

# Seasonal Patterns of Stress, Disease, and Sickness Responses

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**ABSTRACT**—*The combined challenge of low food availability and low temperatures can make winter difficult for survival, and nearly impossible for breeding. Traditionally, studies of seasonality have focused on reproductive adaptations and largely ignored adaptations associated with survival. We propose shifting the focus from reproduction to immune function, a proxy for survival, and hypothesize that evolved physiological and behavioral mechanisms enable individuals to anticipate recurrent seasonal stressors and enhance immune function in advance of their occurrence. These seasonal adaptations, which have an important influence on seasonal patterns of survival, are reviewed here. We then discuss studies suggesting that photoperiod (day length) and photoperiod-dependent melatonin secretion influence immune function. Our working hypothesis is that short day lengths reroute energy from reproduction and growth to bolster immune function during winter. The net effect of these photoperiod-mediated adjustments is enhanced immune function and increased survival.*

**KEYWORDS**—*allostasis; illness; stressors; annual cycles; sickness behavior*

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And as for sickness: Are we not almost tempted to ask whether we could get along without it?

—Nietzsche (1887/1974, p. iv)

In the preface to the second edition of *The Gay Science*, published in 1887, Nietzsche (1887/1974) wrote about the “contradictions” between winter and summer, as well as between sickness and health. Nietzsche emphasized that these apparent contradictions are nonetheless held together in the experience of the body. Over evolutionary time, the experiences of recurrent summers and winters have provoked the evolution of adaptations that allow modern-day individuals to cope with the seasonally fluctuating environments in which they live. Coping with stressors, however, requires energy, and because energy is finite, competing functions within the body must be curtailed

as stressors increase. A primary means by which individuals cope with seasonal stressors is by shifting energy allocations from less critical functions to those most important for immediate survival. This re-allocation of energy allows individuals to adapt to environmental stressors and maximize survival and reproductive success.

Confrontation with a stressor, an agent that disturbs the body’s equilibrium, or homeostasis, triggers a stress response in which an individual releases hormones, such as adrenaline or cortisol, from the adrenal glands. These hormones work in the short term to restore homeostasis, often by shunting resources from nonessential activities to functions necessary for survival. However, if the stressors persist, chronic exposure to the so-called stress hormones may cause problems within several biological systems, including the digestive, cardiovascular, reproductive, metabolic, and nervous systems. Over time, organisms have evolved adaptations that attenuate the stress response during the winter, when energy shortages limit the ability to cope. Chronic exposure to stressors, however, can still leave energy levels low, and because immunity entails high energy costs, it might be compromised. Enhancing immune function in anticipation of seasonally recurring winter stressors could improve the likelihood of survival, but this would be possible only if other energy-demanding activities (e.g., reproduction and growth) are curtailed. Indeed, by monitoring the annual cycle of changing day lengths, organisms can determine the time of year and use this information to switch between winter and summer adaptations.

The cycle of breeding seasons is probably the most salient annual cycle among animals. Generally, breeding is limited in nontropical climates, so that offspring are produced during spring or summer, when food is most abundant and other environmental conditions are optimal for survival. In contrast, when resources are limited, energy is shunted into survival mechanisms. Pathogens introduce a complication into this evolutionary dance between reproductive success and survival, because energy is required to cope with them. The varying availability of energy over the course of the year means that the consequences of pathogenic infection also vary seasonally (Nelson, Demas, Klein, & Kriegsfeld, 2002). Consequently, the seasonal adaptations that have evolved (e.g., inhibition of reproductive functions and behavior) allow trade-offs in whether energy is invested in boosting immune function, fighting disease, or coping with other stressors.

Our working hypothesis is that during winter, animals shift their energy expenditure from reproduction and growth to survival. Immune function can serve as a proxy for measuring this shift. Thus,

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we hypothesize that by attending to day length (photoperiod), animals anticipate the onset of winter stressors and bolster their immune function. Although immune function is in fact compromised by the chronic stressors of winter, we hypothesize that it would be compromised even further without this photoperiodic bolstering.

