J Pineal Res 1995; 19:149–165
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Journal of Pineal Research
ISSN 0742-3098

Minireview

The influence of season, photoperiod, and pineal melatonin on immune function

Nelson RJ, Demas GE, Klein SL, Kriegsfeld LJ. The influence of season, photoperiod, and pineal melatonin on immune function. J. Pineal Res. 1995; 19:149–165. © Munksgaard, Copenhagen

Abstract: In addition to the well-documented seasonal cycles of mating and birth, there are also significant seasonal cycles of illness and death among many animal populations. Challenging winter conditions (i.e., low ambient temperature and decreased food availability) can directly induce death via hypothermia, starvation, or shock. Coping with these challenges can also indirectly increase morbidity and mortality by increasing glucocorticoid secretion, which can compromise immune function. Many environmental challenges are recurrent and thus predictable; animals could enhance survival, and presumably increase fitness, if they could anticipate immunologically challenging conditions in order to cope with these seasonal threats to health. The annual cycle of changing photoperiod provides an accurate indicator of time of year and thus allows immunological adjustments prior to the deterioration of conditions. Pineal melatonin codes day length information. Short day lengths enhance several aspects of immune function in laboratory studies, and melatonin appears to mediate many of the enhanced immunological effects of photoperiod. Generally, field studies report compromised immune function during the short days of autumn and winter. The conflict between laboratory and field data is addressed with a multifactor approach. The evidence for seasonal fluctuations in lymphatic tissue size and structure, as well as immune function and disease processes, is reviewed. The role of pineal melatonin and the hormones regulated by melatonin is discussed from an evolutionary and adaptive functional perspective. Finally, the clinical significance of seasonal fluctuations in immune function is presented. Taken together, it appears that seasonal fluctuations in immune parameters, mediated by melatonin, could have profound effects on the etiology and progression of diseases in humans and nonhuman animals. An adaptive functional perspective is critical to gain insights into the interaction among melatonin, immune function, and disease processes.

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Key words: seasonality – immunity – lymphatic tissue – androgens – estrogens – glucocorticoids – stress – photoperiod – day length – melatonin – prolactin

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Introduction

Seasonal breeding is a salient component of the life history strategies of most animals. Although seasonal breeding is the primary seasonal phenomenon studied, it is only one component of a web of complex seasonal adjustments that permit individuals to maintain a positive energy balance despite fluctuating ambient temperature, food availability, and other challenging environmental conditions [reviewed in Bronson, 1989; Moffatt et al., 1993]. Individuals use photoperiodic information to initiate or terminate specific seasonal adaptations, including reproduction, in order to maintain a positive energy balance [reviewed in Bartness and Goldman, 1989; Heldmaier et al., 1989; Saarcla and Reiter, 1994]. The annual cycle of changing photoperiod can be used by nontropical animals as a very precise temporal cue for the time of year. Ambient pho-

toperiodic information is transduced by the pineal gland into a melatonin signal. The secretory pattern of melatonin allows individuals to ascertain the time of year and thus anticipate predictable seasonal environmental changes [reviewed in Bartness and Goldman, 1989; Reiter, 1991]. These seasonal adaptations ultimately enhance survival and presumably increase fitness [Bronson, 1989].

Although maintenance of a positive energy balance is critical for survival and reproductive success [reviewed in Bronson and Heideman, 1994; Nelson et al., 1990], other threats to survival must also be met in order for individuals to increase their fitness. They must avoid predators and potentially dangerous interactions with conspecific competitors, as well as avoid succumbing to disease. Immunological resistance requires energy. In fact, the cascade of cellular events during the acute phase immune response and inflammation, and the elevation of body temperature in response to cytokine activation, presumably requires substantial energy, although precise quantification is lacking [Henken and Brandsma, 1982: Maier et al., 1994]. Cytokine activation elevates body temperature and the energy requirements of inflammation and acute phase immune responses may increase metabolic rates >10% per degree of body temperature elevation [reviewed in Maier et al., 1994]. Thus, a general energy deficit can increase the risk of infection and death because insufficient energy reserves may be available to sustain immunity. Stress can also compromise immune function [see Ader and Cohen, 1993; Dunn, 1989; O'Leary, 1990 for reviews]. Prolonged or severe food shortages may evoke secretion of glucocorticoid hormones [Nakano et al., 1987; Jose and Good, 1973]; glucocorticosteroids actively compromise aspects of immune function [Kelley, 1985; Munck and Guyer, 1991; Maier et al., 1994; and see below]. Many other conditions perceived as stressful, such as reduced food availability, low ambient temperatures, overcrowding, lack of shelter, or increased predator pressure, can recur seasonally leading to seasonal fluctuations in immune function among individuals, and seasonal changes in population-wide disease and death rates [Lochmiller et al., 1994]. A dynamic relationship exists between longevity and reproductive fitness [Stearns, 1976].

In addition to the well-established seasonal cycles of mating and birth, there are also seasonal cycles of illness and death among many populations of animals [e.g., Bradley et al., 1980; Lochmiller et al., 1994; McDonald et al., 1981; Mihok et al., 1989]. Because many stressful environmental conditions are somewhat recurrent, we hypothesize that animals have evolved mechanisms to combat seasonal stress-induced reductions in immune function. From an evolutionary and ecological perspective, it is reasonable to expect that animals have evolved the ability to forecast recurrent conditions associated with immunosuppression and bolster immune function in advance of these challenging conditions in order to maximize survival.

The working hypothesis of this review is that individuals use photoperiodic information to bolster immune function in anticipation of challenging energetic conditions that may otherwise compromise immune function. All laboratory studies of photoperiodic effects on immune function have reported enhanced immune function in short day lengths (Table 1). Although many field studies support this hypothesis, with data suggesting enhanced immune function and decreased disease prevalence during the winter as compared to the summer, a substantial number of studies have reported the opposite pattern of results (Table 2); i.e., immune function is lowest during short days. These conflicting results can be resolved by considering additional environmental factors, not usually manipulated in laboratory studies. For example, winter-associated stressors (e.g., restricted food and low ambient temperatures) appear to counteract short day enhancement of immune function in the lab [reviewed in Demas and Nelson, 1996). Thus, we predict enhanced immune function should be observed during mild winters, whereas compromised immune function should be expected during challenging winters. Long-term field studies are required to test this hypothesis. Evidence will be presented that pineal melatonin plays a critical role, both directly and indirectly through its effects on other hormones, in mediating photoperiodic modulation of immune function. Although the effects of melatonin on immunity are well-established [see Poon et al., 1994; Giordano et al., 1993; Pioli et al., 1993; Maestroni, 1993; Caroleo et al., 1992; Guerrero and Reiter, 1992 for recent reviews], our goal in this review is to provide an ecological context for the effects of melatonin upon immune function, and to suggest why this phenomenon might be adaptive and functional, rather than merely a physiological oddity. Knowledge of the adaptive and functional significance of seasonal fluctuations in immune function may help to provide an improved understanding of the possibilities, as well as the constraints, of melatonin immunotherapy.

