Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *The Year in Ecology and Conservation Biology*

The effects of anthropogenic global changes on immune functions and disease resistance

Lynn B. Martin,[1] William A. Hopkins,[2] Laura D. Mydlarz,[3] and Jason R. Rohr[1]

[1]Department of Integrative Biology, University of South Florida, Tampa, Florida, USA. [2]Department of Fisheries and Wildlife Sciences, Virginia Polytechnic Institute and State University, Blacksburg, Virginia USA. [3]Department of Biology, University of Texas at Arlington, Arlington, Texas, USA

Address for correspondence: Lynn B. Martin, University of South Florida, Department of Integrative Biology, 4202 E. Fowler Ave., SCA 110, Tampa, FL 33620. lmartin@cas.usf.edu

Humans are changing the environmental conditions of our planet, and animal immune functions are being affected by these modifications. For instance, a diversity of chemical contaminants is entering ecosystems and modifying immune functions directly or indirectly through altered host–parasite interactions. Also, global temperature changes have caused outbreaks of disease that have decimated and even extirpated some host species, outcomes partially driven via immune alterations. Finally, some invasive species are immunologically distinct or impose stress on native species, factors that may facilitate the establishment of nonnative hosts as well as parasite transmission to native species. Here, we summarize the known and likely effects of pollutants, nonnative species introductions, and increases in ambient temperature on host immune functions and infections. We then identify future directions for research given our sparse knowledge of immune variation in natural populations. In sum, we advocate integrative, multidisciplinary work at diverse spatial and temporal scales to assess and prevent anthropogenic global changes from further compromising animal immune functions.

Keywords: disease; health; immunocompetence; parasite

Since the industrial revolution, humans have changed the Earth at a faster rate and larger scale than any other time in history.[1] These changes have already had pronounced effects on global climate, carbon and nitrogen cycles, and biodiversity.[2] Rates of extinction are 100 to 1000 times greater now than before human dominance of the planet,[3] and species are being transported and introduced to new environments where they are profoundly altering natural ecosystems.[4] Some of these global changes have also been implicated as contributors to unprecedented rates of infectious disease emergence in humans and wildlife.[5–7] The study of immune functions in wild animals, or ecological immunology, is relatively new, but there is strong reason to expect that part of this disease emergence is due to the impacts of global change on immune functions. For example, pollutant and pesticide exposures can lead to immune suppression in diverse animals,[8–10] short-term temperature changes can impact various immune functions in both endo- and ectotherms, and introduced species can negatively or positively impact native species if they impose stress on native species or serve as reservoirs for novel (spillover) or native (spillback) parasites due to their unique immune systems. Given the limited data demonstrating direct effects of global changes on animal immune functions though, we review known effects of pollutants, temperature changes, and the introduction of nonnative species on immune processes directly. Then we discuss the effects of these global change elements on parasite burdens in host populations because in many cases such data are more common. We interpret changes in parasite burden to convey information about immune changes in hosts. However, we appreciate that parasite resistance, defined as whether and to what extent an individual harbors a parasite burden, is a consequence of immune processes as well as a variety of host behaviors (e.g., avoidance) and morphological traits (e.g., skin thickness). In other words, we recognize that global change can affect hosts, parasites,

doi: 10.1111/j.1749-6632.2010.05454.x

or both, and that changes in immune functions and infection can be due to all three. Throughout the article, we use the term "parasite" to refer to any infectious organism, regardless of its size, pathogenicity, commonness, or phylogenetic affiliation,[11] as this approach is most conducive to generality. In spite of its limitations, we feel that our approach is appropriate, especially as most ecologists and policy makers are interested in immune variation to the extent that it mitigates disease persistence or emergence.

Animal immune defenses

Before discussing the known and expected effects of global change on immune functions, we review briefly the immune defenses that animals have available to them. The immune system of any organism consists of a suite of interconnected barriers to infection, some expressed at all times (i.e., constitutive) and others induced only when a parasite is encountered (i.e., inducible), and some that are highly specific and others that are broadly protective.[12] Ecological immunologists have begun to provide some generalizations about the potential impacts of global change elements and other environmental factors on animal immune functions, an emphasis that has been lacking historically for immunology. The central paradigm of ecoimmunology is that immune functions represent a balance between the benefits *and* costs of immune functions.[13] It is not always adaptive to mount or maintain the strongest possible immune response; the magnitude of an immune response is contingent on the identity of the parasite and the fitness priorities of the host. This perspective also implicitly includes the nervous and endocrine systems. Classically, the endocrine, nervous, and immune systems have been studied independently, but it is interactions among all three (and perhaps others) that determine the outcomes of a host–parasite interaction.[14] Moreover, this perspective incorporates effects of parasites themselves on immune functions. Hosts can exhibit one of three immune responses upon infection: they can upregulate an immune function, they can exhibit no change, or they can downregulate it. Upregulation would be beneficial when the benefit exceeds the cost of increased immunity. Thus, if an immune response results in considerable collateral damage to the host, if excessive energy or resources are used, or if the parasite can gain a foothold if a particular immune response is deployed, the host might not exhibit an immune response and might even dampen immune activity upon infection. This portrayal of the immune system diverges somewhat from classic immunology and particularly its terminology (e.g., adaptive, innate, humoral, cell-mediated). However, we feel it is useful because not all organisms possess the above immune traits, but all must balance the costs and benefits of immune defense. The salient points here are that the relationship between the immune system and a parasite is bidirectional and dynamic.

It is beyond the scope of this article to describe exhaustively all of the components of animal immune systems much less their connections with other physiological systems. We thus cover the features of animal immune systems and some of the most critical connections with the neuroendocrine system that are most likely to be affected by global changes. The invertebrate immune system is based on self-/nonself-recognition,[15] although invertebrates and vertebrates alike distinguish self from nonself via related pattern-recognition receptors.[16] Most invertebrates mount immune responses that kill or disable invaders such as respiratory burst (of reactive oxygen species), phagocytosis, and melanin and antimicrobial peptide, and protein synthesis.[17] Invertebrates can also recognize and eliminate damaged or diseased self-cells through cell labeling (opsonization).[15] Elements suggestive of immune memory and specificity are seen in invertebrates,[18,19] but the pervasiveness of such traits is presently unknown. The vertebrate immune system includes many of the same elements, including broadly effective antimicrobial enzymes and proteins (e.g., lysozyme, complement, natural antibodies[20,21]) and inflammatory responses, which include heightened local immune surveillance and activity and whole-body fevers and sickness behaviors (as do many invertebrates[22]). Inflammatory responses in particular are coordinated via the neuroendocrine system,[23] and some of the same hormones that regulate these processes in vertebrates are important in invertebrates.[24] Vertebrates also control parasites with natural killer cells, mast cells, and granulocytes,[25] but the most distinguishing aspect of the vertebrate immune response is that it can be finely tuned to specific parasite components within generations. By recombining particular regions of the genome (VDJ

regions), vertebrates produce receptors and soluble molecules (antibodies) with affinity for any parasite component that could exist.[25] The major constraint on these immune responses is that they require time to be effective (7–10 days); in the meantime, the more rapid and broadly effective innate immune defenses must control infections.[26]

In addition to host-driven changes in immune function, parasites too can alter host immune responses. Oftentimes, manipulations are to the parasites' benefit,[27] but some manipulations may have no net effect on hosts or parasites. In still other cases though, parasite alteration of host immune responses may be for the benefit of the host–parasite unit. Such effects make the use of the term "parasite" questionable, but examples of immune-mediated putative mutualisms abound. Recent examples include the production of antimicrobial peptides by skin-dwelling bacteria in frogs,[28] uropygial gland-residing microbes in hoopoe,[29] and the maturation of aspects of the mammalian immune system by gut-residing bacteria.[30] Whether these host–parasite relationships are exceptional or common in wild animals is presently unclear. However, future attempts to understand the impacts of global changes on host immunity should consider that parasites have evolutionary interests too, especially in introduced host–parasite pairs (see below). High virulence, the parasite trait that typically attracts the most attention, is only one way for parasites to maximize fitness.[31] Because hosts will usually be at a disadvantage in evolutionary arms races with microbes (due to longer generation times in the former), it may be more advantageous for hosts to allow some level of infection than to resist infections outright, especially if some immune responses are prone to collateral damage.[32] In many cases, it may be advantageous for the parasite to accept a lower-than-possible level of virulence.[33] For the remainder of the article, we will use classic immunological terminology (e.g., innate, adaptive, humoral, cell-mediated) when discussing the impacts of global changes on immune functions. However, we advocate that future research evaluate immune components relevant to a particular host–parasite interaction instead of coarse measures of immune function, as such techniques are more apt to provide the mechanistic insight sought by ecologists regarding host–parasite interactions.[34]