### SEASONAL PATTERNS OF DISEASE AND SICKNESS RESPONSES

Many human and nonhuman diseases show strong seasonal patterns (Nelson et al., 2002; see Table 1). Often these patterns reflect the life history of the pathogen. In many cases, however, seasonal changes in the host or in the interactions between host and pathogen underlie seasonal patterns in disease. Changes in social behavior may also contribute to seasonal patterns of disease. For example, individuals of many species suspend territorial behaviors during winter and huddle in groups to conserve heat and humidity. These overwintering groups may contain multiple species that normally do not associate during the breeding season. Close proximity increases the potential for pathogens to be shared both within a species and across species. Indeed, many novel influenza variants begin in Asia when the virus “jumps” from swine or fowl as farmers bring their animals indoors for the winter. The incidence of severe acute respiratory syndrome (SARS) may have a seasonal pattern that reflects the vernal interaction between humans and civet cats (the putative native pool of the virus that causes SARS).

One of the greatest challenges that an animal faces on a daily basis is avoiding and overcoming pathogenic infections. Animals have co-evolved with pathogens; therefore, it is reasonable to expect that animals have evolved appropriate responses to fight infection. Indeed, not only have complex cascades of molecular and cellular responses evolved to defend against invading pathogens, but behavioral adaptations are also important for this purpose. Acute exposure to bacteria or other harmful stimuli triggers a highly stereotyped set of responses called the acute phase response (APR). APR includes physiological changes such as fever, increased sleep, alterations in circulating ions (such as decreased iron) and protein synthesis, and elevated numbers of white blood cells circulating in the blood (Berczi, 1993). Behavioral changes resulting from infection and APR include reduced food and water intake, activity, exploration, and social and sexual interactions,

and are collectively called *sickness behaviors* (Hart, 1988). Rather than nonspecific manifestations of illness, these behaviors are organized, adaptive strategies that are critical to the host’s survival (Dantzer, 2001). Individuals that do not express sickness behaviors survive less well than those that do.

Energy shortages during winter should make it difficult for individuals to display prolonged energy-demanding symptoms such as fever or anorexia. The notion that the expression of sickness behaviors is constrained by energy availability was tested in a recent study by measuring these symptoms in infected Siberian hamsters (Bilbo, Drazen, Quan, He, & Nelson, 2002). The duration of fever and anorexia was, in fact, reduced in hamsters housed under simulated winter photoperiods, relative to hamsters maintained under long-day-length conditions. In addition, the animals in the short-day condition had an attenuated response to lipopolysaccharide (LPS; a complex sugar that is present on the cell wall of certain bacteria and to which the immune system responds). Thus, short days can attenuate the symptoms of infection, presumably to optimize energy expenditure and survival outcome. In addition, short-day animals decreased their intake of dietary iron, a nutrient vital to bacterial replication.

### ENERGY AND THE IMMUNE RESPONSE

Mounting an immune response takes considerable energy (reviewed in Lochmiller & Deerenberg, 2000; Nelson et al., 2002). Many diseases (including cancer, AIDS, diabetes mellitus, and arthritis), as well as trauma, can substantially increase energy expenditures in humans, and often result in cachexia (wasting). Fever requires an increase in resting metabolic rate of about 10% for every increase of 1 °C in body temperature. During disease states, abnormal protein metabolism, the breakdown of fatty acids, and the production of humoral and inflammatory mediators (the components of the immune system that fight pathogens) all increase energy expenditure. In addition, mice injected with a novel antigen consume more oxygen (an indication of increased energy expenditure) than noninjected animals (Demas, Chefer, Talan, & Nelson, 1997).

Insufficient food intake, starvation, or malnutrition generally decreases immunity (reviewed in Nelson et al., 2002). A recent study demonstrated that immune responses are diminished in bumblebees during starvation, and energy is instead allocated to cardiac and brain metabolism, processes vital for immediate survival. Mortality rates increase among bees that are infected and mount an immune response during starvation (Moret & Schmid-Hempel, 2000). Similarly, Siberian hamsters in the lab reduce antibody production during short day lengths when the availability of food is reduced to the point that their body mass is significantly decreased (Drazen, Bilu, Bilbo, & Nelson, 2001).

