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Seasonal immune function and sickness responses

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Winter is a particularly difficult time to breed and survive. Animals monitor day length (photoperiod) to engage seasonally appropriate adaptations in anticipation of harsh winter conditions. I propose that photoperiodic information, mediated by melatonin, might also influence immune responses. Individuals could improve survival if seasonally recurring stressors were anticipated and countered. Recent studies suggest that short day lengths reroute energy from reproduction and growth to bolster immune function during winter. Short days can either enhance or suppress components of immune function, as well as reduce fever and the expression of sickness behaviors. The net result of these photoperiod-mediated adjustments is enhanced immune function and increased survival. Melatonin appears to be part of an integrated system that coordinates reproductive, immunological and other processes to cope successfully with energetic stressors during winter and to balance trade-offs between reproductive success and survival.

The annual cycle of changing day length (photoperiod) provides a reliable environmental cue to determine time of year [1,2]. This temporal information is important for timing the onset and termination of seasonally appropriate adaptations that promote reproduction and survival. For example, individuals of many species use photoperiod, encoded by the nightly duration of melatonin secretion, to accurately time their breeding activities. Breeding seasons are probably the most prominent of annual cycles among animals. Outside of the tropics, offspring are typically produced during spring or summer when food is most abundant, and other environmental conditions are optimal for survival. The energetic bottleneck resulting from increased thermoregulatory demands when food availability is scarce makes winter a particularly difficult time to breed and survive.

Immune function often varies on a seasonal basis; it is generally decreased during the winter in the wild but is enhanced in the laboratory during short-day conditions when all other factors are held constant [3]. Based on the premises that (i) immune function is compromised by the chronic stressors of winter and (ii) winter stressors are seasonally predictable, the working hypothesis of our research is that animals use day length information to anticipate winter stressors and accordingly redistribute energy among competing reproductive and survival functions. Thus, investment in reproduction (and growth) is curtailed, whereas investment in immune function is bolstered during winter. Individuals of many species use day length to time the differential investments of resources in anticipation of the onset of winter stressors. Presumably, immune function would be compromised even further during the winter without this short-day bolstering. By analogy, short day lengths 'vaccinate' against stressor-induced compromise in immune function and promote survival (i.e. flu symptoms might still occur after a flu vaccination, but they are generally much less serious). Similarly, stressful low temperatures and lack of food might suppress immune function during the winter; however, this suppression will be ameliorated by the photoperiod-mediated reallocation of resources from reproduction and growth to the immune system [3].

Although photoperiod provides an error-free signal regarding time of the year, other environmental factors could contribute to seasonal changes in the immune system. For example, seasonal availability of nutrients, mediated by leptin, could directly influence immune function. Provisioning male Belding's ground squirrels in the field from the time they emerged from hibernation to the start of breeding dramatically elevated the numbers of lymphocytes and neutrophils [4]. Immune function is also altered during hibernation in golden-mantled ground squirrels. During hibernation, core body temperature is maintained 1–2°C above ambient. Hibernation is not continuous; squirrels arouse at approximately seven-day intervals, during which body temperature increases to 37°, for ~16 h before returning to hibernation [5]. We examined whether immune function would be either enhanced or compromised in hibernators injected with bacterial lipopolysaccharide (LPS). Surprisingly, the acute-phase response (APR) did not occur during hibernation, but it fully emerged when squirrels aroused several days later [5]. Brain infusions with prostaglandin E_2 provoked immediate arousal from hibernation and induced fever, suggesting that neural signaling pathways that mediate febrile responses are functional during hibernation [5]. Periodic arousals might activate a dormant immune system, which can then combat pathogens that might have been introduced immediately before or during hibernation, contributing to a seasonal pattern of immune function and disease. Similarly, the immune modulatory effects of glucocorticoids, in response to food, temperature,

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predators, and conspecific social interactions, could also produce seasonal patterns of immune function.

