SEASONAL PATTERNS OF STRESS, IMMUNE FUNCTION, AND DISEASE

As the seasons change, animals face alterations in environmental stressors. In particular, the prevalence and intensity of pathogenic infection are often seasonal. This book presents evidence that infection is cyclical with the seasons and that this phenomenon is mirrored in cycles of immune function.

The goal of this book is to identify the mechanisms by which the immune system is bolstered to counteract seasonally recurrent stressors, such as extreme temperature reductions and food shortages. The authors consider how such environmental changes create energetically demanding conditions that can compromise host immunity and lead to illness and death. Specifically, stress, infectious diseases, autoimmune diseases, and human cancers are examined, and the role of hormones such as melatonin and glucocorticoids is considered. The book begins with an overview of seasonality, biological rhythms and photoperiodism, and basic immunology, and continues with the characterization of seasonal fluctuations in disease prevalence, energetics, and endocrinology as they relate to immune function. Finally, the clinical significance of seasonal patterns in immune function is addressed to emphasize the role that seasonal changes in host immunity and hormones may play in the development and treatment of infections.

This is the first monograph to examine seasonal immune function from an interdisciplinary perspective. Practitioners as well as advanced undergraduates and graduate students in biology, immunology, human and veterinary medicine, neuroscience, endocrinology, and zoology will find its approach both insightful and relevant.

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For our Families . . .

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Foreword

Most animals exhibit seasonal variation in their reproduction and survival simply because most of them live in environments in which food availability varies seasonally. This is true in the tropics as well as at the higher latitudes, but at the higher latitudes the combined challenge of food shortage and low temperature makes winter a particularly difficult time to reproduce and survive.

Traditionally, vertebrate physiologists interested in seasonal phenomena have focused on reproduction and largely ignored survival. In part, this is because of the discovery 70-odd years ago that some temperate zone animals use variation in day length to synchronize their reproduction with seasonally changing environmental conditions. This discovery meant that researchers interested in seasonality could bring the power of the scientific method into play simply by installing a light timer on the wall of an animal room. The result of several decades of experimentation using this technique is a robust body of knowledge about how photoperiod regulates reproduction. Indeed, this is an epic, albeit an as yet unfinished epic, in biological research.

Randy Nelson and his colleagues have added a whole new dimension to the study of seasonality by shifting the focus from reproduction to survival. This book is a pioneering effort to define this field of study, and it will prove to be a milestone in research on seasonality. The specific hypothesis under consideration is that "individuals have evolved mechanisms to bolster immune function in order to counteract seasonally recurrent stressors that may otherwise compromise immune function." Stated differently, the authors visualize seasonal variation in survival as an interaction between two factors: the suppression of immune response attributable to changing energetic conditions and an endogenous rhythm of enhancement of immune response that is dependent on photoperiod, clocks, and melatonin.

Of particular importance is the authors' postulate that seasonal variation in certain human diseases may be caused at least in part by variation in immune responsiveness and, in turn, by variation in photoperiod. The evolutionary history of humans suggests that almost all ancestral stocks of *Homo sapiens*

have lived at one time or another in situations where photoperiodic regulation of seasonal adjustments might have proven advantageous. Whereas the available evidence suggests that reproduction is not susceptible to photoperiodic regulation in humans, immune function very well may be. This possibility deserves serious consideration, and the publication of this book assures that it will receive the attention it needs.

On a still broader scale, this book will arouse interest in seasonality in general. Research on the way photoperiod regulates reproduction generated intense interest in the way reproduction is regulated seasonally by factors other than photoperiod. Likewise, interest in the way photoperiod regulates immune function seasonally will elicit the question of whether immune function varies seasonally in species that are not responsive to photoperiod and, if so, how this is done.

For those of us that have been around for awhile, it is exciting to see a renewed interest in the way animals, including humans, respond physiologically to seasonal variation and to visualize how this renewed interest might expand our knowledge in the future.

Frank Bronson
Austin, TX
July 2001

Preface

Our environment changes seasonally. From the amount of light that we are exposed to each day to the availability of food and water, we are confronted with an ever-changing environment. As a consequence of these environmental changes, all inhabitants of Earth show fluctuations in energetically expensive physiological and behavioral processes throughout the year. Thus, adaptations have evolved so that energetically demanding processes coincide with abundant resources or other environmental conditions that promote survival and, ultimately, reproductive success. The study of seasonal changes in physiology and behavior in the field is typically limited to population dynamics among nondomesticated animals. Seasonal patterns of behaviors, including those associated with reproduction, social behavior, and daily activity, as well as seasonality in the physiology that underlies these behaviors, are well documented (Bronson and Heideman, 1994). Most studies of seasonality involve some aspect of seasonal breeding, such as mating, birth, or parental care. Seasonal patterns of illness and death are equally salient among natural populations of animals in the wild, but the underlying factors driving these seasonal patterns are much less studied than the extrinsic factors driving seasonal patterns of breeding. Generally, illness and death are most common during the fall and winter, compared with spring and summer, for most nontropical species.