Pollutants

Pollution represents one of the greatest global threats to environmental health. In the European Union (EU) and United States, there are over 100,000 registered chemicals,[35,36] and there are over a billion tons of pesticide products used annually in the United States alone.[36] Since 1981, the safety of new pesticides has been systematically evaluated on just a few animal species in laboratory conditions, and for many chemicals developed before 1981, effects have not been thoroughly addressed in any nonmodel taxa.[37] This lack of oversight includes 97% of the major chemicals in use and more than 99% of chemicals produced by volume.[37] In contrast, pharmaceuticals and personal care products are carefully tested prior to their widespread usage, but these compounds too (and their bioactive byproducts) have been released in unsafe quantities into the environment, particularly near metropolitan areas.[38,39] These compounds, many of which are deliberately designed to influence immune and endocrine responses, can reach concentrations in surface and drinking waters that may pose serious health risks. Industrial practices too, such as the mining and combustion of fossil fuels, release large quantities of metals and metalloids into the environment. Each year in the United States the combustion of coal for electricity generation emits more than 120 million tons of industrial waste containing very high concentrations of many toxic trace elements.[40] Consequently, it is not surprising that pollutants are the second greatest threat to aquatic and amphibious organisms in the United States[41] and one of the factors most often associated with the emergence of wildlife diseases,[42] some of which are implicated in host extinctions or declines.[43–46] Past reviews have unequivocally demonstrated that many chemical contaminants modulate immune functions and affect disease resistance.[47–51] Below, we characterize the effects of pollutants on immune functions: (1) working through effects on the physiology and/or behavior of hosts and (2) working to alter disease transmission via changes in rates and types of species interactions.

Pollutant effects on immune functions

Perhaps the best documented effect of pollutants is direct toxicity to components of the immune system.[47–50] Isolating immune cells, exposing them to

particular contaminants, and quantifying survival and function has been an effective way to demonstrate direct toxicity of contaminants. Taken together, current evidence suggests that pollutants can compromise immune defenses via direct cell and tissue mortality, alterations in production or function of leukocytes, modified antibody production, and reduced cytokine production. However, most of this work has focused on laboratory rodents, and far less is known about the effects of pollutants on immune responses of wildlife, particularly to the extent that immune changes compromise disease resistance. More complex and less well studied are the manifold ways pollutants can alter immune functions via other physiological processes and/or behaviors. Many contaminants directly affect the nervous system (e.g., mercury and acetocholinesterase inhibitors) and act as endocrine disruptors (e.g., many pesticides, plasticizers, and flame retardants).[52] The neuroendocrine and immune systems are tightly linked,[53,54] so contaminant changes to the neuroendocrine system should often cause immune alterations. It is beyond the scope of this article to cover all the ways in which such changes can arise, but indeed they do.[55,56] We briefly address some of the most common ways in which contaminants can cause short- and long-term effects on immune functions via neuroendocrine alterations.

Estrogenic and thyroid-disrupting pollutants represent two examples of compounds with high potential for immunomodulation. Estrogens influence the growth of immune tissues including the thymus, bone marrow, spleen, and lymph nodes[57] as well as the synthesis of immunoglobulins and the abundance of B lymphocyte precursors.[55] Thyroid hormones, which are critical for early immune development,[58,59] can be disrupted by pharmaceuticals, mercury, and perchlorates.[60,61] Glucocorticoids (GCs) too can be impacted by pollutants and have pervasive effects on the immune system.[62,63] In response to aversive stimuli, including interactions with predators, competitors, and extreme environmental conditions (e.g., severe winter storms),[64,65] GCs are released. If stressors resolve within a short period, plasma GCs decrease and homeostasis is restored, but if a stressor persists, circulating GCs remain elevated and many immune functions are suppressed.[54] For example, exogenous GC administration in birds resulted in dampened immune responses during critical reproductive life history stages.[66] Anthropogenic factors, such as habitat loss and pollution, can modify GC levels for protracted periods of time,[63,67,68] but the role of pollutants as immune modulators working through GCs has been little studied in natural systems, and whether endocrine-disrupting compounds (EDCs) work directly through GC receptors is unknown. Nevertheless, if pollutants elevate GCs during critical windows of development, immune impacts are likely to be pervasive. In rodents, GC exposure early in life dramatically alters GC regulation in adulthood.[53,62,69–74] Early-life exposures to chemical contaminants or GCs are already known to have long-term adverse effects on immune functions, disease resistance, and fitness in diverse taxa.[75–80] Also, as GCs (and other steroids) can be transferred across the placenta or deposited into eggs, immune effects of some pollutants may even be passed across generations.

Pollutants might also indirectly influence immune processes by evoking trade-offs with other physiological systems. Perhaps the most important of such trade-offs is the reallocation of nutrients and energy from one portion of an individual's resource budget to other functions.[81] Exposure to environmental pollutants can be energetically costly because pollutants impose demands on animals above those normally required to sustain life.[82] For example, crayfish, freshwater shrimp, water snakes, and amphibians exposed to industrial effluent exhibit abnormally high standard metabolic rates, effects that translated into reduced growth in some species.[83] Thus, in the absence of acquisition of additional nutrients and energy, animals must compensate for increased energy demands imposed by pollutants by redistributing resources normally used for other life processes. Because the immune system is expensive to maintain and use,[84–86] energy deficits generated because of pollutant exposure could compromise immune functions. Although these trade-offs have not been explicitly explored in relation to pollutants, similar resource allocation decisions have been observed between immunity and other biological processes.[87] For example, increased energy demands for reproductive processes in lizards detracted energy from immune responses necessary for wound healing,[88] birds faced with increased reproductive demands exhibit dampened humoral immune responses,[89] and food-restricted rodents were unable

to mount secondary antibody responses to an antigen.[86] Studies should thus consider whether the energy costs of defending against the harmful effects of pollutants trigger similar resource trade-offs with the immune system.

Community-level effects on immune functions via pollutants

Many of the aforementioned effects of pollutants (changes in endocrinology and energy balance) can also influence the behavior and performance of animals, which can subsequently affect infections and immune responses. Neurotoxicants affect animal activity patterns and performance due to direct effects on the central or peripheral nervous system,[90,91] and pesticides can affect locomotor activity and refuge use,[92,93] water conserving postures,[77] and reproductive behaviors.[94] EDCs and compounds that alter GCs could also influence behaviors related to territoriality, aggression, reproduction, and feeding.[95] Many of these changes in behavior could affect risk of infection[96] with subsequent effects on the immune system.

Contaminants might also influence individual immune functions (and consequent disease dynamics) by modifying species interactions. For example, contaminants can alter host exposure to parasites and thus whether they maintain or develop antibodies against parasites in an environment. Contaminants can also be directly toxic to many parasites,[97–99] altering rates of exposure for some hosts. Similarly, densities of both hosts and parasites could be affected by contaminants if contaminants affect the densities of their predators or competitors.[100,101] Additionally, if contaminants reduce food resources, hosts might have less energy to invest in immunity.[81] Alternatively, if contaminants reduce the densities of species that prey on hosts, hosts might forage more freely thus having greater energy to invest in immunity. There are also several ways that contaminants can alter the parasite diluting effect of biodiversity.[102,103] For instance, if a contaminant reduces densities of incompetent hosts, per capita parasite attack rates may be increased for the remaining hosts. This change in density might then increase parasite prevalence and thus the need to invest in immunity.[100,101] On the other hand, just because a contaminant has an effect on the density or the traits of a parasite or host, average parasite prevalence, host immune functions, and/or parasite resistance may not be affected. If a contaminant influences the host and parasite simultaneously in the same direction, there may be no net effect on the host–parasite interaction despite effects on immune functions. Furthermore, the contaminant might also affect other species that can also influence parasite transmission (e.g., intermediate hosts). Thus, to understand the community-level effects of contaminants on immunity and parasitism, it will be important to distinguish between the effects of contaminants on the densities and traits of parasites, their hosts, and nonhost species.[78,104]