Seasonal changes in lymphatic tissue

Seasonal cycles in the development, regression, and regeneration of the thymus, spleen, and bursa of Fabricius have been described in a wide variety of vertebrate species [Brainard et al., 1987; 1988;

Table 1. Laboratory studies of photoperiodic changes in immune parameters

Immunological parameters measured	Species	Enhanced in short days?	Reference
Splenic mass	Norway rats (*Rattus norvegicus*)	Yes	Wurtman et al., 1973
	Deer mice (*Peromyscus maniculatus*)	Yes	Vriend and Lauber, 1973
	Golden hamsters (*Mesocricetus auratus*)	Yes	Brainard, 1985 Vaughan et al., 1987
Thymic mass	Norway rats (*Rattus norvegicus*)	Yes	Mahmoud et al., 1994
Lymphocyte count	Deer mice (*Peromyscus maniculatus*)	Yes	Blom et al., 1994
Neutrophil count	Deer mice (*Peromyscus maniculatus*)	Yes	Blom et al., 1994
White blood cell count	Deer mice (*Peromyscus maniculatus*)	Yes	Blom et al., 1994
	Common voles (*Microtus arvalis*)	Yes	Dobrowolska & Gromadzka-Ostrowska,1984
Antibody levels	Deer mice (*Peromyscus maniculatus*)	Yes	Nelson & Blom, 1994
Wound healing rates	Deer mice (*Peromyscus maniculatus*)	Yes	Nelson & Blom, 1994

Champney and McMurray, 1991; Zapata et al., 1992]. In common with seasonal fluctuations in reproductive organ mass, seasonal changes in lymphatic organ size were presumed to reflect changing organ function. Regression of the thymus, bursa, and spleen after puberty and the obvious link among these organs to seasonal changes in reproductive function, prompted many early hypotheses suggesting that these lymphatic organs regulated or influenced breeding [Aimé, 1912; Riddle, 1928]. For example, the avian thymus was originally suggested to provide the "egg envelope" [Riddle, 1924]. Other investigators hypothesized that the thymus was somehow involved with the onset of puberty because it was noted that castration "caused" hypertrophy of the thymus [Hammar, 1929; Gregoire, 1945].

The thymus and pineal gland have been functionally linked since early in this century. For example, the thymus and pineal gland were reported to function together to enhance somatic growth and development [Berman, 1921]. Treatment with pineal extracts increased thymic mass and induced lymphoidal cell hyperplasia [Milcu and Pitis, 1943]. Furthermore, perinatal pinealectomy caused thymic regression [Devecerski, 1963]. The discovery that the thymus, bursa, and spleen are major components

Table 2. Field studies of seasonal changes in immune parameters

Immunological parameter measured	Species	Suppressed in winter?	Reference
Splenic mass	Short-tailed voles (*Microtus agrestis*)	Yes	Newson, 1962
Splenic lymphoid tissue	European ground squirrels (*Citellus citellus*)	Yes	Shivatcheva & Hadjioloff, 1962
Reticulocyte count	Short-tailed voles (*Microtus agrestis*)	Yes	Newson, 1962
Lymphocyte response to CON-A	Beagle dogs (*Canis familiarus*)	Yes	Shiffrine et al., 1980
White blood cells	Cotton rats (*Sigmodon hispidus*)	Yes	Lochmiller et al., 1994
Hemagglutinins raised against SRBC	Ground Squirrels (*Citellus richardsoni*)	Yes	Sealander, 1956
Antibodies raised against J substance	Cattle (*Bos taurus*)	Yes	Stone, 1956
Thymic mass	Turtles (*Clymnysleprosa Testudo mauritonica*)	Yes	Aimé, 1912
	Lizards (*Scinus scinus*)	Yes	Hussein, et al.,1979
Lymphatic organ mass	Colubrid snakes (*Psammophis schokari*)	Yes	el Ridi et. al., 1981
Antibodies raised against SRBC	Lizards (*Scinus scinus*)	Yes	Hussein, et al., 1979

of the immune system, and the subsequent pursuit of molecular analyses of immune function have ignored, until very recently, the molar relationship, and possible bidirectional interactions, between immune function and the reproductive system [Maier et al., 1994].

The topic of seasonal variation in the immune systems of poikilothermic animals has recently been reviewed [Zapata et al., 1992]. There seems to be no consistent seasonal pattern of immune responsiveness in poikilotherms; however, steroid hormones profoundly affect immune function in these animals and seasonal fluctuations in immune function have been linked in some cases to interactions among different steroid hormones [Zapata et al., 1992]. The role of melatonin in mediating these effects in poikliotherms is largely unknown.

In the field, seasonal changes in lymphatic tissue have been thoroughly investigated in birds, but much less so in mammals. Avian splenic and thymic sizes are minimal when the gonads undergo vernal recrudescence [e.g., Krause, 1922; Riddle, 1928; Oakeson, 1953; 1956; Höhn, 1947; 1956; Fänge and Silverin, 1985; John, 1994]. Mallard ducks (*Anas platyrhynchos*), in common with other homeothermic vertebrates, undergo thymic involution at puberty [Höhn, 1947]. A pronounced regeneration of thymic tissue has been observed at the end of each breeding season in the middle of summer. In both male and female adult mallards, however, thymic tissue regresses again prior to the autumnal migration [Höhn, 1947]. The physiological stress associated with migration and breeding was considered to be incompatible with full thymic size and function [Höhn, 1947]. Similar observations have been made for house sparrows (*Passer domesticus*) and robins (*Turdus migratorius*) [Höhn, 1956].