Energy and seasonal immune function

Species-specific strategies for optimal partitioning of resources among growth, reproduction and survival mechanisms are called life-history strategies [6]. Because long-lived individuals generally produce more offspring than short-lived conspecifics, whereas breeding often compromises health and survival, natural selection operates on the mechanisms mediating both survival and reproductive success to maximize Darwinian fitness. Adaptive functional studies generally consider immune function as a 'proxy' for survival. The trade-offs between investing in reproduction and survival have been documented previously [7–13]. Although the amount of energy required to maintain immune defenses in the absence of infection remains unspecified [14], activation of immune function can be costly [15,16]. For example, bumblebees downregulate immune responses during starvation, and shunt energy into processes crucial for immediate survival such as cardiac and cerebral metabolism. Bees that are forced to mount an immune response during starvation suffer increased mortality [17]. The onset and maintenance of inflammation and fever, as well as the production of humoral immune factors, also require significant resources in birds and mammals [16]. Fever requires an increase in resting metabolic rate of ~10–20% at ambient temperatures ranging from 21° to 25°C [18]. Mice producing antibodies to a novel antigen consume more oxygen than control animals [19]. Furthermore, many diseases, including cancer, diabetes mellitus, arthritis, AIDS and other infectious diseases, lead to significant energy deficits in humans, often resulting in cachexia [20]. Starvation and protein malnutrition compromises immune function [16]. During disease states, abnormal protein metabolism, the breakdown of fatty acids, tissue degradation and the production of humoral and inflammatory mediators each increases energy expenditure [9].

Energy is required to cope with pathogens; however, energy availability varies across the year, and the consequences of infection by pathogens vary seasonally [16]. Outside the tropics, adaptations have evolved that allow individuals to cope with the seasonal changes in resource availability. One common tactic for coping with winter is to shift energy allocations from non-essential functions to those most important for immediate survival [16]. When the odds of successful reproduction are low, resources are shunted from reproduction and growth to survival. Consequently, over evolutionary time, seasonal patterns in the expression of adaptations have emerged that allow redistribution of energy resources to mediated trade-offs between traits such as immune function and reproductive effort.

Although stressors are pervasive, they vary throughout the day and across the seasons. Chronic exposure to stressors often compromises immunity and could have serious consequences for health and survival [16]. Ideally, optimal immune status should be maintained throughout the year; however, this is not generally possible because immune function requires energy and energy availability and utilization varies seasonally. Thus, individuals can bolster immune function when susceptibility to disease or prevalence of pathogens peaks. Many human and nonhuman diseases show strong seasonal patterns [16,21] (Figure 1; Table 1). Often these patterns reflect seasonality associated