Future studies

Much remains to be understood about the effects of pollutants on immune responses and disease resistance. Although the biomedical and toxicological literatures offer valuable insights into how pollutants affect immune cells and tissues, far less is known about the alterations in immune functions or resistance due to endocrine disruption, changes in energy balance, or modified species interactions. In addition, many other fundamental knowledge gaps exist. For example, sex-related differences between immunity and risk of infection are well known,[105] but does exposure to immunomodulating contaminants present different risks to males and females.[106] Similarly, how does maternal transfer of neurotoxicants or EDCs influence the development and function of animal immune systems, especially as both toxicants and immune mediators (e.g., immunoglobulins) can be transferred across generations? Although the development of some immune disorders may be related to *in utero* exposure to carcinogens in laboratory mammals,[107] transgenerational effects on the immune system remain poorly studied in wild animals. Another tremendous challenge is the sheer number of pollutants that need to be evaluated for immunotoxicity. Because all pollutants and all species cannot be adequately tested, can generalizations be made based on the chemical structure of pollutants?[108] Similarly, can generalities be drawn regarding taxonomic or functional groups of hosts and/or parasites based on specific traits? Perhaps by using life history traits as a guide, potentially susceptible species[109] or functional groups with the greatest community level ramifications[110] might be identified and given first priority for study. Meta-analyses too might reveal generalities given

the vast complexity associated with the thousands of contaminants, diverse host and parasite species, and the intricacies of host immune systems.[111] Finally, there are few studies that link contaminant-induced immune alterations to changes in resistance of infections, but available evidence from two studies suggests that exposure to common chemicals such as atrazine and malathion can increase infection rates in amphibians.[67,71]

Temperature change

Climate change associated with the release of greenhouse gases and aerosols to the atmosphere has already influenced global temperature variability, sea level, storm frequency, and other climatic variables.[112] Since 1880, global mean surface temperatures have increased by about 0.9° F, with the warmest years all occurring since 2001, and global temperatures are expected to increase between 1.8 and 4.0° C by the end of the century.[112] Warming, however, is expected to occur heterogeneously, with land warming faster than oceans, high latitudes warming faster than mid-latitudes, and winters warming more than summers.[112] Because animals inhabiting these different regions of the globe are adapted to operate under different thermal environments, species will vary widely in how they respond to temperature changes.[118] The effects of these climate changes on wildlife disease outbreaks are already evident in some systems, and quite controversial in others.[113,114] In many cases, the mechanism by which changes in climate affects disease processes is still unknown. Parasite growth, virulence, and distribution can all be affected by changes in temperature and rainfall expected in the future.[115] However, animal immune functions are well known to respond to temperature changes, especially in ectotherms, and alterations of immune functions are implicated in some disease outbreaks. In this section, we review the known effects of global temperature changes on animal immune functions and its impacts on disease incidence.

Temperature is one of the most studied abiotic environmental variables because of its ability to affect many physiological processes.[116] The effect of temperature on immune functions likely differs among groups of organisms though, although systematic comparisons have not been made. Ectotherms are more sensitive to ambient temperature changes due to their need to obtain heat from the environment[117] and many terrestrial ectotherms are projected to be greatly affected by even small changes in global temperatures.[118] While some ectotherms can offset temperature challenges by altering their behavioral patterns, using more suitable microhabitats, or relocating to more suitable environments, sessile or range-limited species must adapt or use existing physiological plasticity.[119] Even though some ectotherms may behaviorally compensate for unsuitable temperature changes, shifts in microhabitat use or activity profiles could influence energy budgets as well as contact rates with parasites and other hosts. Endothermic hosts by contrast are not as susceptible to changing temperatures as they can regulate body temperature endogenously or migrate to new areas given their generally larger body size. Still, the effects of temperature on immune processes vary greatly, even within ectotherms. Typically, acute thermal changes are detrimental to immune functions, such as phagocytosis,[120] respiratory burst,[121] the prophenoloxidase cascade,[122] and antibody synthesis.[123] However, for some fish and amphibians, immune responses can be stimulated or at least positively correlated with increases in temperatures,[117,124] including lysozyme and immunoglobulin M levels.[124–126] Effects of temperature change on endotherms are generally weaker,[127–129] although results are contingent on what is measured and the magnitude of temperature perturbation. For instance, cytokine-stimulated T-cell proliferative responsiveness was sensitive to temperature in some rodents,[130] and heat stress (up to 40° C) reduced multiple innate and adaptive immune functions in chickens[131,132] and egg-laying hens.[133] However, insufficient studies have been conducted in any taxon to provide definitive generalities regarding temperature impacts on immune functions.

One particularly promising area for future research involves the effects of ambient temperature on fever, or behavioral hyperthermia. Fever is used by almost all animals and is one of the fastest-acting and broadly protective immune defenses they possess.[134,135] Fever combats infectious organisms predominantly by elevating the activity of immune cells, biochemical reaction rates, and generally making the body uninhabitable for most microbes.[136] Endotherms generate fever by adjusting the set-point of body temperature (via changes in prostaglandin metabolism in the brain),

but ectotherms induce fever by moving into areas in which more ambient heat is present.[137] In rats, transient exposure to above average ambient temperatures had positive effects on fever,[138] whereas below average temperatures reduced fever duration and magnitude.[139,140] For grasshoppers (*Zonocerus variegatus*), an increase in daytime maximum temperatures of just 2° C enabled faster recovery from fungal infections.[141] Although studies in which the duration, magnitude, and direction of temperature modifications on fever are assessed are rare, future focus is especially warranted given the pervasiveness of fever as a defense and its obvious sensitivity to environmental perturbation in ectotherms. Intriguingly, global increases in temperature may be protective for some ectotherm infections, although the outcome is probably contingent on the host–parasite interaction.[142,143]

Perhaps the best studied system in which temperature-dependent changes in immune functions have been evaluated is corals. Most corals inhabit warm waters near the limits of their thermal tolerance.[115] Coral mortality due to heat waves typically occurs as a result of coral bleaching, which is characterized by the loss of the obligate algal symbionts and/or their associated pigments.[144] In recent years, coral mortality due to epizootics has increased in frequency and severity,[145–149] with over 20 disease syndromes affecting over 60 hosts globally.[147] Many coral disease outbreaks follow heat waves and bleaching events.[149,150] Because diverse immune responses including antifungal activity, cellular immune components, and prophenoloxidase activity are induced upon parasite exposure or infection[151–154] and elevated[153,155,156] or suppressed[156,157] by increased temperatures, it is plausible that temperature increases elevate infection risk via immune alterations. Additional support is exemplified by work in shore crabs (*Carcinus maenas*). The antimicrobial properties of hemocytes and expression of antibacterial proteins in crabs were most active at very low and very high environmental temperatures.[158] However, the higher expression of antimicrobial proteins did not confer disease resistance at elevated temperatures and the crabs succumbed to parasite exposure regardless. These studies highlight the nuanced relationships between temperature and host immune functions and reinforce the context dependency of most host–parasite interactions.[159]

Future directions

A central theme of future work on anthropogenic temperature changes and immune functions should be to make links with disease outbreaks. It is still unclear whether and how many temperature-driven immune alterations influence the outcome of host–parasite interactions. In some cases, temperature changes impacted immune functions and were directly correlated to disease outbreaks,[160,161] but in others, temperature-stimulated immune changes were not related to disease-induced mortality.[155,162,163] The one generality that presently seems robust is that temperature extremes contribute to lowered immune functions and disease outbreaks. Temperature anomalies, such as heat waves, are particularly implicated,[164] perhaps because hosts cannot acclimate as rapidly to the new temperature regime as the parasite. An example involves the protozoan parasite, *Perkinsus,* and its Atlantic oyster (*Crassostrea virginica*) host. *Perkinsus* outbreaks most often occur in warm, summer months and end in winter because of temperature limitations on their life cycle.[165] During the anomalously warm winters of the 1990s, *Perkinsus* spread northward into oyster populations in New York to Maine where it did not occur before.[165–167] Whether immune changes in oysters fostered *Perkinsus* spread is unclear, but the oyster example is not alone. In 2003, central and northern Europe experienced anomalously high temperatures, and this heat wave triggered high mortality to disease in sticklebacks (*Gasterosteus aculeatus*).[168] Comparable examples for extreme cold associated disease outbreaks include Cold-water Vibriosis,[169] brown ring disease,[161] and Epizootic Ulcerative Syndrome,[117] but whether immune functions were altered by temperature in these cases remains unknown. In all of the above studies, an additional missing element is whether and how many immune processes can acclimate to temperature changes. Oftentimes, if animals are allowed to acclimate to temperature swings, they can perform at comparable levels to normothermic temperatures.[170] In deer mice (*Peromyscus maniculatus*), neither cell-mediated[127] nor humoral[128] immune activities differed between groups acclimated for 6 days at low temperatures prior to measurement and mice housed at normothermic temperatures. Studies of temperature acclimation will be particularly important in the future, as changes in temperature variability may be more

important than changes in temperature averages.[112] Such lability may also compromise immune adjustments to typical (seasonal) fluctuations in temperature, as has been noted in Red-spotted newts (*Notophthalamus viridescens*).[171]