Experimentally reducing body fat via surgical removal is an effective way to mimic the decreases in body fat seen in lab animals housed under short-day conditions. We recently examined the effects of partial surgical removal of body fat on antibody production in two seasonally breeding rodent species, prairie voles and Siberian hamsters (Demas, Drazen, & Nelson, 2003). In general, removal of body fat reduced antigen-induced antibody production in the short term in both species. Several weeks later, however, the hamsters who underwent this treatment had compensatory increases in their remaining fat tissues compared with control hamsters, and their antibody levels no

**TABLE 1**

*Seasonal Patterns of Infectious Diseases in Humans in the Northern Hemisphere*

Disease	Peak occurrence
Diphtheria	Winter
HIV	Summer
Influenza	Winter
Legionnaire’s disease	Summer
Malaria	Winter
Measles	Summer
Parainfluenza virus	Fall
Pneumococcal disease	Winter
Polio	Summer
Rotavirus	Winter
Rubella	Spring
Tuberculosis	Winter

longer differed from those of control hamsters. Voles, in contrast, never displayed compensatory increases in body fat, and their immune function remained depressed. Thus, reductions in energy stores in the form of body fat correlate with reduced immunity. Collectively, these results support the idea that immunity is energetically expensive.

### MELATONIN AND PHOTOPERIODIC CHANGES IN IMMUNE FUNCTION

Ultimately, seasonal breeding patterns are driven by the availability of food and water. However, animals need to forecast the onset of environmental changes well in advance in order to initiate appropriate seasonal adaptations. The autumnal collapse of the reproductive system in seasonally breeding animals, for example, requires several weeks to accomplish; it would not prove useful for this response to be directly initiated by low temperatures or limited food, as energy savings would not be realized for several weeks. Seasonally breeding animals have evolved the ability to detect and respond to environmental cues that accurately signal, in advance, the arrival or departure of particular seasons; of these cues, the most reliable are changes in photoperiod. With only two pieces of information, the current day length and whether day length is increasing or decreasing, animals can precisely determine the time of year.

Substantial research demonstrates that changes in day length induce not only changes in reproduction, but also changes in immunity (reviewed in Nelson et al., 2002). Furthermore, these photoperiod-induced changes in immune function appear to be adaptive responses. For example, deer mice housed in short, "winterlike" day lengths for 8 weeks display increased antibody responses compared with animals housed in long, "summerlike" days (Fig. 1). In addition, low temperatures reduced antibody levels in long-day deer mice, but this effect was blocked by moving deer mice to short days (Fig. 1). Thus, short-day conditions not only increase immunity, but also counteract the reductions in antibodies seen in response to other environmental

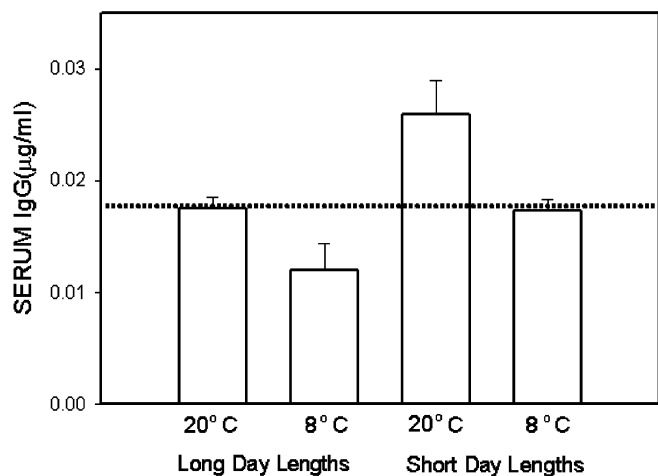


Fig. 1. Effects of day length on level of serum antibodies (Immunoglobulin G, or IgG) in deer mice maintained at low (8 °C) and normal (20 °C) room temperatures. Baseline immune function (i.e., function of animals housed in long-day conditions and at room temperature) is indicated by the horizontal dotted line. Redrawn after Demas and Nelson (1996).

stressors (e.g., low temperatures), preventing the immune system from falling below baseline levels.