The spleen of white-crowned sparrows (*Zonotrichia leucophrys gambelii* and *Z. l. nuttalli*) also regresses at the beginning of their breeding season. This splenic regression cannot be attributed to the "stress of migration" because both migratory and nonmigratory populations displayed similar seasonal patterns of splenic size [Oakeson, 1953; 1956]. Splenic size (corrected for lean body mass) was lowest prior to breeding and highest at the end of the breeding season in white-crowned sparrows. Similarly, migratory pied flycatchers (*Ficedula hypoleuca*) in Sweden also displayed a seasonal cycle of splenic development. Splenic regression was observed at the onset of the vernal breeding season; subsequent splenic development was exhibited by the adults during incubation and feeding of the hatchlings [Fänge and Silverin, 1985]. The adaptive significance of the development of the spleen prior to the autumnal migration has been suggested to reflect enhancement of immune function, particularly of the young birds after hatching, in advance of winter [Fänge and Silverin, 1985]. One parsimonious proximate explanation for the seasonal pattern of lymphatic organ development among birds is that the high gonadal steroid levels associated with breeding are incompatible with highly developed lymphatic tissue. The role of melatonin in mediating seasonal fluctuations in avian immune function has not been examined.

The proximate explanation that high gonadal steroid levels are associated with low lymphatic organ weights might also account for some of the data concerning seasonal fluctuations in mammalian lymphatic organ size. For example, mean splenic reticular cell counts varied seasonally in red-backed mice (*Clethrionomys rutilus*), with the main peak observed in early winter and lesser peaks observed in late winter and midsummer [Sealander and Bickerstaff, 1967]. Thymus weights were largest in February and spleen weights were largest in September and October; the lowest weights for both organs occurred in July [Sealander and Bickerstaff, 1967]. Similarly, thymus masses of pine voles (*Microtus pinetorum*) were highest in early autumn when reproductive organ masses were declining [Valentine and Kirkpatrick, 1970]. Adult and subadult cotton rats (*Sigmodon hispidus*) display a seasonal cycle of thymic development and regression; thymic masses were depressed during the summer and were maximal during the winter of some, but not all, years [Lochmiller et al., 1994]. Peak splenic masses and peak number of splenocytes were recorded in autumn and late winter, respectively in cotton rats.

Seasonal changes in lymphatic tissue have also been noted in hibernating mammals. The spleen and gut-associated lymphoid tissues of both hibernating and non-hibernating European ground squirrels (*Citellus citellus* L.) were examined and a circannual rhythm in the morphology of the splenic lymphoid tissue, as well as the lamina propria of the mucosa, and Peyer's patches was reported [Shivatcheva and Hadjioloff, 1987a; 1987b]. These lymphatic tissues regressed in the autumn in both hibernating and nonhibernating squirrels, but regression was reported to be more complete in hibernating animals. Notably, proliferation and hypertrophy of splenic and gut-associated lymphoid tissues were observed in squirrels *prior to* arousal in the spring [Shivatcheva and Hadjioloff, 1987a; 1987b]. The physiological effects of torpor and hibernation on immune function remain unspecified. Although suggestive, seasonal changes in lymphatic tissue do not directly inform about alterations in immune function, per se. In the following section, the literature on seasonal

changes in immune function and disease prevalence is briefly reviewed.

Seasonal changes in immune function and disease prevalence

Lymphatic organ development is suppressed among birds when gonadal steroid levels are elevated. Breeding coincides with an increased prevalence of some avian diseases, and this increased disease rate apparently reflects reduced immune function [John, 1994]. Numerous studies have demonstrated a seasonal change in parasite and pathogen prevalence [Lord, 1992; Descôteaux and Mihok, 1986; Lochmiller et al., 1994]. In some cases, this seasonal variation seems to reflect seasonal changes in the prevalence of the vector. For example, autumnal epidemics of typhus (*Rickettsia prowazekii*) in wild flying squirrels (*Glaucomys volans*) correspond closely to the maximal numbers of the arthropod vectors, *viz,* fleas and lice [Sonenshine et al., 1978].

The overwhelming evidence, however, indicates that seasonal fluctuations in disease and death rates reflect a seasonal change in the immune function of the host, rather than seasonal changes in the parasite or pathogen [John, 1994]. For example, house sparrows (*Passer domesticus*) infected with avian malaria (*Plasmodium relictum*) display a relapse of symptoms occurring synchronously throughout a population of infected birds and coincident with the onset of vernal breeding activities [Applegate and Beaudoin, 1970]. Gonadotropin treatment, either alone or in combination with corticosterone, stimulated gonadal development, but did not change the timing of incidence of the relapse. These results suggest that gonadal steroids are not involved in the prevalence of avian malaria, but that another factor associated with breeding affects susceptibility to this disease. The interaction between steroid hormones and immune function is described more fully below.

Ducks infected with *Leucocytozoon*, a parasite related to avian malaria, also display a vernal relapse of symptoms [Chernin, 1952]. When day lengths were experimentally increased during the winter, the relapse could be phase-advanced. Malaria among humans has also been reported to show increased vernal relapses, but these relapses have been considered to be due to a fixed interval of disease progression following autumnal infections [Coatney and Cooper, 1948; also see below]. Suppression of immune function during breeding has also been reported for birds with viral infections. For example, homing pigeons (*Columba livia*) maintained in semi-natural conditions and latently infected with pigeon herpes virus displayed an increased rate of viral shedding during breeding [Vindervogel et al., 1985]. Also, infected chickens significantly increased shedding of laryngotracheitis virus after egg laying had commenced [Hughes et al., 1989].

Seasonal changes in mammalian immune function and disease prevalence have also been reported. For instance, seasonal variation exists in the ability of bank voles (*Clethrionomys glareous*) to infect larval ticks with Lyme disease (*Borrelia burgdorferi*) [Talleklint et al., 1993]. Although larval tick infestations of voles were highest in June and July, nearly 70% of *Borrelia* infections occurred during August and September. Virtually no infections occurred during the winter. Whether these data reflect a seasonal alteration in the immune function of the host or reflect the latency to infection from year to year requires further study. Lymphocyte proliferation in response to the mitogens, concanavalin A (Con A) and an extract of pokeweed (*Phytolacca americana*) (PWM) was assessed in cotton rats (*S. hispidus*) [Lochmiller et al., 1994]. In addition to elevated humoral responses, cotton rats trapped in February 1990 also displayed elevated lympho-proliferative responses to Con A and pokeweed coinciding with increased numbers of total splenocytes harvested [Lochmiller et al., 1994] (Table 2). Total white blood cell (WBC) numbers reached minimum values in December 1989, July 1990, February 1990, and February 1991. The highest numbers of plaque-forming cells (PFC) were recorded in December 1989 and February 1990.