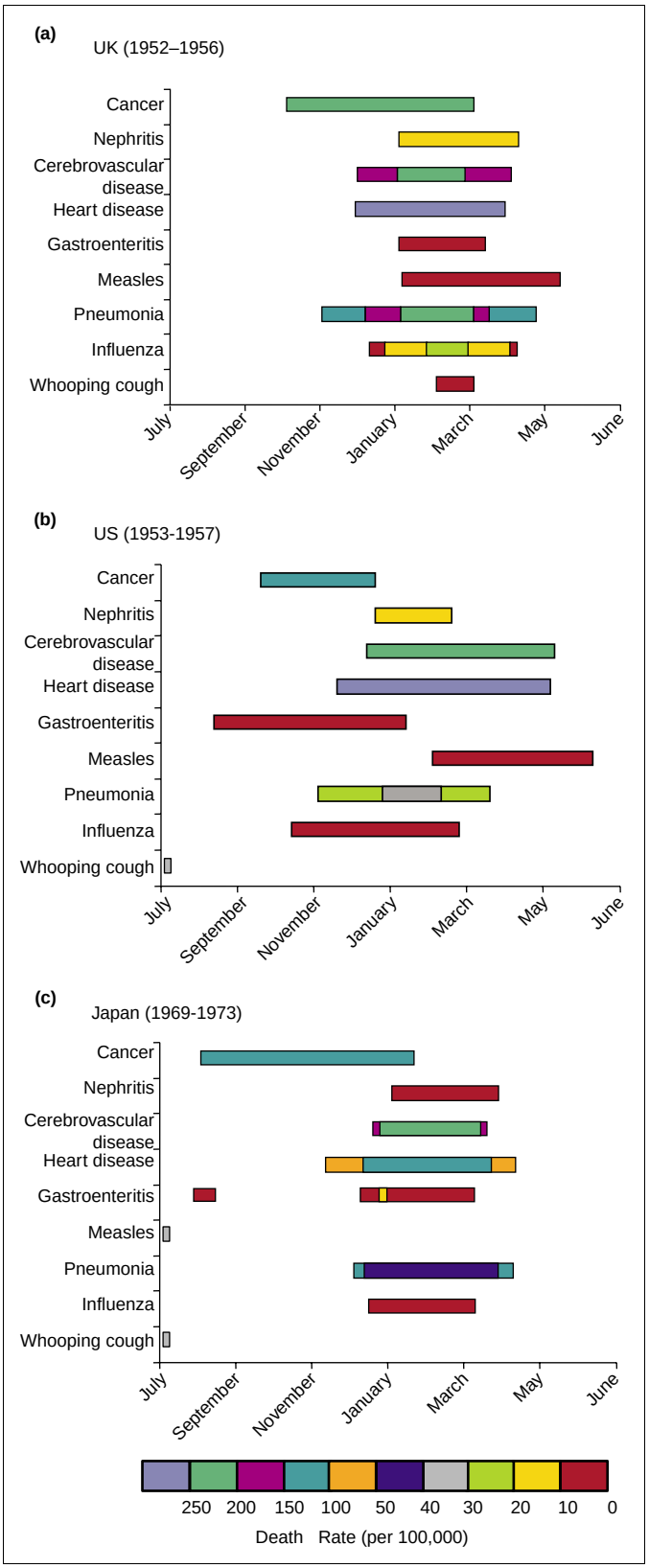

Figure 1. Seasonal disease calendar for three different countries showing peak incidence of common cause of death due to illness. Incidence ranged from 10–250 deaths per 100 000 in the population. Adapted with permission from Ref. [21].

Table 1. Seasonal patterns of disease

Pathogen or disease	Species	Season of highest incidence	Refs
Malaria	Human	Winter–Spring	[56]
Influenza	Human	Winter–Spring	[57]
Influenza	Bird	Fall–Winter	[58]
Tuberculosis	Human	Winter	[59]
Pneumonia	Human	Fall–Winter	[60]
Pneumonia	Swine	Winter–Spring	[61]
Multiple sclerosis	Human	Spring–Summer	[62]
Lung cancer	Human	Summer–Fall	[63]
Campylobacter	Rhesus monkey	Spring	[64]
Avian lice	Bird	Summer	[58]
Nematode infection	Cattle	Summer	[65]
Gastrointestinal nematode load	White-tailed deer	Summer	[66]
Lungworm infection	Swine	Fall	[67]
Lyme disease	Bank vole	Summer	[68]

with the life history constraints of the pathogen. For example, seasonality of malaria probably reflects the link between the rainy seasons and the abundance of mosquitos, the primary vector of *Plasmodium*. In many cases, however, seasonal changes in the host or in the interactions between the host and the pathogen underlie seasonal patterns in disease.