One goal of our book is to describe an emerging hypothesis that individuals have evolved mechanisms to bolster immune function to counteract seasonally recurrent stressors that may otherwise compromise immune function. Seasonally recurrent stressors include food shortages, low ambient temperatures, and lack of cover from hungry predators. Survival thus represents maintaining the well-known energy budget and also maintaining a balance between stress-induced immunosuppression and endogenous rhythms of enhanced immune function. In Chapter 1, we briefly review the geophysical factors leading to seasons and the development of annual and daily biological rhythms to reflect these seasons. Then, the biological and phenomenological

features of biological clocks and their associated rhythms are summarized. Sufficient information will be provided to allow the reader who is naive to the field of biological timing to understand the evolutionary and physiological issues related to temporal organization that are referred to throughout the book.

The concept that seasonal patterns in the prevalence of infection exist is not new. In fact, the "flu season" has been documented for hundreds of years (Sakamoto-Momiyama, 1977). The novelty of our approach is that we consider how changes in the environment (e.g., reduced temperatures, reduced food and water availability) act as stressors to create energetically demanding conditions that can indirectly cause illness and death by compromising host immunity. Thus, we argue that mechanisms have evolved to resist seasonal stress-induced susceptibility to infection as a temporal adaptation to promote survival. To understand the immunological processes that underlie susceptibility and resistance to infection, Chapter 2 provides a detailed overview of the immune system and responses important for overcoming infection.

In Chapter 3, we review the substantial evidence for seasonal cycles in disease prevalence in both humans and nonhuman animals. Not surprisingly, most animals, including humans, are more likely to become ill and die during the winter, compared with summer. A number of factors contribute to this pattern, but we will support the notion in Chapters 3 and 4 that, without "programmed" bolstering of immune function during the winter, the incidence of disease and death would be elevated. The studies presented in Chapter 3 illustrate that seasonality in the intensity and prevalence of infection occurs in many species and may be linked to changes in the host as opposed to seasonal changes in the prevalence of the pathogen or vector. In Chapter 4, we focus on the literature that reports a seasonal change in immune function. In this chapter, we will argue that seasonal fluctuations in immune function represent changes in the host, rather than changes in the vector or presence of the pathogen. In some cases, immune function is compromised and disease rates are elevated during the winter. Although this observation may seem to rule out our working hypothesis of enhanced immune function during the winter, we will argue that seasonal stressors (reduced food availability, low temperatures, etc.) may be too pronounced to override the endogenous enhancement of winter immune function. The support for this notion is presented in Chapters 5 and 6. Many extrinsic factors co-vary across the year, but photoperiod (or day length) is an environmental cue that seems to be used by many individuals to time seasonal events. The effects of photoperiod on immune function is reviewed in Chapter 5; in virtually all reported cases, short days evoke enhancement of immune function. Melatonin, a

hormone secreted from the pineal gland, mediates photoperiod, and the immunoenhancing effects of melatonin also will be reviewed in this chapter.

If animals (including humans) are capable of enhancing immune function during the winter, then why has natural selection not favored the enhancement of immune function during the summer when many more social and sexual interactions are occurring and diseases are likely to be spread? The energetic costs of maintaining immunologic function and the incompatibility between these costs and reproductive costs is discussed in Chapter 6. Also, the concept of energetic stressors and their effects on immune function is addressed in this chapter. Several hormones, including sex steroids, glucocorticoids, and prolactin, affect immune function and are affected by environmental perturbations. Thus, Chapter 7 provides evidence that steroid and peptide hormones affect the immune system and may mediate seasonal patterns in infection.

Why study seasonal patterns in immune function and illness? From a clinical perspective, understanding the role of host hormones and immunity in seasonal changes in infection may influence the development and administration of treatments for infections. From a biological perspective, the data reviewed in this book suggest that seasonal stressors impact host resistance and susceptibility to infection possibly via changes in endocrine–immune interactions. In Chapter 8, we examine seasonal changes in infection from both a clinical and basic science perspective to address why studies examining seasonal changes in immunity and infection are important. We will also examine what role these studies could play in the treatment of disease, as well as in increasing our understanding of organism–environment interactions. Perhaps more aggressive antibiotic treatment is warranted during the winter than summer for some conditions. Seasonal changes in the immune function of the host individual are rarely, if ever, considered in the clinical treatment of patients (both human and nonhuman). There are several gaps in our knowledge of seasonal patterns in population dynamics; we hope this book provides alternative hypotheses and an understanding that host immunity and susceptibility to infection play a role in mediating population fluctuations among both human and nonhuman animals.

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