In another study of rodents, Richardson's ground squirrels (*Citellus richardsoni richardsoni*) were trapped during the spring and summer and maintained in natural photoperiods at 22–24°C [Sidky et al., 1972]. Five days after immunization with sheep red blood cells (SRBC), the animals were bled and their spleens removed. Antibody response to SRBC decreased significantly during the winter, reaching the lowest level in January. Spleen cell suspensions were tested for the presence of hemolysin-forming cells by a modification of the PFC assay. PFCs decreased significantly during the winter, reaching the lowest levels in January. However, the number of nucleated cells per spleen increased during the winter, reaching a maximum in January (150% of May values). The fact that these squirrels normally hibernate through the winter may explain the lack of winter enhancement of immune function. Again, the effects of hibernation on immune function are virtually unknown.

A study of cattle in the southern hemisphere revealed seasonal variation in naturally occurring antibody production against the antigen, substance J, a compound detected on the erythrocytes of some cattle [Stone, 1956]. Blood samples were drawn from cattle monthly and added to culture plates con-

taining substance J. Low antibody titers were present in January (summer), with levels rising thereafter to peak levels in August (winter). After this peak, levels began to drop, again returning to a minimum in January. Similarly, the rate of seropositive responses in cattle to *Borrelia burgdorferi* varied seasonally with the population infection incidence highest during the summer (up to 23.4%) and lowest during the winter (0% in January) [Isogai et al., 1992].

The seasonal occurrence of the equid herpes virus-4 (EHV-4) in foals was studied in Australia [Gilkerson et al., 1994]. Nasal swabs were obtained once a month for a year in order to detect the presence of EHV-4 antibodies. Twenty-six foals were EHV-4 positive, and all of these seropositive animals were discovered in the summer months of January, February, and March (25 in January and March, 1 in February) [Gilkerson et al., 1994]. No seropositive animals were detected in the winter months.

Outbreaks of European brown hare syndrome (EBHS) displayed a strong seasonal fluctuation among *Lepus europeus* in Sweden with peak occurrence observed during the winter [Gavier-Widen, 1991]. Similarly, rabbit viral hemorrhagic disease (VHD) exhibited a peak incidence during the winter. Again, the extent to which these animals were engaged in winter breeding was not reported.

Outbred male and female beagle dogs (50 days of age) maintained in open colonies were examined to assess seasonal changes in immune function [Shifrine et al., 1980a]. Whole blood lymphocyte proliferation tests were conducted by adding either phytohemagglutinin (PHA) or Con A to the monthly samples. The results of the lymphocyte proliferation tests demonstrated a peak in June/July and a trough observed in January. The reproductive status of these dogs was not described. In a follow-up study, blood samples were taken from 32 beagles at various times throughout the year [Shifrine et al., 1980b]. Another lymphocyte proliferation test was conducted on the samples. Greatest lymphocyte proliferation in response to both mitogens occurred during the summer, but the peak for samples incubated with PHA was phased-advanced several weeks as compared to samples incubated with Con A.

In summary, immune function in birds and some mammals appears to be generally compromised, and diseases are more prevalent, during the breeding season. Although there are data from many sources indicating seasonal changes in lymphatic tissue size and morphology, as well as immune function, there is significant variation among different populations of animals. Because so many factors can influence steroid hormone levels and these factors vary across populations, field studies are difficult to compare. Determining the causative agents and understanding the additive effects of these agents on the immune system requires laboratory studies in which one or more factors are altered in an otherwise stable and controlled environment. When only photoperiod has been experimentally manipulated in a controlled environment, the results clearly indicate that short days are coincident with elevated lymphatic organ mass and immune function. These studies are reviewed in the following section.

Photoperiodic changes in immune function

Laboratory strains of rats (*Rattus norvegicus*) are traditionally considered to be reproductively nonresponsive to photoperiodic information [Nelson et al., 1994]. Nevertheless, maintaining adult Wistar male rats in constant dark (DD) for 4 weeks increased thymic mass by 315% over rats maintained in an LD 12:12 photoperiod; most of the increase was observed in the lymphatic tissue within the thymic medulla [Mahmoud et al., 1994]. The number of thymocytes also increased in DD animals. Rats maintained for 4 weeks in constant bright light (LL) decreased thymic mass to 53% of values of LD 12:12 rats; the reduction in total volume represented mainly reductions in the thymic cortex [Mahmoud et al., 1994]. Because photoperiod does not affect steroid hormones in male rats [Nelson et al., 1994], these data strongly suggest that melatonin acts directly upon immune function [Mahmoud et al., 1994]. Previous studies on rats have indicated slight photoperiod-induced changes in splenic weight [Wurtman and Weisel, 1969].

Laboratory strains of house mice (*Mus musculus*) also display seasonal rhythms of immune function despite insignificant reproductive response to photoperiod. For instance, young C57BL/6 mice (*Mus musculus*) were maintained in an LD 12:12 photoperiod [Brock, 1983]; splenic lymphocytes were stimulated with mitogens and viable and non-viable lymphocytes were counted throughout the year. Peak responses in T and B lymphocyte populations were 2–5 times higher in March–April 1978 and February–March 1977 than in either of the two previous Decembers. Summer comparisons were not reported. Again, these animals, like laboratory strains of rats, typically are reproductively nonresponsive to photoperiod [Nelson, 1990]. Differences in seasonal patterns have been reported between strains of *Mus*. The maximal numbers of splenic PFC to SRBC injection occurred in spring for CD1 females and in summer for $B6C3F_1$ mice [Ratajczak et al., 1993].

Short day lengths appear more effective at me-

diating immune function in individuals with robust reproductive responses to photoperiod. For instance, splenic weights of deer mice (*Peromyscus maniculatus*) [Vriend and Lauber, 1973], and Syrian hamsters (*Mesocricetus auratus*) [Brainard, 1987] were reduced in short days. Splenic masses, total splenic lymphocyte numbers, and macrophage counts were significantly higher in hamsters exposed to short days, as compared to animals exposed to long photoperiods [Brainard et al., 1987; 1988]. However, photoperiod did not affect thymic weight or antibody production in hamsters [Brainard et al., 1987]. Photoperiodic influences on lymphocyte number and total white blood cell count have been reported for deer mice [Blom et al., 1994]. Animals maintained in short day lengths (LD 8:16) possessed more white blood cells than animals maintained in long day lengths (LD 16:8); neutrophil numbers were unaffected by day length in adult female mice. More recently, deer mice maintained in short days displayed faster healing rates than long day mice [Nelson and Blom, 1994].

