Most vertebrate animals are highly rhythmic in their behavior and physiology. As reviewed by Barbara Murphy of the School of Agriculture, Food Science and Veterinary Medicine at University College Dublin and published in this issue of *The Veterinary Journal*, chronobiological research is most concerned with the biological clock systems that regulate the circadian (~24 h) and annual rhythms (Murphy, 2009). These rhythms are pervasive in living systems, having arisen evolutionarily in adaptation to a cyclic natural environment, and their genetic mechanisms deeply impact health and disease at all levels of organization, from biochemical to ecological (Takahashi et al., 2008).

Circadian mechanisms are also critical in mediating the timing of seasonal reproduction and other annual physiological and behavioral fluctuations that are regulated and synchronized by day length. In mammals, this regulation derives particularly from the action of light to control both the timing and duration of the nightly peak in melatonin secretion. The melatonin rhythm then transmits this time-of-year information to the neuroendocrine gonadal system (Goldman, 2001). As addressed in Murphy’s (2009) review and below, circadian rhythmicity and photoperiodism also importantly impact immune function, an area of particular practical importance to veterinary medicine.

Central to circadian biology are the mechanisms by which innate circadian rhythms are synchronized by the 24 h day–night cycle (Johnson et al., 2003). This entrainment mechanism depends on a circadian rhythm in the clock-resetting responses to light which normally peaks in the relative dark of night. This light response rhythm is likewise critical in mediating the adjustment of circadian rhythms to shift–work and time zone travel, and in detecting the change in day length that mediates seasonality. In this context, the unexpected rapid adjustment of equine melatonin rhythms to a time-shift of the light cycle raises many questions for future study.

Foremost, as suggested by Murphy (2009), is to ask whether other endocrine rhythms, metabolism, and peripheral circadian clocks adjust with similar speed, or, alternatively, whether horses experience the temporal disorder that characterizes human jet-lag? In the latter case, consequences for athletic performance and health may exist even if delayed with respect to initial travel. But what may be the influence of prior and prevailing lighting conditions? In rodents, the amplitude of the circadian resetting response to light, the rhythm that mediates light–dark entrainment, is increased by the long nights of short day lengths (Evans et al., 2004; vanderLeest et al., 2009). Additionally, circadian adaptation to photoperiod (lengthened nights) or to simulated time zone travel (8 h advance of dawn) are each accelerated by providing naturalistic dim nocturnal illumination (Gorman et al., 2006; Evans et al., 2009). Thus, we wonder: would exposure to long and/or dimly illuminated nights improve circadian photoperiodic adjustments in the horse?

As emphasized by Murphy (2009), we expect that circadian-time-specified treatments, or chronotherapeutics, will become increasingly important to veterinary practitioners as additional advances are made in large animal chronobiology. Understanding, for example, the circadian physiology of cortisol and the sickness responses of fever and energy-saving lethargy, will help in diagnoses and treatment strategies. Although stressors and their biological markers, glucocorticoids, are generally immunosuppressant, especially when chronically elevated, acutely elevated glucocorticoids improve immune cell trafficking and other aspects of immunity (Dhabhar and McEwen, 1999). Because glucocorticoids show dramatic daily fluctuations, immune function can similarly display strong daily fluctuations in both compromise and enhancement, particularly when basal glucocorticoid concentrations are elevated in response to stress (see, for example, Dhabhar et al., 1994). Additionally, melatonin can be both pro- and anti-inflammatory (Wang et al., 2007).

Seasonal changes in immune function and disease incidence are equally important and may be tied to breeding (Martin et al., 2008). In nature, lengthening vernal photoperiods induce estrus in mares with births the following spring when food availability and other conditions are most conducive to foal survival. In horse breeding management, onset of estrus is hastened by mid-winter exposure to evening illumination so that foaling occurs closer to the start of the year (and the traditional 1 January birthday of thoroughbreds). Thus, improved understanding of photoperiodic influences on equine breeding has improved infertility treatments and general breeding programs, and future research can further optimize artificial lighting conditions.

Photoperiod is transduced into a physiological signal by the nightly duration of melatonin secretion from the pineal gland. During the long nights of winter, the duration of melatonin secretion is extended compared to the short nights of summer. Differential duration of melatonin secretion provides a time-of-year signal to peripheral tissues, including immune cells (Valenzuela et al., 2008) and in common with reproduction, immune function varies with season (Nelson, 2004; Nelson et al., 2002).

Although stressors are pervasive, they vary throughout the day and across the seasons and differentially affect immune function and susceptibility to disease. Chronic exposure to stressors often...
compromises immunity and may have serious consequences for health and survival, especially during winter. Ideally, optimal immune status would be maintained throughout the year; however, this is not generally possible: immune function requires energy, and energy availability and utilization vary seasonally. Thus, photoperiod acting through longer bouts of nightly melatonin secretion provides a mechanism by which animals can bolster immune function in anticipation of the stressors of winter (Martin et al., 2008).

Many diseases show strong seasonal patterns (Nelson, 2004). Often these patterns reflect seasonality associated with the life history constraints of the pathogen. For example, seasonality of many equine diseases is linked to the seasonal availability of their vectors: West Nile Virus infections, Eastern, Western, and Venezuelan equine encephalitis reflect the availability of mosquito vectors, whereas the seasonality of equine ehrlichiosis, piroplasmosis, spotted fever, and granulocytic anaplasmosis are caused by the seasonal prevalence of ticks. In many cases, however, seasonal changes in the host or in the interactions between the host and the pathogen underlie seasonal patterns in disease (Martin et al., 2008; Nelson, 2004).

To date, most efforts have not advanced much beyond describing the changes that occur in immune function and disease prevalence with season, and the involvement of photoperiod and melatonin in these processes. Further research into the cellular and molecular mechanisms that mediate circadian and seasonal influences on immune function and sickness behavior will vitally improve the application of chronobiology to veterinary medicine. The current explosion of information pertaining to the genetics of the mammalian circadian timing system and its pervasive influence on endocrinology and metabolism, has enormous promise for improving veterinary, as well as, human medicine (Takahashi et al., 2008).

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