Overall, there appears little consistency in how immune elements respond to temperature changes with the exception that extreme temperatures tend to be detrimental. It may even be premature to make this generalization because most studies have involved experimental manipulation of temperatures in a lab setting. While there are obvious limitations to temperature manipulations in the field, capitalizing on natural temperature variations, climate anomalies and seasonal variation would complement existing lab studies. Furthermore, in addition to temperature, other climate events, such as heavy rainfall, drought, and increased cloud cover have the potential to exacerbate disease outbreaks and related mortality not only by directly affecting host immune functions but through coinfections with additional parasites.[172] The generation of long-term and large-scale data sets combined with immune data from free-living organisms will be useful for understanding and predicting changes in immune function and disease incidence as winters and summers get warmer.

Introduced species

Introduced organisms can extirpate native species,[173] compromise ecosystem functions,[174] and disrupt native communities.[175,176] They are responsible for billions of dollars of damage annually,[177] and with growing global commerce, the number of introductions will continue to increase.[178] The impacts that introduced species have on immune functions and disease resistance in native hosts are not clear however. Whereas more pollutants or temperature anomalies might tend to reduce immune functions, the effects of introduced species on (native) immune functions could take at least three forms. If the introduced organisms are hosts, they may compete with native species directly and thus elevate disease risk by reducing host immune defenses (by consuming resources necessary to power a competent immune system), they may compete indirectly by harboring native or introduced parasites that spillover into native populations, or they may even dilute parasite risk for native populations by serving as better reservoirs for native parasites. On the other hand, if the introduced organisms are parasites, they could harm native populations if they are able to infect native hosts, especially if they cause greater morbidity or mortality than native parasites. However, in some cases introduced parasites might even aid native host populations if introduced parasites outcompete native parasites once they infect.[179,180] Because of this complexity and the fact that context dependency could have strong impacts on each host–parasite interaction, we focus here on (1) whether introduced hosts alter native host immune functions by inducing elevations in stress hormones,[181] and (2) whether introduced hosts possess distinct immune systems relative to native hosts, which would make them (invaders) likely sources (or sinks) for parasites.[182] Only recently has the possibility been raised that introduced organisms might be immunologically distinct from native ones,[182] although a growing literature indicates that organisms with life history characteristics similar to many invasive species (e.g., large clutch sizes, rapid rates of maturation) have immune systems that are distinct from other species.[109,183]

Introduced hosts as stressors

Many of the negative effects of anthropogenic global changes on immune functions may be mediated via stress hormones, most notably the GCs. As discussed above, interactions between GCs and immune functions are dynamic: over short-time scales, immune activities tend to be enhanced by GCs but over the long term they are suppressed.[23] As introductions of nonnative species would typically be enduring (i.e., a chronic stressor), if anything, introduced species should suppress native species' immune defenses if they elevate GCs. Although only one study has demonstrated that introduced species can elevate stress hormones in native species,[181] most aversive stimuli induce the release of GCs,[184] so it is highly probable that the introduction of nonnative competitors/predators frequently elevate GCs in native species. However, the time scales and periodicity over which encounters with introduced organisms occur will affect GC coordination of immunity. Repeated exposure will likely cause (1) GC hyporesponsiveness to stressors because stimuli lose their novelty (2) or a reduced capacity of GCs to be

elevated in response to future stressors (because of compromised hypothalamic control of GCs or reduced adrenal function). For the immune system of native organisms, initial exposure to introduced organisms would probably elevate GCs and hence dampen most immune functions. Over time though, individuals could come to ignore or attenuate GC responses to introduced organisms,[185] which would leave their immune systems minimally affected, or, if GC regulation is permanently altered, immune functions could be permanently affected too. One of the most important regulatory roles of GCs is to dampen inflammation. With altered GC negative feedback, the host may be negatively impacted, as collateral damage via inflammation, which is usually minimized via positive GC effects on antiinflammatory cytokines,[186] may be increased.

The difficulty of considering introduced species as stressors is that what constitutes a stressor for one organism might not induce a stress response (and thus minimal immune alterations) in another. This point is reflected in comparisons of GC regulation in avian populations at different points along an urbanization gradient. In Germany, city-dwelling European blackbirds (*Turdus merula*) released less corticosterone in response to a restraint stressor than forest-dwelling birds.[187] In Arizona, USA, multiple urban-dwelling bird species showed the reverse pattern, releasing less corticosterone than rural-dwelling species.[188] For urban-dwelling white-throated sparrows (*Zonotrichia leucophrys*), habitat differences in corticosterone were sex specific with males having more baseline GCs in urban than rural habitats but females exhibiting no significant differences.[189]

Immune distinction in introduced hosts

A separate line of research suggests that introduced species might impact native hosts because their immune systems might have a particular configuration that facilitates their colonization of new areas.[190,191] This hypothesis was derived from recurrent observations of *enemy release*[192] and the *evolution of increased competitive ability*[193] in introduced hosts. Enemy release recognizes that introduced organisms harbor lower parasite diversity than native populations, an outcome that arises because some parasites cannot be sustained in the new environment and others are lost when transporting hosts from one place to another (e.g., highly virulent ones or those requiring intermediate hosts).[194,195] This loss of burden would favor those individuals that sacrifice those (immune) defenses that would impart the greatest costs but provide the fewest benefits,[182] especially given that many (but not all) parasites in the introduced range would require time to evolve mechanisms to exploit introduced hosts.[196] In vertebrates, the most likely immune defenses to be sacrificed are cell mediated and inflammatory immune functions.[197] Cell-mediated immune functions predominantly control intracellular infections, which should be rare in hosts with little to no coevolutionary history with parasites in their new range. Inflammatory responses might be expected to be robust in introduced organisms due to their broad efficacy. However, they (1) are prone to collateral damage, (2) require high rates of protein turnover, and (3) elevate metabolic rates substantially, traits that would conflict with the lifestyles of many introduced organisms.[198,199] A comparison of house sparrows (*Passer domesticus*) and Eurasian tree sparrows (*P. montanus*) from St. Louis, Missouri, supported the hypothesis that inflammation and cell-mediated immune functions should be sacrificed in introduced organisms. House sparrows, which are one of the world's most broadly distributed introduced vertebrates, mounted weak inflammatory and cell-mediated immune responses to the same immune challenges that induced strong responses in tree sparrows.[191] However, antibody production against a novel antigen exhibited the reverse pattern. These outcomes are consistent with the introduction history of each species: both species were introduced to the United States 150 years ago but house sparrows have come to occupy all of North America whereas tree sparrows have expanded little from the area where they were initially introduced. A second experiment implicated immune organization further as an influence on current distribution: simulated infection of tree sparrows decreased reproductive output by half whereas the same challenge had no effect on egg output in house sparrows.[190]

In the future, it will be important to ascertain whether diminutions in inflammatory defenses occur in other invasive species and whether they solely represent attenuated parasite resistance or additionally a requirement of encountering novel parasites. Indeed, another interpretation of the above studies

is that damped inflammation is imperative in introduced hosts because they would otherwise die from the novel parasites they would encounter in new areas.[182] Novel infectious diseases are notorious for causing mortality and morbidity via immunopathology. Pathogenic avian influenza (HPAI) kills hosts by overactivating inflammatory mechanisms,[200] and West Nile causes encephalitis (e.g., inflammation of neuronal tissues) in individuals lacking prior exposure.[201] In invasive cane toads (*Bufo marinus*), an otherwise benign soil microbe appears responsible for an arthritis-like disease in individuals that are otherwise most disposed to rapid colonization.[202]

A related possibility is that by favoring an anti-inflammatory phenotype, introduced hosts foster the parasites that travel with them and the symbiosis as a unit experiences greater success in the new area than it would experience alone. Indeed, anecdotal evidence indicates that tolerating (e.g., limiting damage without affecting burden) certain, relatively parasites favors the success of establishment and persistence of hosts in new areas. First, parasite prevalence, but not diversity, can be as high or higher in introduced populations as in the native range.[203,204] Second, even after generations in new areas, many introduced hosts do not become infected with the same parasite diversity as in their native range.[205] The specific role of the host immune system is not known in these cases, but the currently best known mediators of parasite tolerance include anti-inflammatory cytokines.[206,207] However, reduced diversity is to be expected early after introductions (see above), but why diversity would remain intransigent but prevalence become comparable or even greater than the native range is perplexing.