Short day lengths appear to bolster immune function (Table 1). One likely physiological mechanism by which photoperiod affects immune function is via alterations in the pattern of melatonin secretion. Importantly, lymphatic cells of both birds and mammals possess melatonin receptors [reviewed in Calvo et al., 1995]. *In vivo* melatonin treatment bolsters immune function. The pattern of melatonin release induced by short days affects the secretion of other hormones. The precise mechanisms through which photoperiod interacts with the endocrine system and exerts influences on the immune system are not known. The presence of receptors for both androgens in the thymus and for estrogens in the cytosol of circulating lymphocytes might explain why these steroid hormones play an important role in the mediation of immune function [Grossman, 1985; Hall and Goldstein, 1984]. Prolactin is another hormone that is profoundly affected by day length and also affects immune function. Thus, photoperiodic effects on immune function may reflect photoperiod-mediated changes in blood concentrations of prolactin. Consequently, the possibility that melatonin might act both directly and indirectly on the immune system is strong. The effects of these specific endocrine interactions upon immunity are reviewed in the following sections.

Effects of melatonin on immune function

The pineal gland and the primary secretory pineal product, melatonin, can affect lymphatic tissue sizes. For example, exposure of male and female hamster to short days or daily afternoon melatonin injections elevated splenic mass [Vaughan et al., 1987]. Elevated splenic mass could be prevented in short-day hamsters by pinealectomy [Vaughan et al., 1987]. Importantly, melatonin mediates immune *function* [Maestroni, 1993]. In virtually all cases examined, melatonin enhanced humoral and cell-mediated immunity [Maestroni, 1993; Guerrero and Reiter, 1992]. Melatonin treatment of both normal and immunocompromised house mice elevated in vitro and in vivo antibody responses [Caroleo et al., 1992; Maestroni, 1993]. Impaired T-helper cell activity in immunocompromised mice is restored by melatonin treatment [Caroleo et al., 1992]. Antigen presentation by splenic macrophages to T cells is also enhanced by melatonin; furthermore, this enhancement is coincident with an increase in major histocompatibility (MHC) class II molecules, as well as interleukin (IL)-1 and tumor necrosis factor (TNF_α) production [Pioli et al., 1993]. Murine antibody-dependent cellular cytotoxicity (ADCC) is reduced in adult mice that were pinealectomized prior to 7 days of age [Vermeulen et al., 1993]. ADCC is a lytic process that occurs when lymphocytes bind to specific antibody-coated target cells through receptors for the Fc portion of the Ig molecule expressed on their membrane. The impairment in ADCC appears peripubertally, around 60 days of age, suggesting an involvement of sex steroid hormones [Vermeulen et al., 1993]. Pinealectomy also ameliorates collagen II-induced arthritis in mice [Hansson et al., 1993], as well as inhibits humoral immune function and suppresses bone marrow progenitors for granulocytes and macrophages [Kuci et al., 1983]. Additionally, natural killer (NK) cell activity and IL-2 production are reduced in mice after pinealectomy [del Gobbo et al., 1989].

As predicted [Maestroni, 1993; Guerrero and Reiter, 1992], melatonin receptors have been isolated on circulating lymphocytes [Calvo et al., 1995; Pang and Pang, 1992; Pang et al., 1993; Poon and Pang, 1992; Liu and Pang, 1993], as well as on thymocytes and splenocytes [Lopez-Gonzales et al., 1993; Martin-Cacao et al., 1993; Rafii-El-Idrissi et al., 1995]. The melatonin receptors on lymphatic tissue appear similar in Kd values to melatonin receptors localized in rat and hamster brains, and also seem to be coupled to G-protein(s) [Calvo et al., 1995]. Melatonin partially inhibits cyclic AMP production in human lymphocytes, but only at pharmacological doses [Rafii-El-Idrissi et al., 1995].

The circadian synthesis and release of melatonin modulates antibody response and also alters tumorigenesis [see Blask, 1985]. At the normal cellular level, melatonin is believed to affect antimitotic processes as well as cytotoxic activity [Boucek and Alvarez, 1970; Poffenbarger and Fuller, 1976; Win-

ston et al., 1974]. When the synthesis of endogenous melatonin is blocked, antibody production is depressed [Maestroni and Pierpaoli, 1981; Maestroni, et al., 1986]. In contrast, transplantation immunity is not affected by pinealectomy [Maestroni and Pierpaoli, 1981; Maestroni, et al., 1986]. Pharmacological and surgical pinealectomy also modulate other immune parameters including plaque-forming cells and blastogenic responses of splenocytes and thymocytes to various mitogens [Becker et al., 1988; Kuci et al., 1983]. Furthermore, elimination of melatonin synthesis by pinealectomy profoundly decreased the proliferation of bone marrow progenitors for granulocytes and macrophages (CFU-MG); disruption of the night-time peak of melatonin completely abolished CFU-MG proliferation [Kuci et al., 1983]. Whenever examined, compromised immune function caused by pinealectomy could be ameliorated by melatonin replacement therapy [Maestroni, 1993].

The effects of melatonin on immune function appear to be related to seasonal changes in tissue sensitivity to this indoleamine. For example, in BALB/c mice melatonin injections enhanced ADCC in response to chicken red blood cells (CRBC) when given during the summer [Giordano et al., 1993]. Melatonin treatment during the winter failed to enhance ADCC.

Melatonin is important in many disease processes, especially cancer [Blask, 1985; Maestroni, 1993; Guerrero and Reiter, 1992; Poon et al., 1994; Giordano et al., 1993; Pioli et al., 1993; Caroleo et al., 1992; Nelson and Demas, 1996]. The overwhelming majority of studies indicate that melatonin is an oncostatic hormone. A number of treatments for cancer now incorporate melatonin as part of the immunomodulatory therapy [e.g., see Barni et al., 1995; Neri et al., 1994; Lissoni et al., 1994; 1995].

In summary, melatonin appears to enhance immune function in most cases. In common with reproductive responses mediated by melatonin, there may be a temporal component to the biological actions of this indoleamine. Most studies of melatonin effects on immune function have used animals that are not particularly responsive to this hormone (e.g., laboratory rodent strains) and may have overlooked the temporal components of melatonin influences. Again, sustained release of melatonin is higher in short, as compared to long days. Short-day induced changes in melatonin secretion evoke a cascade of other endocrine changes. Notably, steroid hormone and prolactin secretion declines dramatically in short days.