Another recent test of this hypothesis was conducted in a study on toxic shock and survival after challenge with LPS (Prendergast, Hotchkiss, Bilbo, Kinsey, & Nelson, 2003). Short days significantly improved survival of hamsters treated with high doses of LPS, which mimicked a severe infection. Immune system cells obtained from short-day hamsters produced significantly lower amounts of specific cytokines (chemical messengers of the immune system) than similar cells obtained from long-day hamsters. Excessive cytokine production can lead to toxic shock (physiological reactions that include blood vessel damage, low blood pressure, and respiratory problems), so one explanation of these results is that diminished cytokine responses to LPS in short-day animals may reduce their mortality from toxic shock and provide several additional days for recovery (Prendergast et al., 2003).

Because melatonin, a hormone from the pineal gland, is a biological signal of day length and is a well-established modulator of immunity, we propose that it plays a pivotal role in seasonal adjustments of immunity. The synthesis and secretion of melatonin occurs exclusively at night, and is inhibited directly by light. Melatonin serves as the biological signal for day length because the duration of its release is proportional to the duration of the night. Animals experience longer durations of melatonin when daylight hours are few than when the day is long and use this information to determine time of year.

The role of melatonin in modulating immunity is well established for many species, including humans (reviewed in Guerrero & Reiter, 1992; Nelson et al., 2002). Melatonin receptors have been identified on cells of the immune system, such as lymphocytes, and treating immune cells of rodents with melatonin increases the rate at which they divide and produce new cells (Drazen et al., 2001). Enhancement of immune function in mice appears to be mediated directly via one of the specific types (MT-2) of melatonin receptors on lymphocytes (Drazen et al., 2001). Melatonin also stimulates the production of opioids directly from certain immune cells, and this effect may play a role in the immunoenhancing effects of melatonin, as well as modulate the effects of stressors on immune function during the winter (reviewed in Nelson et al., 2002).

Melatonin has been investigated therapeutically (e.g., for the treatment of infection), and has been implicated as an antitumor agent (reviewed in Nelson et al., 2002). Furthermore, some reports suggest that melatonin has antioxidant properties and may slow damage caused during aging (Reiter, 1993). Melatonin may also counteract the suppression of immune function that can follow drug treatments or accompany viral disease (reviewed in Nelson et al., 2002). Melatonin should not be considered a miracle drug, but it does have immunomodulatory effects that may have clinical relevance. Careful clinical research is necessary to delineate the benefits and costs of melatonin treatment.

### CONCLUSIONS

Both the incidence of and responses to stressors vary on a seasonal basis. Furthermore, it is well established that stress can impair immune function and increase susceptibility to disease. We hypothesize that a seasonal bolstering of immune function has evolved as an adaptive mechanism to counter the immune suppression that is induced by seasonal stress; these changes in immunity appear to be

constrained by seasonal fluctuations in energy availability. This hypothesis provides a means for resolving the apparent discrepancy between field studies reporting immunosuppression during the winter and laboratory investigations reporting that immunity is enhanced under short-day conditions. Experimental manipulations of energy availability alter immune function in the expected direction: Low energy availability limits immune responses. The environmental regulation of seasonal changes in immunity is mediated primarily by day length, which also plays a central role in mediating the development of other seasonally appropriate adaptations (e.g., in reproduction and metabolism).

Thus far, research suggests that melatonin coordinates photoperiodic changes in immune function. Whether the immunoenhancing effects of melatonin are unique to seasonally breeding rodents or generalize to humans is an important empirical question that requires further study. Although physiological responses are important mediators of seasonal, photoperiodic changes in immune function, behavioral alterations may play an equally critical role in mediating seasonal strategies of coping with stress and thus coping with infection. There are many gaps in current knowledge, but we believe research on the interplay between the behavioral and physiological mechanisms underlying seasonality of immune function will likely provide important insights into the role of the environment and stressors in influencing health and well-being. Ongoing studies of the physiological mechanisms underlying sickness behavior will continue to provide novel and important clinically relevant information. And as for sickness, perhaps people cannot do without it, but an integrative approach to the study of the mechanisms underlying responses to it may provide better tools with which to control it.