The most obvious explanation of greater prevalence but lower diversity is that introduced hosts and parasites maximize fitness in new areas via selective tolerance (host) and low virulence (parasite). For the host, coping with known, low virulence parasites is more feasible than combating the unknown.[208] Moreover, parasites can be effective competitors within hosts, especially if they are already present when a second infection occurs,[180] and sterilizing immunity (i.e., complete clearance of a parasite burden) is rare for most host–parasite interactions,[209] probably because the shorter generation time of parasites in the majority of host–parasite pairs enables parasites to limit host populations in spite of host immune defenses.[26] Together, resistance of many parasites will be futile, so introduced hosts may foster success in new areas and avoid infection with novel parasites by favoring their "dear enemies." For the parasite too, there would be advantages of being tolerated (e.g., maintaining low virulence). The conditions into which nonnative parasites are introduced would not be conducive to high virulence; high virulence would eliminate the introduced host population before novel parasite variants could evolve to infect native hosts.[210] In support, the parasites that typically arrive with introduced hosts are minimally virulent and vertically transmitted to the hosts with which they arrive,[211] or they are generally infective to all hosts regardless of origin. The former element probably occurs because some parasites possess key (exploitative) innovations that allow them to exploit diverse hosts. The latter, however, would positively affect the fitness of the introduced host–parasite unit.[32] In some cases, the introduction of tolerant host/low virulence parasite pairs could have strong negative impacts on native communities. One of the best examples involves the colonization of Western Europe by the grey squirrel (*Sciurus carolinensis*) and the subsequent extirpation of the native red squirrel (*S. vulgaris*[212]). Grey squirrels carry a parapoxvirus, which does little harm to them but greatly affects red squirrels.[213] Little is known about how the grey squirrel tolerates the virus, but rates of decline of the red squirrel are impacted by the grey squirrel more where the parasite occurs.[214] A similar pattern has been seen for the American signal crayfish (*Pacifastacus leniusculus*), which carries a fungus that has decimated native crayfish species.[215] Although rarely considered in evolutionary ecology, most large organisms are effectively communities of animal, fungal, and microbial genomes,[216] so host introduction success may be as much due to the parasites it brings with it as the parasites it leaves behind.

Future studies

Feral predators elevate GCs in some native species to levels that compromise immune functions in others,[181] but to what extent and over what time scales other introduced organisms can act as stressors and

impact native host immune systems, and hence disease, requires additional study. Similarly, we know that immune variation between house and tree sparrows is consistent with what would be predicted for strong and weak invaders,[190,191] but we do not know whether similar patterns occur in other introduced species and whether tolerance of a specific set of parasites can foster the success of introduced species via parasite-mediated apparent competition with native hosts.[217] In some cases, introduced hosts have had negative impacts on native communities via disease spillover, spillback, or apparent competition,[218] and it will be particularly useful to ascertain the extent to which immune variation is responsible. A recent example of spillover involves the American bullfrog (*Rana catesbiana*) and the subsequent introduction of chytrid fungus.[219] Bullfrogs are somehow more tolerant of chytrid than other species; the extensive farming of this species, more so than any other amphibian, is implicated in the decline of several native species by providing a chytrid reservoir in areas where the parasite would otherwise have been unsustainable. If we know whether anti-inflammatory processes are responsible for greater tolerance, these pathways could be pharmacologically or genetically manipulated to compromise the ability of bullfrogs to tolerate infections. Furthermore, we might learn how immunologically native hosts are protected against parasites by introduced hosts.[220] The European wood mouse (*Apodemus sylvaticus*) is protected against some parasites in areas where the invasive bank vole (*Clethrionomys glareolus*) has become established.[221] If we knew how bank voles tolerated certain infections, we might be able to identify species or populations particularly prone to infection based on their immunological profile. In the future, an explicit focus on the particular immune mechanisms involved in a particular host–parasite interaction will provide the greatest insights.

Conclusion

Global change elements seem to impact animal immune functions, but to what extent disease emergence, prevalence, and distribution are influenced remains poorly known. Unfortunately, for the foreseeable future, the threats of pollutants, introductions of nonnative species, and temperature (climate) changes are unlikely to subside. Thus it will become increasingly important to identify how human activities alter the immune defenses of animals and do our best to prevent or mitigate the emergence or persistence of certain parasites in natural communities. To this end, we propose three efforts: (1) better communication among scientists in different fields, (2) focused study on innate immune functions, and (3) an emphasis on environments where multiple global change threats interact.

First, we propose that immunologists, parasitologists, and ecologists work to understand one another's terminologies. Given that disease ecologists are often interested in population and community-level processes whereas immunologists tend to focus on cellular or molecular processes, it is not surprising that cross-talk among disciplines has been difficult. We use different terminologies (e.g., virulence, pathogenicity, competency), but there are common immune mediators for these processes that both groups of scientists can measure and use toward identifying insightful generalizations.[12]

Second, we suggest that ecologists and immunologists interested in global change focus on inflammatory processes and other innate immune defenses. These immune defenses clearly impact resistance (and tolerance) of diverse parasites,[22,206,222] they are the most likely to be traded off with other physiological processes,[13] they are evolutionarily conserved,[223–226] and they are implicated as the causes of immunopathology,[206,222] a common source of mortality or morbidity in hosts exposed to novel parasites. Of course, other elements of immune function too should be considered, especially because of their particular implications for disease persistence (e.g., antibody-mediated immune memory). However, given their historical neglect but conserved and broadly protective nature, innate immune defenses warrant greater consideration than they presently receive.

Our final recommendation entails a focus on settings where multiple global changes are interacting. As humans continue to encroach on habitats across the globe, wildlife will be faced with multiple challenges to their immune systems[227] and it will be difficult to disentangle which are having the greatest impacts. In spite of this limitation, the magnitude of these problems necessitates immediate attention. Close to 80% of the U.S. population lives in cities or suburban areas where the threats of pollutant exposure, introduced species contacts,

and heat waves are greatest.[228] What impacts urban conditions have on the organisms that live there are as yet poorly known, but disease emergence is more common in urban areas than all other habitat types.[229] Much of urban disease emergence is related to high availability of breeding sites for vectors, climate moderation, or high densities of some hosts,[230] but some may also be attributable to variation in host immune functions.[231] For instance, greater pollutant exposure could suppress immune defenses directly or indirectly through stress hormone changes, and thus increase mortality in the urban "adapter" species that opportunistically exploit human-modified habitats.[232] Conversely, the provisioning of resources (e.g., bird feeders, landfills, nest cavity or burrow sites) could allow individuals to resist or recover from infections better than they would in unmodified habitats,[233] especially urban "exploiter" species, which tend to be nonnative and sources of parasite spillback or spillover. In terms of temperature, heat waves that are common in cities could suppress host immune functions to lower levels than would otherwise occur. A particular benefit to focusing research attention on urban centers is that the same rodents that are models for understanding human immune functions are common there. Indeed, we have more tools for characterizing immune functions in Norway rats (*Rattus norvegicus*) and house mice (*Mus musculus*) than almost any other species, and recent work has indicated that urban-dwelling populations of these species can serve as reservoirs for zoonotic parasites[234] and that immune functions in these species vary along urbanization gradients.[235] In sum, we advocate integrative, multidisciplinary work at diverse spatial and temporal scales to assess and prevent anthropogenic global changes from further compromising animal immune functions.