The effects of androgens on immune function

Short days, or timed melatonin treatments, elicit gonadal regression in many species. Gonadal regression in males is coincident with reduced circulating levels of testosterone. Testosterone generally suppresses immune function. Castration of adult male rodents results in increased humoral and cell-mediated immunity, as well as increased lymphatic organ size, including thymic, splenic, and lymph nodal masses [Schuurs and Verheul, 1990]. Castration of male rodents leads to immune parameters that are similar, but not equivalent to females [Grossman, 1985]; this suggests that some of the sex difference in immune function is organized prior to puberty. Treatment of adult castrated males with physiological doses of testosterone restores (i.e., compromises) immune function to pre-castration levels [Schuurs and Verheul, 1990; Grossman, 1984]. Testosterone treatment of castrated or intact male rats or mice significantly suppresses humoral and cell-mediated immunity, as well as thymic mass [Schuur and Verheul, 1990; Grossman, 1984]. Androgen receptors have been identified in thymic tissues, particularly in the epithelial, lymphatic portion of the thymus [McCruden and Stimson, 1991; Sasson and Mayer, 1981]. Because no androgen receptors have been identified on circulating lymphocytes, androgenic effects on lymphocytes may be indirect or act through aromatization of androgens to estrogens [McCruden and Stimson, 1991]. Because blood androgen levels decrease in short days, this photoperiodic treatment is similar to a functional castration. Thus, enhancement of immune function could be due to removal of the immunosuppressive effects of androgens in short-day animals.

Dehydroepiandrosterone (DHEA) is a weak androgen that is produced primarily in the adrenal cortex. DHEA serves as an intermediate in the production of androstenedione from 17α-hydroxyprogesterone. In addition to its role in the steroid biosynthesis pathway, a number of recent reports suggest that DHEA may have potent physiological effects on immune function [Casson et al., 1993; Morales et al., 1994]. DHEA acts as an antiglucocorticoid, and enhances IL-2 production and cytotoxicity of activated T cells in mice and humans [Suzuki et al., 1991]. DHEA also increases immunological protection against a herpes virus type 2 encephalitis, and also protects against systemic coxsackievirus B4 infection [Loria and Padgett, 1992]. DHEA-treatment also prevented the reduction in humoral and cellular immune function usually observed after thermal injury [Araneo et al., 1993]. The role of DHEA in seasonal fluctuations in immune function requires investigation.

Effects of estrogens on immune function

In contrast to the pattern of androgen receptor localization, estrogen receptors have been localized in

the cytosol of circulating lymphocytes [Danel et al., 1983; Grossman, 1984], CD8+ cells [Cohen et al., 1983; Stimson, 1988], and thymic cells [Danel et al., 1983; Nilsson et al., 1984; Weusten et al., 1986]. Physiological treatments with estrogen or the estrogen receptor antagonists, tamoxifen or FC-1157a, enhance pokeweed mitogen (PWM)-induced immunoglobulin synthesis of B-lymphocytes [Paavonen and Andersson, 1985; Sthoeger et al., 1988].

Treatment of intact male or gonadectomized male or female mice and rats with physiological or supraphysiological doses of estrogens increases antibody responses to a variety of T-dependent and T-independent antigens [Inman, 1978; Myers and Peterson, 1985; Brick et al., 1985]. Cyclic exposures to pharmacological doses of estrogens are more effective in boosting antibody formation than chronic exposure to pharmacological estrogen doses [Schuurs and Verheul, 1990]. However, prolonged pharmacological doses of estrogens may also suppress cell-mediated immunity [Grossman, 1985; Kuhl et al., 1983]. Taken together, the effects of physiological doses of estrogen appear to enhance immune function. Blood estrogen (and androgen) levels are low in short-day females. Thus, enhancement of winter immune function is unlikely to involve photoperiod-mediated changes in blood levels of estrogens. The proximate effects of estrogens probably account for the superiority of female immune function as compared to males [Grossman, 1985; Schuurs and Verheul, 1990].

Effects of prolactin on immune function

Exposure to short day lengths reduces blood prolactin levels in every mammalian species thus far examined [Goldman and Nelson, 1993]. Treatment with melatonin in ways that mimic release patterns associated with short day lengths also suppresses blood prolactin titers [Goldman, 1983; Bittman, 1984]. Prolactin has pronounced effects upon immune function in a variety of species [reviewed by Bernton et al., 1991; 1992; Reber, 1993; Arkins et al., 1993; Matera et al., 1992; Castanon et al., 1992]. Generally, prolactin maintains or enhances normal immunological activities, but there are also examples of prolactin compromising immune function, particularly at high or low circulating levels [Reber, 1993]. Because exposure to short day lengths suppresses circulating prolactin levels, this hormone is a possible candidate for mediating some of the reported seasonal changes in immune function.

Hypophysectomy of rats results in compromised humoral and cell-mediated immunity; immune function can be restored by prolactin replacement therapy [Reber, 1993]. Prolactin elevates the respiratory burst and phagocytosis of peritoneal macrophages from both young and old mice [Chen and Johnson, 1993]. Prolactin induces resting lymphocytes to divide, and can also affect the magnitude of their response to polyclonal stimuli. Prolactin also influences the effector phase of the immune response, including increased response of NK cells, T-cells, and B-cells to mitogenic signals [Matera et al., 1992]. Membrane-bound prolactin receptors have been discovered on lymphocytes [Reber, 1993; Bernton et al., 1991; 1992]. Furthermore, prolactin-like substances have been identified in mouse splenocytes and human B-lymphoblastoid cell lines [Sabharwal et al., 1992; Reber, 1993]. Cyclosporin A directly competes with prolactin for binding of the lymphatic receptors. It has been proposed that the immunocompromising effects of cyclosporin A may result from interference with a prolactin-like autocrine growth factor for lympho-proliferation [Sabharwal et al., 1992; Reber, 1993].

Effects of glucocorticoids on immune function

Many interactions between glucocorticoids and immune cell function have been reported in relation to environmental stress [reviewed in Nakono et al., 1987]. However, the mechanisms underlying seasonal changes in stress hormones and immune function have not been elucidated. Adrenocortical hormones, especially glucocorticoids, suppress immune function in both humans and nonhuman animals [Baxter, 1972; Clamin, 1972; Hauger, 1988; Ader and Cohen, 1993; Black, 1994]. Glucocorticoids are released in response to stressful stimuli, and can compromise cellular and humoral immune function [Berczi, 1986; Levi et al., 1988]. Adrenalectomy enhances lymphatic organ masses and B-cell activities [del Rey et al., 1984]. The precise mechanisms by which the immune system is affected by the hypothalamo-hypophysial-adrenocortical axis are unknown, but probably involve cytokine release rates from activated immunological cells [Besedovsky et al., 1981; 1983; Besedovsky et al., 1986; Besedovsky and del Rey, 1991]. Regardless of mechanism, substantial evidence links glucocorticoids with suppressed immune function.