Altered social behaviors might also contribute to seasonal patterns of immune function and disease. During the mating season, animals often maintain territories, refrain from intrasexual cohorts and actively avoid potential mates that display signs of infection [22]; humans also judge sick individuals as less attractive than healthy people [23]. Suspension of mating and feeding territories often lead to increased population densities during the winter (e.g. formation of avian feeding flocks, bachelor herds of ungulates or burrow sharing by mixed rodent species) that facilitate infection and interspecies transmission of pathogens [24]. For instance, overwintering groups might contain multiple species that normally do not associate during the breeding season [25]. Close proximity increases the possibility of pathogen-sharing within a species and facilitates transmission across species. Indeed, transmission of chronic wasting disease (CWD) in mule deer is probably facilitated by winter herding [26], and the close quarters among humans, coupled with the low humidity during winter, is thought to contribute to the pattern of the 'flu season' each year (Figure 2). Incidence of sudden acute respiratory syndrome (SARS) might reflect the seasonal proximity between humans and masked palm civets in rural China [27,28]. As noted above, most human diseases show seasonal fluctuations, and many are most prevalent during the winter (Figure 1; Table 1) [21].

Individuals that bolstered immune function in anticipation of seasonally recurring winter stressors and group contact could improve the probability of their survival. As noted previously, however, winter-enhancement of immune function requires curtailing other energetically demanding activities such as reproduction and growth [9,11,15,29]. Individuals monitor the annual cycle of changing photoperiods to determine the time of the year and use this information to anticipate seasonal changes in energetic demands.

The initial response to an infectious agent often determines the outcome of infection and thus is a very important part of survival mechanisms. The extent to which photoperiod influences specific proinflammatory cytokines, toll-like receptors, natural killer (NK) cells and dendritic cells remains unspecified but important to pursue. There are possible differences in the energetics of mounting an innate versus an acquired immune response; however, direct assessments are rare and require additional studies.

Importantly, many factors other than photoperiod influence seasonality in the prevalence of disease; in addition to these 'main-stream' factors, seasonal variation in host immunity exists. For example, the relationship between the rainy season and prevalence of disease vectors has been reported for malaria, St Louis encephalitis virus and West Nile virus [30,31]. For individuals with distinct breeding seasons, the incidence of sexually transmitted diseases will presumably vary seasonally. Among humans, HIV infection varies seasonally in relation to sexual behavior [32]. To complicate matters further, some diseases, such as malaria and HIV, can vary seasonally with coinfections [33].

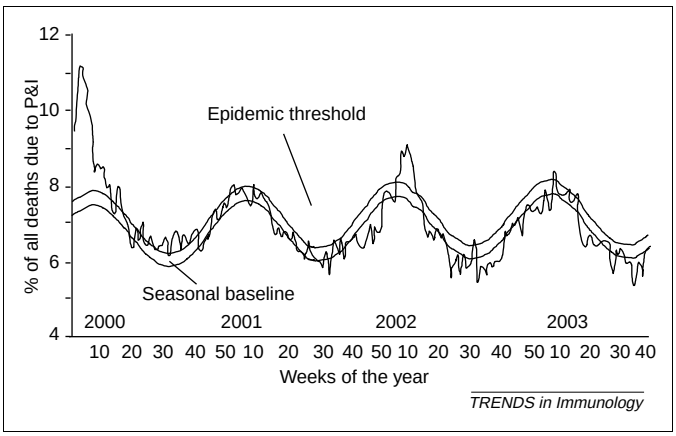

Figure 2. Graphical representation of Pneumonia and Influenza (P & I) Mortality Surveillance data captured by the USA Centers for Disease Control and Prevention (CDC): Data are plotted weekly over 3 years. During Week 41 of 2003 – the most recent week for which data were available – the percentage of all deaths caused by P & I was 6.3%. This incidence is below the epidemic threshold of 6.8% for this time of the year. These data were compiled by the CDC from the vital statistics offices of 122 cities in the USA. Graph reproduced with permission from the CDC (http://www.cdc.gov/ncidod/diseases/flu/weekly.htm).

