rhythms under constant long days in five individual HPD Soay rams exposed to a change from short days (8L:16D) to long days (16L:8D) at week 0. Plasma prolactin values are ng mL^{-1}. The horizontal bars indicate the timing of the spring wool moult, known to be prolactin dependent (white bar, full moult; line, partial moult) (reproduced with permission from *Science*[49])

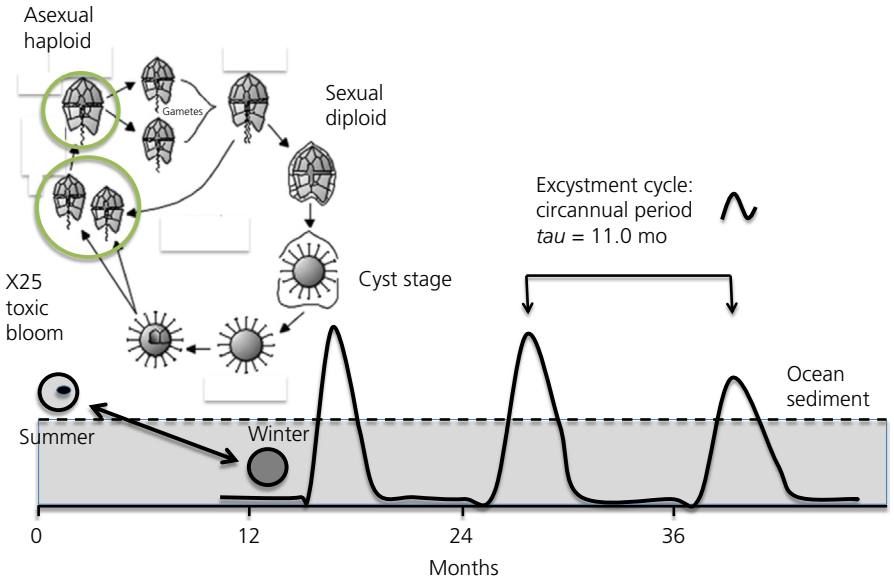

FIGURE 5 A living unicellular example, the life cycle of the marine alga *Alexandrium tamarense*: haploid cells propagate vegetatively during the summer, producing the renowned toxic bloom in ocean surface waters. These cells conjugate in autumn to form the sexual diploid phase, which transforms into a dense resistant cyst that sinks to the seabed to overwinter. Remarkably, encystment in subsequent year(s) is regulated by an endogenous circannual timer that anticipates spring (reproduced with permission from the *Journal of Neuroendocrinology*[46])

long days (16L:8D) but not under constant short days (8L:16D) and the period length of the testicular cycle was clearly shorter than 52 weeks, and so was described at the time as "photorefractoriness".[47] This term encapsulates the view that the reversal of the expected reproductive response to a given photoperiod was the result of a loss of responsiveness to that particular daylength. This conceptualisation works well for photoperiodic rodents with a short life span, although analysis of melatonin rhythms in 'photorefractory' mammals indicates that they still are tracking ambient photoperiod, and the persistence of these long-term reproductive cycles was very clear in ganglionectomised Soay rams that had no pineal melatonin information.[48] Even in 1989, Gerald shied away from describing innate rhythmicity in ganglionectomised rams as 'circannual',[48] although the steady increase in documented examples from the mammalian and avian literature led him to express the view that "*Because the dynamics of the physiological changes during the development of photorefractoriness and during the onset of circannual rhythms are similar and can be revealed by exposure to constant photoperiod, it is likely that they share common underlying control mechanisms*".[45]

A detailed study of prolactin concentration and downstream moult cycles in HPD sheep maintained for almost 3 years (144 weeks) in constant long days provided robust evidence for the persistence of innate rhythmicity (Figure 4) and the long duration of this study meant that the periodicity of individual rams could be determined, and, because these differed, the loss of synchrony between the experimental subjects became evident.[49] These long-term 'circannual' rhythms could be resynchronised in HPD rams but not in those that had also been ganglionectomised to remove endogenous melatonin secretion. This elegantly demonstrated the role of daily melatonin rhythms in conveying the synchronising effect of changing photoperiod on circannual rhythmicity.[49] Gerald spent the later years of his career considering what mechanisms might underlie circannual rhythm generation, and was an advocate of a cyclical histogenesis theory. Studies on the pars tuberalis as a target for melatonin action and as a driver of downstream seasonal neuroendocrine rhythms, combined with evidence that this structure showed clear seasonal changes in cell division and differentiation (histogenesis), underpinned this theory.[50] Hazlerigg and Lincoln wrote that they "*conceptualize circannual rhythm generation as a phenomenon involving cyclic tissue growth and remodelling*", and noted that this may take place in many structures in the adult but it is in the pituitary and hypothalamic regions that also input photoperiodic information where this process is co-ordinated and can be re-synchronised.[50] The demonstration that thyrotrophs in the ovine pars tuberalis exist in one of two states, either βTSH positive in the long day state under the control of Eya 3, or βTSH negative in the short day state characterised by high chromogranin A expression, strongly supports the cyclical histogenesis theory.[51] Moreover, Gerald was enthusiastic about recent work demonstrating an epigenetic component to the mechanism by which a changing daily melatonin signal might be detected by the pars tuberalis but then interact with a rhythmically changing cellular chromatin state, perhaps an annual recapitulation of developmental mechanisms regulating βTSH cells.[42]

Towards the end of his career, Gerald* became particularly interested in the question of when and how circannual rhythmicity might have evolved in primitive organisms despite their relatively short life span.[46] His broad understanding of biology stimulated this interest, and he eloquently presented a beautiful example of how annual rhythmicity occurs across the haploid and diploid components of the life cycle of the marine dinoflagellate *Alexandrium* (Figure 5). The progressive sequence of vegetative propagation of the haploid stage in summer then the sexual diploid phase and ensheathment of cysts to survive winter still persisted in algae maintained in constant conditions, such that circannual rhythmicity is innate and is transferred across generations (Figure 5). His view was that circannual timing evolved in free-living eukaryotic cells, the alternation between growth and dormancy across life history is adaptive regardless of the short lifespan of any individual cell.[46] This hypothesis predicts that circannual clocks are genetically regulated, cell autonomous and transgenerational, and so a fitting legacy to Gerald's work would be that these predictions are tested in the *pars tuberalis* and other 'calendar' regions in higher organisms.

AUTHOR CONTRIBUTIONS

Francis Ebling: Conceptualisation; Writing – original draft; Writing – review & editing. **John Fletcher:** Conceptualisation; Writing – review & editing. **David Hazlerigg:** Conceptualisation; Writing – review & editing. **Andrew S. I. Loudon:** Conceptualisation; Writing – review & editing.

PEER REVIEW

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DATA AVAILABILITY

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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ENDNOTES

* One of Gerald's last contributions to the scientific literature was a chapter for a book titled *Neuroendocrine Clocks and Calendars*,[52] part of the Masterclass in Neuroendocrinology series that benefits the International Neuroendocrine Federation. His chapter provided a historical overview of how we have arrived at our current understanding of seasonality, photoperiodism and circannual rhythmicity. That book, published in December 2020, is dedicated to his memory: "*No person could have been better placed to contribute a chapter as Gerald played a leading role in these fields. He was an outstanding naturalist and scientist, a deep thinker, and a vibrant and engaging communicator … . Gerald was passionate about his research, and his enthusiasm for understanding mechanisms and explaining the natural world stimulated and enthused everyone he came into contact with. The scientific community has lost an inspirational biologist and a wonderful person.*"

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