Recently, a direct link between melatonin and glucocorticoid biology has been established. Generally, melatonin enhances immune function, whereas glucocorticoids compromise immune function [Gupta, 1990; Maestroni et al., 1986; Maestroni, 1993; Maier et al., 1994]. Melatonin treatment can ameliorate the immunocompromising effects of glucocorticoids [Maestroni et al., 1986; Aoyama et al., 1986; 1987]. Cortisol treatment of ducklings reduced the number of thymic melatonin receptors

[Poon et al., 1994]. Similarly, chronic melatonin treatment decreased the density of thymic glucocorticoid and progestin receptors in rats [Persengiev et al., 1991].

Previous studies have demonstrated that environmental stressors elevate blood glucocorticoid levels and that high glucocorticoid levels suppress immune function [Baxter, 1972; Clamin, 1972; Hauger, 1988; Ader and Cohen, 1993; Black, 1994; Fauci, 1975; Kawate et al., 1981; Besedovsky and del Rey, 1991]. For example, low ambient temperatures are often perceived as stressful, and can potentially depress immune function [e.g., Clamin, 1972; MacMurray et al., 1983; Monjan, 1981]. Winter survival in small animals is hypothesized to require a positive balance between short-day enhanced immune status and glucocorticoid-induced immunosuppression [Demas and Nelson, 1996]. This immunosuppression may be due to many factors, including overcrowding, increased competition for scarce resources, low temperatures, reduced food availability, increased predator pressure, or lack of shelter. Each of these potential stressors may cause high blood concentrations of glucocorticoids. Winter breeding with its concomitant elevation in sex steroid hormones may also cause immunocompromise [e.g., Tang et al., 1984; Lochmiller et al., 1994]. Presumably, winter breeding occurs when other environmental stressors such as temperature and food availability are not severe. The balance of enhanced immune function (i.e., to the point where autoimmune disease becomes a danger) against stress-induced immunosuppression (i.e., to the point where opportunistic pathogens and parasites overwhelm the host) must be met for animals to survive and become reproductively successful. Thus, the mediation of reproductive function and immune function will likely be intertwined [Besedovsky and del Rey, 1991]. Although stress generally results in compromised immune function, the degree of immunological response to stress varies seasonally. For example, rat hemagglutination titer response to SRBC was suppressed in response to electric-shock stress compared to control animals during the winter. In the summer, however, shock-stressed rats displayed *enhanced* antibody response to SRBC relative to control animals [Amat and Torres, 1993].

Recently, the interaction between photoperiod and temperature was examined on antibody levels and splenic mass in male deer mice [Demas and Nelson, 1996]. Animals were maintained in LD 16:8 or LD 8:16 photoperiods in either 20° or 8°C temperatures. Serum IgG levels were elevated in short-day mice maintained at normal room temperature as compared to long-day animals (Fig. 1). Long-day deer mice kept at 8°C temperatures had reduced IgG

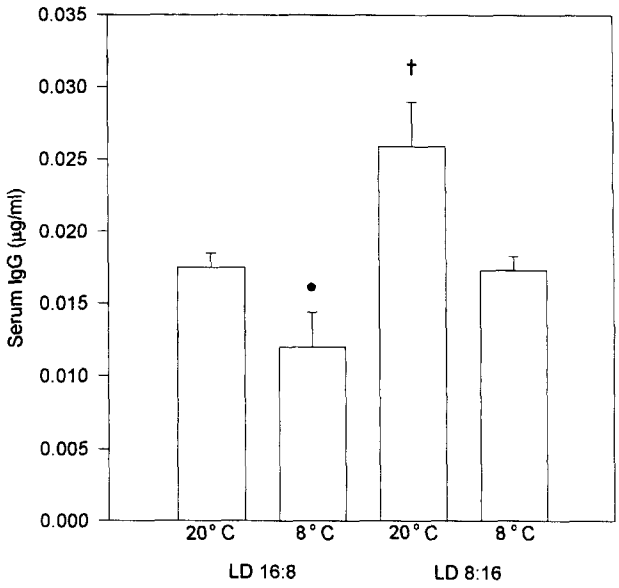

Fig. 1. Mean (± Standard Error of the Mean [SEM]) serum immunoglobulin G (IgG) levels (µg/ml) of male deer mice (*Peromyscus maniculatus*) maintained for 8 weeks in either long (LD 16:8) or short (LD 8:16) day lengths and ambient temperatures of either 20° or 8°C. Columns with dissimilar symbols differ significantly ($P < 0.05$). Note that short days enhance antibody levels and that low temperatures compromise antibody levels. Short-day animals in low temperatures exhibited antibody levels comparable to mice housed in long days at mild ambient temperatures.

levels; mice exposed to short days and low temperatures had IgG levels comparable to long-day mice maintained at 20°C. In other words, short days elevated IgG levels over long days. Low temperatures caused a significant reduction in IgG levels. The net effect of short-day enhancement and low temperature reduction of IgG levels is no appreciable difference from baseline (i.e., long-day mice kept at 20°C). This adaptive system may help animals cope with seasonal stressors and ultimately increase reproductive fitness.

Clinical significance of seasonal changes in immune function

The possibility that photoperiod affects human reproductive function remains open [see Bronson, 1995]. Similarly, the possibility that photoperiod affects human immune function is largely unexplored. Many human diseases show remarkable seasonal fluctuations (Table 3). Malaria is a common seasonal disease among humans residing in the tropics [Theander et al., 1990]. There are a number of reports of seasonal changes in immune function associated with malaria. As noted previously, malaria has been reported to show increased vernal relapses in humans. Typically, these relapses have been at-