Photoperiod effects on the immune system

Exposure to short day lengths affects several parameters of the immune system. Short days correlate closely with the seasonal peak in invasive pneumococcal disease among humans [34]. Earlier reports indicated that spleen mass is elevated in deer mice and Syrian hamsters kept in a short photoperiod [35,36]. Photoperiod affects the immune system of several rodent species (Table 2). Short days increase the number of circulating blood leukocytes, lymphocytes, T cells and NK cells, as well as spontaneous blastogenesis in whole blood and isolated lymphocytes and the cytolytic capacity of natural killer cells [37,38]. Moreover, short days suppress phagocytosis and oxidative burst activities of granulocytes and monocytes [37]. Short days also enhance lymphocyte proliferation in species ranging from mice to primates [16,39]. There are species differences in photoperiodic influences on immune function. In addition, certain specific components of immune function might be more costly to maintain, although methods for precise measurements are generally not available. Finally, the types of immune responses, such as enhanced primary defenses in the skin, lymph nodes and gastrointestinal tract, could vary because the types of infectious risks vary seasonally. However, the general pattern is that short day lengths are usually associated with enhanced immune function.

Although complex cascades of molecular and cellular responses have evolved to fight against invading pathogens, behavioral adaptations are also important for overcoming invading pathogens. The most basic defense against infection is avoidance. It seems reasonable to predict that, among animals that form winter aggregations, short days would increase avoidance behaviors of infected animals; this hypothesis appears to be untested.

Acute exposure to bacteria or other harmful stimuli elicits the evolutionary conserved APR. APR includes physiological changes such as fever, increased slow-wave sleep, alterations in plasma ions and protein synthesis and elevated numbers of circulating white blood cells [40]. Such behavioral changes in response to infection are collectively called sickness behaviors; they include reduction in food and water intake, activity, exploration and social and sexual interactions [41]. Sickness behaviors are organized adaptive strategies that are crucial to host survival and not merely the side effects of infection [42].

With energy shortages during winter it might be too difficult for individuals to maintain prolonged, energetically demanding sickness responses such as fever or anorexia. If the expression of sickness behaviors is constrained by energy availability, then cytokine production, fever and anorexia should be attenuated in infected animals kept in short photoperiods. As predicted, when Siberian hamsters are maintained under either long or short photoperiods, short days attenuate the fever and anorexic responses to LPS [43]. Short-day hamsters also limit dietary intake of iron, a nutrient vital to bacterial replication [43]. Thus, short day lengths can weaken the symptoms of infection and, presumably, optimize energy expenditure and survival outcome.

Indeed, short-day hamsters treated with high doses of LPS display significantly improved survival [44]. In response to LPS stimulation, *in vitro* production of tumor necrosis factor-α (TNF-α) was significantly reduced in peritoneal macrophages obtained from short-day hamsters compared with those from hamsters kept in long photoperiods. Diminished cytokine responses to LPS under short-day conditions might reduce mortality from endotoxemia and provide several additional days for recovery [44].

Melatonin: endocrine photoperiod signal

Melatonin, an indole amine, is secreted by the pineal gland. This hormone functions as the biological signal for day length or, more precisely, night length. Melatonin synthesis and secretion occurs exclusively at night and is inhibited directly by light. The duration of its release is proportional to night length; consequently, short-day animals experience longer durations of melatonin secretion, than do long-day animals, and use this temporal information to determine the time of the year.

Melatonin mediates seasonal changes in many traits including reproduction and body mass. Melatonin might have been co-opted during evolution to enhance immune function when energetic constraints compromise survival [16]. Immune function often varies on a seasonal basis and is generally decreased during the winter in the wild but is enhanced in the laboratory during short-day conditions when all other factors are held constant [16,45]. For instance, seasonally breeding deer mice stop breeding during short days and experience a concomitant enhancement of immune responses [immunoglobulin G (IgG) levels].