Acknowledgments

LB Martin thanks members of the Martin lab, Raoul Boughton and Mike McCoy for constructive feedback, and the University of South Florida and NSF (IOS 0920475) for financial support during writing. JR Rohr thanks the National Science Foundation (DEB 0516227), U.S. Department of Agriculture (NRI 2006-01370, 2009-35102-05043), and U.S. Environmental Protection Agency STAR (R833835) for funding.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Vitousek, P.M., H.A. Mooney, J. Lubchenco & J.M. Melillo. 1997. Human domination of Earth's ecosystems. *Science* **277:** 494–499.
2. Parmesan, C. & G. Yohe. 2003. A globally coherent fingerprint of climate change impacts across natural systems. *Nature* **421:** 37–42.
3. Galvin, T. 2000. *The Sixth Extinction: Journeys among the Lost and Left Behind*. Thomas Dunne Books. New York.
4. Chapin, F.S. *et al.* 1998. Ecosystem consequences of changing biodiversity – experimental evidence and a research agenda for the future. *Bioscience* **48:** 45–52.
5. Carey, C. 2000. Infectious disease and worldwide declines of amphibian populations, with comments on emerging diseases in coral reef organisms and in humans. *Environ. Health Persp.* **108:** 143–150.
6. Daszak, P., A.A. Cunningham & A.D. Hyatt. 2000. Wildlife ecology – emerging infectious diseases of wildlife – threats to biodiversity and human health. *Science* **287:** 443–449.
7. Harvell, C.D. *et al.* 2002. Climate warming and disease risks for terrestrial and marine biota. *Science* **296:** 2158–2162.
8. Christin, M.S. *et al.* 2004. Effects of agricultural pesticides on the immune system of Xenopus laevis and Rana pipiens. *Aquat. Toxicol.* **67:** 33–43.
9. Gilbertson, M.K., G.D. Haffner, K.G. Drouillard, *et al.* 2003. Immunosuppression in the northern leopard frog (Rana pipiens) induced by pesticide exposure. *Environ. Toxicol. Chem.* **22:** 101–110.
10. Langerveld, A.J. R. Celestine, R. Zaya, *et al.* 2009. Chronic exposure to high levels of atrazine alters expression of genes that regulate immune and growth-related functions in developing Xenopus laevis tadpoles. *Environ. Res.* **109:** 379–389.
11. Raffel, T.R., L.B. Martin & J.R. Rohr. 2008. Parasites as predators: unifying natural enemy ecology. *Trends Ecol. Evol.* **23:** 610–618.
12. Schmid-Hempel, P. & D. Ebert. 2003. On the evolutionary ecology of specific immune defence. *Trends Ecol. Evol.* **18:** 27–32.
13. Lochmiller, R.L. & C. Deerenberg. 2000. Trade-offs in evolutionary immunology: just what is the cost of immunity? *Oikos* **88:** 87–98.

14. Dantzer, R., J.C. O'Connor, G.G. Freund, *et al*. 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* **9:** 46–57.
15. Loker, E.S., C.M. Adema, S.M. Zhang & T.B. Kepler. 2004. Invertebrate immune systems – not homogeneous, not simple, not well understood. *Immunol. Rev.* **198:** 10–24.
16. Akira, S., S. Uematsu & O. Takeuchi. 2006. Pathogen recognition and innate immunity. *Cell* **124:** 783–801.
17. Nappi, A.J. & B.M. Christensen. 2005. Melanogenesis and associated cytotoxic reactions: applications to insect innate immunity. *Insect Biochem. Mol. Biol.* **35:** 443–459.
18. Bigger, C.H., P.L. Jokiel, W.H. Hildemann & I.S. Johnston. 1982. Characterization of alloimmune memory in a sponge. *J. Immunol.* **129:** 1570–1572.
19. Hildemann, W.H., C.H. Bigger & I.S. Johnston. 1979. Histoincompatibility reactions and allogeneic polymorphism among invertebrates. *Transplant. Proc.* **11:** 1136–1142.
20. Baumgarth, N., J.W. Tung & L.A. Herzenberg. 2005. Inherent specificities in natural antibodies: a key to immune defense against pathogen invasion. *Springer Semin. Immunopathol.* **26:** 347–362.
21. Morgan, B.P., K.J. Marchbank, M.P. Longhi, *et al*. 2005. Complement: central to innate immunity and bridging to adaptive responses. *Immunol. Lett.* **97:** 171–179.
22. Medzhitov, R. 2008. Origin and physiological roles of inflammation. *Nature* **454:** 428–435.
23. Martin, L.B. 2009. Stress and immunity in wild vertebrates: timing is everything. *Gen. Comp. Endocrinol.* **163:** 70–76.
24. Adamo, S.A. 2008. Bidirectional connections between the immune system and the nervous system in insects. In *Insect Immunology*. N. E. Beckage, Ed.: 127–148. Academic Press. Amsterdam; Boston.
25. Janeway, C.A., P. Travers, M. Walport & M.J. Schlomchik. 2004. *Immunobiology*. Garland Science. New York.
26. Hedrick, S.M. 2004. The acquired immune system: a vantage from beneath. *Immunity* **21:** 607–615.
27. Graham, A.L. 2002. When T-helper cells don't help: immunopathology during concomitant infection. *Q. Rev. Biol.* **77:** 409–434.
28. Harris, R.N. *et al*. 2009. Skin microbes on frogs prevent morbidity and mortality caused by a lethal skin fungus. *ISME J.* **3:** 818–824.
29. Martin-Vivaldi, M. *et al*. 2009. Antimicrobial chemicals in hoopoe preen secretions are produced by symbiotic bacteria. *Proc. R. Soc. B-Biol. Sci.* **277:** 123–130.
30. Mazmanian, S.K., C.H. Liu, A.O. Tzianabos & D.L. Kasper. 2005. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* **122:** 107–118.
31. Lloyd-Smith, J.O. *et al*. 2009. Epidemic dynamics at the human-animal interface. *Science* **326:** 1362–1367.
32. Restif, O. & J.C. Koella. 2004. Concurrent evolution of resistance and tolerance to pathogens. *Am. Nat.* **164:** E90–E102.
33. Ewald, P.W. 1994. *The Evolution of Infectious Disease*. Oxford University Press. Oxford.
34. Bradley, J.E. & J.A. Jackson. 2008. Measuring immune system variation to help understand host-pathogen community dynamics. *Parasitology* **135:** 807–823.
35. Commission of the European Communities. 2001. White paper: strategy for a future chemicals policy. Report No. 27.2.2001, COM(2001) 88 final. http://www.eeb.org/activities/chemicals/COM%20Chemicals%20WP%20EN.pdf. Brussels.
36. Kiely, T., D. Donaldson & A. Grube. 2004. Pesticide industry sales and usage: 2000 and 2001 market estimates. U.S. Environmental Protection Agency. Washington, DC.
37. Hartung, T. 2009. Toxicology for the twenty-first century. *Nature* **460:** 208–212.
38. Daughton, C.G. & T.A. Ternes. 1999. Pharmaceuticals and personal care products in the environment: agents of subtle change? *Environ. Health Perspect.* **107:** 907–938.
39. Ellis, J.B. 2006. Pharmaceutical and personal care products (PPCPs) in urban receiving waters. *Environ. Pollut.* **144:** 184–189.
40. N.R.C. 2006. *Managing Coal Combustion Residues in Mines*. The National Academies Press. Washington, DC.
41. Wilcove, D.S. & L.L. Master. 2005. How many endangered species are there in the United States? *Front. Ecol. Environ.* **3:** 414–420.
42. Dobson, A. & J. Foufopoulos. 2001. Emerging infectious pathogens of wildlife. *Philos. Trans. R. Soc. Lond. Ser. B-Biol. Sci.* **356:** 1001–1012.
43. Daszak, P. & A.A. Cunningham. 1999. Extinction by infection. *Trends Ecol. Evol.* **14:** 279–279.
44. Lips, K.R. *et al*. 2006. Emerging infectious disease and the loss of biodiversity in a Neotropical amphibian community. *Proc. Natl. Acad. Sci. USA* **103:** 3165–3170.
45. Rohr, J.R., T.R. Raffel, J.M. Romansic, *et al*. 2008. Evaluating the links between climate, disease spread, and amphibian declines. *Proc. Natl. Acad. Sci. USA* **105:** 17436–17441.