TABLE 3. Seasonal variation in peak prevalence of human illness and disease

Disease	Peak prevalence	Reference
Gonorrhea	Summer-early fall	Cornelius, 1971
Respiratory syncytial virus	Winter-early spring	Hall, 1991 Miller, 1992
Coronaviruses	Winter-early spring	Cavallaro and Monto, 1970 Hamre and Beem, 1972 Hendley et al., 1972
Sudden infant death syndrome[a]	Winter	Beal, 1983 Carpenter and Gardner, 1990
Influenza	Winter-early spring	Glezen et al., 1982
Human reovirus	Winter	Kapikian et al., 1976
Malaria	Winter-early spring	Chougnet et al., 1990
Coronary heart disease	Winter	Douglas et al., 1990
Stroke		
Cerebral infarction	Spring-summer	Biller et al., 1988
Ischemic attacks	Winter-spring	Dunnigan and Harland, 1970
Intracerebral hemorrhage	Winter-early spring	Biller et al., 1988
Insulin-dependent diabetes	Autumn-winter	Blom and Dahlquist, 1985
Breast Cancer		
# of cases diagnosed	Winter	Ownby et al., 1986
Occurrence	Spring-early summer	Chleboun and Gray, 1987 Cohen et al., 1983 Kirkham et al., 1985
Risk of death	Summer	Sankila et al., 1993
Initial detection	Spring-summer	Jacobsen and Janerich, 1977 Kirkham et al., 1985 Mason et al., 1985
Urinary bladder carcinoma	Fall-winter	Hostmark et al., 1984

[a]For cases speculated to be caused by a respiratory virus.

tributed to a fixed interval of disease progression following autumnal (onset of the wet season) infections [Coatney and Cooper, 1948]. Antigen-induced cellular immune responses to *Plasmodium falciparum* are compromised during acute malaria onset [Abu-Zeid et al., 1992; Chougnet et al., 1990; Theander et al., 1990]. Lymphocyte proliferation responses (against non-malaria antigens) of healthy individuals were also compromised during the malaria transmission season [Theander et al., 1990]. This suggests that immune function might be suppressed during the time of *Plasmodium falciparum* infections. As is the case for nonhuman animals, the extent to which the seasonal changes in human disease and death rates reflect changes in the host or in the pathogen requires further study in most cases. The interaction among melatonin deficiencies, immune function, and disease processes may be profound.

There is evidence from several sources that day length may affect human immune function and disease prevalence. Individuals suffering from seasonal affective disorder (SAD) often exhibit aberrations in their immune cell counts, especially during their winter-depression [Rosen et al., 1991]. For example, some patients with SAD display aberrant lymphocyte proliferation in response to mitogenic stimulation [Skwerer et al., 1988]. Treatment of the SAD symptoms with bright illumination ameliorates these immunological abnormalities [Skwerer et al., 1988]. Total number of circulating NK cells was reduced among SAD patients in another study [Kasper et al., 1991]; the reduction was inversely related to the score attained on a test of depression. After bright light therapy, the symptoms of depression ameliorated and NK cell numbers increased. Furthermore, lymphocyte proliferation in response to Con A and PWM improved after phototherapy [Kasper et al., 1991]. Thus, these studies indicate that immune function is significantly compromised in the winter among patients who suffer from SAD [Rosen et al., 1991].

Another observation that is consistent with a photoperiodic influence on human immune function is the association between latitude and multiple sclerosis (MS) [Davenport, 1922; Limburge, 1950; Kurtzke, 1975; 1980]. The prevalence of MS increases at higher latitudes, both north and south [reviewed in Rosen et al., 1991]. A consistent correlate with MS is the amount of December solar radiation (i.e., high numbers of sunny hours in December are associated with low numbers of MS cases in the region) [Acheson et al., 1960].

Seasonal changes in human immune function have also been established in healthy people. Accordingly, both measurements of cellular and humoral immunity display seasonal variation. For

example, the percentage of viable B and T cells was significantly elevated in winter subjects compared to those tested in the summer [MacMurray et al., 1983]. In another study, a group of six blood donors was tested, and absolute values and percentage of B and T-cells in peripheral blood were examined over the course of 1 year [Bratescu and Teodorescu, 1981]. Although the total number of lymphocytes and leukocytes did not vary throughout the year, the proportion of B cells to T cells was nearly doubled during the winter months compared to the summer months [Bratescu and Teodorescu, 1981]. Seasonal differences in mitotic activity of normal human peripheral blood lymphocytes have also been examined [Boctor et al., 1989]. In healthy males and females, increased proliferative responses of peripheral blood lymphocytes to Con A and PHA were observed in the summer months compared to the winter months [Boctor et al., 1989].

Observations of humoral immunity in humans have yielded conflicting results. In one study, blood samples of patients from five different VA hospitals had significantly higher IgG levels in the winter samples compared to those of summer for four out of five hospitals [MacMurray et al., 1983]. Conversely, examination of seasonal variation in a variety of serum proteins from adult and children outpatients, revealed that concentrations of IgG were greater during the summer months as compared to the winter months [Lyngbye and Krøll, 1971]. IgA and IgM levels did not differ significantly across seasons in these studies [Lyngbye and Krøll, 1971; MacMurray et al., 1983]. In another study of healthy adults and children, no significant seasonal changes were observed on serum IgG, IgM, or IgA levels [Stoop et al., 1969]. Similarly, serum sampled over a 24 month period from healthy adults and children, revealed no seasonal changes in immunoglobulin concentrations, though serum IgM showed the greatest variability in the fall-winter period [Nordby and Cassidy, 1983].

Taken together, the seasonal, photoperiodic, and pineal melatonin studies suggest that melatonin enhances immune function. Although progress is being made to determine the physiological mechanisms underlying the effects of melatonin on immune function, new insights may be gained by understanding the adaptive significance of melatonin effects on immune function. Answers at this level of analysis might guide questions on the proximate, physiological level of analysis. Similar to humans, laboratory strains of rats and mice are traditionally unresponsive to melatonin. These laboratory species may be useful for understanding the effects of melatonin on human immune function. Alternatively, these artificially selected species, especially albino strains, may present limitations on our understanding [e.g., Turek et al., 1976; Vollrath et al., 1989; Champney et al., 1986; Olcese and Reuss, 1986; Webb et al., 1985; Lynch et al., 1984]. The effects of timed infusions of melatonin that mimic naturally occurring patterns of endogenous secretion are also required to understand melatonin-immunity interactions.

Melatonin may enhance immune function to help the individual cope with seasonal stressors that would otherwise compromise immune function to critical levels. Fluctuating immune function may represent adaptations that have evolved to increase the odds of surviving changes in energy availability. This review systematically examined the interaction of melatonin, photoperiod, and immune function in an ecologically-relevant manner. The clinical implications of seasonal fluctuations in immune function may be significant in forecasting and treating human diseases.

Acknowledgments

Preparation of this review and funding of unpublished experimental data were supported by USPHS grants HD 22201 and CA 58168. We thank Drs. Thomas Hahn and Courtney DeVries for reading the manuscript.

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