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### Recommended Reading

- Bilbo, S.D., Dhabhar, F.S., Viswanathan, K., Saul, A., Yellon, S.M., & Nelson, R.J. (2002). Short day lengths augment stress-induced leukocyte trafficking and stress-induced enhancement of skin immune function. *Proceedings of the National Academy of Sciences, USA*, *99*, 4067–4072.
- Demas, G.E. (2004). The energetics of immunity: A neuroendocrine link between energy balance and immune function. *Hormones and Behavior*, *43*, 75–80.
- Konsman, J.P., Parnet, P., & Dantzer, R. (2002). Cytokine-induced sickness behaviour: Mechanisms and implications. *Trends in Neurosciences*, *25*, 154–159.
- Nelson, R.J., Demas, G.E., Klein, S.L., & Kriegsfeld, L.J. (2002). (See References)
- Yellon, S.M., & Tran, L.T. (2002). Photoperiod, reproduction, and immunity in select strains of inbred mice. *Journal of Biological Rhythms*, *17*, 65–75.
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### REFERENCES

- Berczi, I. (1993). Neuroendocrine defence in endotoxin shock (a review). *Acta Microbiologia Hungary*, *40*, 265–302.
- Bilbo, S.D., Drazen, D.L., Quan, N., He, L., & Nelson, R.J. (2002). Short day lengths attenuate the symptoms of infection in Siberian hamsters. *Proceedings of the Royal Society of London B*, *269*, 447–454.
- Dantzer, R. (2001). Cytokine-induced sickness behavior: Where do we stand? *Brain, Behavior and Immunity*, *15*, 7–24.
- Demas, G.E., Chefer, V., Talan, M., & Nelson, R.J. (1997). Metabolic costs of mounting an antigen-stimulated antibody response in adult and aged C57BL/6J mice. *American Journal of Physiology*, *273*, R1631–R1637.
- Demas, G.E., Drazen, D.L., & Nelson, R.J. (2003). Reductions in total body fat decrease humoral immunity. *Proceedings of the Royal Society of London B*, *270*, 905–911.
- Demas, G.E., & Nelson, R.J. (1996). Photoperiod and temperature interact to affect immune parameters in male deer mice (*Peromyscus maniculatus*). *Journal of Biological Rhythms*, *11*, 95–103.
- Drazen, D.L., Bilu, D., Bilbo, S.D., & Nelson, R.J. (2001). Melatonin enhancement of splenocyte proliferation is attenuated by luzindole, a melatonin receptor antagonist. *American Journal of Physiology*, *280*, R1476–R1482.
- Guerrero, J.M., & Reiter, R.J. (1992). A brief survey of pineal gland-immune system interrelationships. *Endocrine Research*, *18*, 91–113.
- Hart, B.L. (1988). Biological basis of the behavior of sick animals. *Neuroscience and Biobehavioral Reviews*, *12*, 123–137.
- Lochmiller, R.L., & Deerenberg, C. (2000). Trade-offs in evolutionary immunology: Just what is the cost of immunity? *Oikos*, *88*, 87–98.
- Moret, Y., & Schmid-Hempel, P. (2000). Survival for immunity: The price of immune system activation for bumblebee workers. *Science*, *290*, 1166–1168.
- Nelson, R.J., Demas, G.E., Klein, S.L., & Kriegsfeld, L.J. (2002). *Seasonal patterns of stress, immune function, and disease*. New York: Cambridge University Press.
- Nietzsche, F.W. (1974). *The gay science; with a prelude in rhymes and an appendix of songs* (W. Kaufmann, Trans.). New York: Vintage Books. (Original work published 1887)
- Prendergast, B.J., Hotchkiss, A.K., Bilbo, S.D., Kinsey, S.G., & Nelson, R.J. (2003). Photoperiodic adjustments in immune function protect Siberian hamsters from lethal endotoxemia. *Journal of Biological Rhythms*, *18*, 51–62.
- Reiter, R.J. (1993). Interactions of the pineal hormone melatonin with oxygen-centered free radicals: A brief review. *Brazilian Journal of Medical and Biological Research*, *26*, 1141–1155.