46. Wikelski, M., J. Foufopoulos, H. Vargas & H. Snell. 2004. Galapagos birds and diseases: invasive pathogens as threats for island species. *Ecol. Soc.* **9**. Available at: http://www.ecologyandsociety.org.
47. Dunier, M. & A.K. Siwicki. 1993. Effects of pesticides and other organic pollutants in the aquatic environment on immunity of fish – a review. *Fish Shellfish Immunol.* **3:** 423–438.
48. Schuurman, H.J., C.F. Kuper & J.G. Vos. 1994. Histopathology of the immune-system as a tool to assess immunotoxicity. *Toxicology* **86:** 187–212.
49. Voccia, I., B. Blakley, P. Brousseau & M. Fournier. 1999. Immunotoxicity of pesticides: a review. *Toxicol. Ind. Health* **15:** 119–132.
50. Banerjee, B.D. 1999. The influence of various factors on immune toxicity assessment of pesticide chemicals. *Toxicol. Lett.* **107:** 21–31.
51. Galloway, T.S. & M.H. Depledge. 2001. Immunotoxicity in invertebrates: measurement and ecotoxicological relevance. *Ecotoxicology* **10:** 5–23.
52. Colborn, T., F.S.V. Saal & A.M. Soto. 1993. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. *Environ. Health Persp.* **101:** 378–384.
53. Sternberg, E.M. 2006. Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. *Nat. Rev. Immunol.* **6:** 318–328.
54. Dhabhar, F.S. 2009. A hassle a day may keep the pathogens away: the fight-or-flight stress response and the augmentation of immune function. *Integr. Comp. Biol.* **49:** 215–236.
55. Ahmed, S.R. 2000. The immune system as a potential target for environmental estrogens (endocrine disrupters): a new emerging field. *Toxicology* **150:** 191–206.
56. Pruett, S.B., R.P. Fan, Q. Zheng, *et al.* 2003. Modeling and predicting immunological effects of chemical stressors: characterization of a quantitative biomarker for immunological changes caused by atrazine and ethanol. *Toxicol. Sci.* **75:** 343–354.
57. Grossman, C.J. 1984. Regulation of the immune-system by sex steroids. *Endocrine Rev.* **5:** 435–455.
58. Lam, S.H., Y.M. Sin, Z. Gong & T.J. Lam. 2005. Effects of thyroid hormone on the development of immune system in zebrafish. *Gen. Comp. Endocrinol.* **142:** 325–335.
59. Rollins-Smith, L.A. 1998. Metamorphosis and the amphibian immune system. *Immunol. Rev.* **166:** 221–230.
60. NRC, N.R.C. 2005. *Health Implications of Perchlorate Ingestion.* The National Academies Press. Washington DC.
61. Wada, H., D.A. Cristol, F.M.A. McNabb & W.A. Hopkins. 2009. Suppressed adrenocortical responses and thyroid hormone levels in birds near a mercury-contaminated river. *Environ. Sci. Technol.* **43:** 6031–6038.
62. Bellinger, D.L., C. Lubahn & D. Lorton. 2008. Maternal and early life stress effects on immune function: relevance to immunotoxicology. *J. Immunotoxicol.* **5:** 419–444.
63. Hopkins, W.A., M.T. Mendonca & J.D. Congdon. 1997. Increased circulating levels of testosterone and corticosterone in southern toads, Bufo terrestris, exposed to coal combustion waste. *Gen. Comp. Endocrinol.* **108:** 237–246.
64. Belden, L.K., M.J. Rubbo, J.C. Wingfield, & J.M. Kiesecker. 2007. Searching for the physiological mechanism of density dependence: Does corticosterone regulate tadpole responses to density? *Physiological and Biochemical Zoology* **80:** 444–451.
65. Fraker, M.E. *et al.* 2009. Characterization of an alarm pheromone secreted by amphibian tadpoles that induces behavioral inhibition and suppression of the neuroendocrine stress axis. *Horm. Behav.* **55:** 520–529.
66. Bourgeon, S. & T. Raclot. 2006. Corticosterone selectively decreases humoral immunity in female eiders during incubation. *J. Exp. Biol.* **209:** 4957–4965.
67. Hayes, T.B. *et al.* 2006. Pesticide mixtures, endocrine disruption, and amphibian declines: are we underestimating the impact? *Environ. Health Persp.* **114:** 40–50.
68. Hopkins, W.A., M.T. Mendonca & J.D. Congdon. 1999. Responsiveness of the hypothalamo-pituitary-interrenal axis in an amphibian (Bufo terrestris) exposed to coal combustion wastes. *Comp. Biochem. Physiol. C-Pharmacol. Toxicol. Endocrinol.* **122:** 191–196.
69. Avitsur, R., J. Hunzeker & J.F. Sheridan. 2006. Role of early stress in the individual differences in host response to viral infection. *Brain Behav. Immun.* **20:** 339–348.
70. Denver, R.J. 2009. Stress hormones mediate environment-genotype interactions during amphibian development. *Gen. Comp. Endocr.* **164:** 20–31.
71. Denver, R.J. 2009. Structural and functional evolution of vertebrate neuroendocrine stress systems. In *Trends in Comparative Endocrinology and Neurobiology*. H. Vaudry, E. W. Roubos, G. M. Coast & M. Vallarino, Eds.: Vol. 1163, 1–16.
72. Meaney, M.J. *et al.* 1996. Early environmental regulation of forebrain glucocorticoid receptor gene expression: implications for adrenocortical responses to stress. *Dev. Neurosci.* **18:** 49–72.

73. Plotsky, P.M. & M.J. Meaney. 1993. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) messenger-RNA, median-eminence CRF content and stress-induced release in adult-rats. *Mol. Brain Res.* **18:** 195–200.
74. Kitaysky, A.S., E.V. Kitaiskaia, J.F. Piatt & J.C. Wingfield. 2006. A mechanistic link between chick diet and decline in seabirds? *Proc. R. Soc. B-Biol. Sci.* **273:** 445–450.
75. Belden, L.K. & J.M. Kiesecker. 2005. Glucocorticosteroid hormone treatment of larval treefrogs increases infection by Alaria sp. trematode cercariae. *J. Parasitol.* **91:** 686–688.
76. Budischak, S.A., L.K. Belden & W.A. Hopkins. 2008. Effects of malathion on embryonic development and latent susceptibility to trematode parasites in ranid tadpoles. *Environ. Toxicol. Chem.* **27:** 2496–2500.
77. Rohr, J.R. & B.D. Palmer. 2005. Aquatic herbicide exposure increases salamander desiccation risk eight months later in a terrestrial environment. *Environ. Toxicol. Chem.* **24:** 1253–1258.
78. Rohr, J.R., T.R. Raffel, S.K. Sessions & P.J. Hudson. 2008. Understanding the net effects of pesticides on amphibian trematode infections. *Ecol. Appl.* **18:** 1743–1753.
79. Rohr, J.R., T. Sager, T.M. Sesterhenn & B.D. Palmer. 2006. Exposure, postexposure, and density-mediated effects of atrazine on amphibians: breaking down net effects into their parts. *Environ. Health Persp.* **114:** 46–50.
80. Rohr, J.R. *et al*. 2008. Agrochemicals increase trematode infections in a declining amphibian species. *Nature* **455:** 1235–1239.
81. Moore, I.T. & W.A. Hopkins. 2009. Interactions and tradeoffs among physiological determinants of performance and reproductive success. *Integr. Comp. Biol.* doi:10.1093/icb/icp081
82. Hopkins, W.A., C.L. Rowe & J.D. Congdon. 1999. Elevated trace element concentrations and standard metabolic rate in banded water snakes (Nerodia fasciata) exposed to coal combustion wastes. *Environ. Toxicol. Chem.* **18:** 1258–1263.
83. Rowe, C.L., W.A. Hopkins, C. Zehnder & J.D. Congdon. 2001. Metabolic costs incurred by crayfish (Procambarus acutus) in a trace element-polluted habitat: further evidence of similar responses among diverse taxonomic groups. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **129:** 275–283.
84. Martin, L.B., A. Scheuerlein & M. Wikelski. 2003. Immune activity elevates energy expenditure of house sparrows: a link between direct and indirect costs? *Proc. R. Soc. Lond. B-Biol. Sci.* **270:** 153–158.
85. Ots, I., A.B. Kerimov, E.V. Ivankina, *et al*. 2001. Immune challenge affects basal metabolic activity in wintering great tits. *Proc. R. Soc. Lond. B-Biol. Sci.* **268:** 1175–1181.
86. Martin, L.B., K.J. Navara, Z.M. Weil & R.J. Nelson. 2007. Immunological memory is compromised by food restriction in deer mice, *Peromyscus maniculatus*. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **292:** R316–R320.
87. Sheldon, B.C. & S. Verhulst. 1996. Ecological immunology: costly parasite defences and trade-offs in evolutionary ecology. *Trends Ecol. Evol.* **11:** 317–321.
88. French, S.S., M.C. Moore & G.E. Demas. 2009. Ecological immunology: the organism in context. *Integr. Comp. Biol.* **49:** 246–253.
89. Ardia, D.R., K.A. Schat & D.W. Winkler. 2003. Reproductive effort reduces long-term immune function in breeding tree swallows (*Tachycineta bicolor*). *Proc. R. Soc. Lond. B-Biol. Sci.* **270:** 1679–1683.
90. Hopkins, W.A. & C.T. Winne. 2006. Influence of body size on swimming performance of four species of neonatal natricine snakes acutely exposed to a cholinesterase-inhibiting pesticide. *Environ. Toxicol. Chem.* **25:** 1208–1213.
91. Scholz, N.L. *et al*. 2000. Diazinon disrupts antipredator and homing behaviors in chinook salmon (Oncorhynchus tshawytscha). *Can. J. Fish. Aquat. Sci.* **57:** 1911–1918.
92. Rohr, J.R. *et al*. 2003. Lethal and sublethal effects of atrazine, carbaryl, endosulfan, and octylphenol on the streamside salamander, *Ambystoma barbouri*. *Environ. Toxicol. Chem.* **22:** 2385–2392.
93. Rohr, J.R. *et al*. 2004. Multiple stressors and salamanders: effects of an herbicide, food limitation, and hydroperiod. *Ecol. Appl.* **14:** 1028–1040.
94. Park, D., S.C. Hempleman & C.R. Propper. 2001. Endosulfan exposure disrupts pheromonal systems in the red-spotted newt: a mechanism for subtle effects of environmental chemicals. *Environ. Health Persp.* **109:** 669–673.
95. Wingfield, J.C. & A.S. Kitaysky. 2002. Endocrine responses to unpredictable environmental events: stress or anti-stress hormones? *Integr. Comp. Biol.* **42:** 600–609.
96. Gompper, M.E. & A.N. Wright. 2005. Altered prevalence of raccoon roundworm (Baylisascaris procyonis) owing to manipulated contact rates of hosts. *J. Zool.* **266:** 215–219.