Table 2. Photoperiod-induced changes in the immune system

Non-specific immune parameter	Species	Short-day effect	Refs
Splenic mass	Deer mouse	Increase	[69]
Splenocyte proliferation	Deer mouse	Increase	[69]
Splenocyte proliferation	Syrian hamster	Increase	[36]
Lymphocyte count	Deer mouse	Increase	[70]
T cells	Siberian hamster	Increase	[37]
Lymphocyte proliferation	Siberian hamster	Decrease	[70]
Circulating leukocytes	Siberian hamster	Increase	[38]
Innate immune parameters			
Natural killer-cell cytolytic activity; phagocytosis and oxidative burst activity	Siberian hamster	Decrease	[37]
Spontaneous blastogenesis	Siberian hamster	Increase	[37]
Leukocyte trafficking	Siberian hamster	Increase	[38]
Delayed-type hypersensitivity	Siberian hamster	Increase	[38]

However, laboratory-housed deer mice maintained in low temperatures had significantly reduced splenic masses and basal IgG when housed under long day conditions. Animals maintained in both short days and low temperatures displayed IgG levels comparable to those of mice kept under long-day and mild-temperature conditions [46]. These results suggest that short days bolster immune function that is compromised by low temperatures (and other stressors such as low food availability in nature).

Melatonin: influences on the immune system

The role of melatonin as an immunomodulator is well established for many species, including humans [16]. Melatonin receptors have been localized on lymphocytes, and *in vitro* melatonin treatment enhances splenocyte proliferation (the division of immune cells) in rodents [47]. Enhancement of immune function in mice is mediated directly through type 2 melatonin receptors (mt-2) on lymphocytes [48]. Melatonin also stimulates the production of endogenous opioids directly from T cells, which might mediate the immunoenhancing effects of melatonin; it also modulates the effects of stressors on immune function during the winter [16,49].

Melatonin has been investigated therapeutically, as well as for the treatment of infection, and has been implicated as an antitumor agent [16]. Furthermore, some reports suggest that melatonin has antioxidant properties by scavenging free radicals and could slow damage caused during aging [50] or by sepsis in neonates [51]. The antioxidant effects of melatonin increase survival of mice infected with *Schistosoma mansoni* [52]. Melatonin might also counteract immunosuppression following drug treatment or during viral disease [16]. Melatonin enhances *in vitro* production of interleukins and interferons by circulating human $CD4^+$ cells [53]. The number of white blood cells of chickens injected with melatonin was significantly higher than that of saline-injected birds [54]. Melatonin should not be considered a miracle drug, but it does have immunomodulatory effects that might have clinical relevance [55]. Carefully conducted clinical research is required to determine the costs and benefits of melatonin treatment. Importantly, other immune modulators, such as prolactin, sex steroid hormones and glucocorticoids, could contribute to the seasonal pattern of immune function.

Concluding remarks

Both the incidence and responses to stressors varies on a seasonal basis. Furthermore, stress can impair immune function and increase disease susceptibility. Consequently, seasonal changes in immune responses have evolved as adaptive mechanisms to counter seasonal stress-induced immune suppression [16]; these changes appear to be defined by seasonal fluctuations in energy availability. Experimental manipulations of energy availability alter immune function in the expected direction; that is, low energy availability limits immune responses. The environmental regulation of seasonal changes in many traits, including reproduction, metabolism and immunity, is primarily mediated by photoperiod. From a physiological prospective, the pineal hormone melatonin appears to coordinate photoperiodic changes in immune function. To what extent the immune-enhancing effects of melatonin are unique to seasonally breeding rodents or whether it is a generalized feature of seasonal immune function in humans, remains largely unspecified [34]. Although physiological responses are important mediators of seasonal and/or photoperiodic changes in immune function, behavioral alterations might also have an important role in avoiding infection and reducing their energetic effects. Careful integration of the behavioral and physiological mechanisms underlying seasonality of immune function at both ultimate and proximate levels should provide important and novel insights into the interaction among seasonal environmental factors, stressors, immune function and the pattern of diseases and mortality. To date, most efforts have not advanced much beyond describing the changes that occur in immune function and disease prevalence with season and the potential involvement of photoperiod and melatonin in these processes. The next step is to identify the cellular and molecular mechanisms that mediate the effects of season and photoperiod on immune function. Ongoing studies of the physiological mechanisms underlying sickness behavior will continue to provide novel and important clinically relevant insights.

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