97. Blanar, C.A., K.R. Munkittrick, J. Houlahan, *et al*. 2009. Pollution and parasitism in aquatic animals: a meta-analysis of effect size. *Aquat. Toxicol.* **93:** 18–28.
98. Morley, N.J., S.W. Irwin & J.W. Lewis. 2003. Pollution toxicity to the transmission of larval digeneans through their molluscan hosts. *Parasitology* **126:** S5–S26.
99. Lafferty, K.D. 1997. Environmental parasitology: what can parasites tell us about human impacts on the environment? *Parasitol. Today* **13:** 251–255.
100. Rohr, J.R., J.L. Kerby & A. Sih. 2006. Community ecology as a framework for predicting contaminant effects. *Trends Ecol. Evol.* **21:** 606–613.
101. Raffel, T.R., L.B. Martin & J.R. Rohr. 2008. Parasites as predators: unifying natural enemy ecology. *Trends Ecol. Evol.* **23:** 610–618.
102. Keesing, F., R.D. Holt & R.S. Ostfeld. 2006. Effects of species diversity on disease risk. *Ecol. Lett.* **9:** 485–498.
103. Dobson, A. *et al*. 2006. Sacred cows and sympathetic squirrels: the importance of biological diversity to human health. *PLoS Med.* **3:** 714–718.
104. Raffel, T.R., J.L. Sheingold & J.R. Rohr. Lack of pesticide toxicity to *Echinostoma trivolvis* eggs and miracidia. *J. Parasitol.* **95:** 1548–1551.
105. Grear, D.A., S.E. Perkins & P.J. Hudson. 2009. Does elevated testosterone result in increased exposure and transmission of parasites? *Ecol. Lett.* **12:** 528–537.
106. Snoeijs, T. *et al*. 2005. The combined effect of lead exposure and high or low dietary calcium on health and immunocompetence in the zebra finch (Taeniopygia guttata). *Environ. Pollut.* **134:** 123–132.
107. Selgrade, M.K. 2007. Immunotoxicity: the risk is real. *Toxicol. Sci.* **100:** 328–332.
108. Clements, W.H. & J.R. Rohr. 2009. Community responses to contaminants: using basic ecological principles to predict ecotoxicological effects. *Environ. Toxicol. Chem.* **28:** 1789–1800.
109. Martin, L.B., Z.M. Weil & R.J. Nelson. 2007. Immune defense and reproductive pace of life in *Peromyscus* mice. *Ecology* **88:** 2516–2528.
110. Keesing, F., J. Brunner, S. Duerr, *et al*. 2009. Hosts as ecological traps for the vector of Lyme disease. *Proc. R. Soc. B-Biol. Sci.* **276:** 3911–3919.
111. Rohr, J.R. & K.A. McCoy. 2010. A qualitative meta-analysis reveals consistent effects of atrazine on freshwater fish and amphibians. *Environ. Health Persp.* **118:** 20–32.
112. IPCC, W. Climate Change 2007. 2007. The physical science basis. *Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change*. Cambridge University Press. New York.
113. Lafferty, K.D. 2009. The ecology of climate change and infectious diseases. *Ecology* **90:** 888–900.
114. Rohr, J.R., T.R. Raffel, J.M. Romansic, *et al*. 2008. Evaluating the links between climate, disease spread, and amphibian declines. *Proc. Natl. Acad. Sci. USA* **105:** 17436–17441.
115. Harvell, D., S. Altizer, I.M. Cattadori, *et al*. 2009. Climate change and wildlife diseases: when does the host matter the most? *Ecology* **90:** 912–920.
116. Lazzaro, B.P. & T.J. Little. 2009. Immunity in a variable world. *Philos. Trans. R. Soc. B-Biol. Sci.* **364:** 15–26.
117. Bowden, T.J., K.D. Thompson, A.L. Morgan, *et al*. 2007. Seasonal variation and the immune response: a fish perspective. *Fish Shellfish Immunol.* **22:** 695–706.
118. Deutsch, C.A. *et al*. 2008. Impacts of climate warming on terrestrial ectotherms across latitude. *Proc. Natl. Acad. Sci. USA* **105:** 6668–6672.
119. Peck, L.S. 2008. Brachlopods and climate change. *Earth Environ. Sci. Trans. R. Soc. Edinb.* **98:** 451–456.
120. Wang, F.Y., H.S. Yang, F. Gao & G.B. Liu. 2008. Effects of acute temperature or salinity stress on the immune response in sea cucumber, Apostichopus japonicus. *Comp. Biochem. Physiol. A-Mol. Integr. Physiol.* **151:** 491–498.
121. Coteur, G., N. Corriere & P. Dubois. 2004. Environmental factors influencing the immune responses of the common European starfish (Asterias rubens). *Fish Shellfish Immunol.* **16:** 51–63.
122. Vargas-Albores, F., P. Hinojosa-Baltazar, G. Portillo-Clark & F. Magallon-Baraja. 1998. Influence of temperature and salinity on the yellowleg shrimp, Penaeus californiensis Holmes, prophenoloxidase system. *Aquacult. Res.* **29:** 549–553.
123. Maniero, G.D. & C. Carey. 1997. Changes in selected aspects of immune function in the leopard frog, Rana pipiens, associated with exposure to cold. *J. Comp. Physiol. B-Biochem. Syst. Environ. Physiol.* **167:** 256–263.
124. Chen, W.H., L.T. Sun, C.L. Tsai, *et al*. 2002. Cold-stress induced the modulation of catecholamines, cortisol, immunoglobulin M, and leukocyte phagocytosis in tilapia. *Gen. Comp. Endocrinol.* **126:** 90–100.
125. Dominguez, M., A. Takemura, M. Tsuchiya & S. Nakamura. 2004. Impact of different environmental factors on the circulating immunoglobulin levels in the Nile tilapia, Oreochromis niloticus. *Aquaculture* **241:** 491–500.
126. Ndong, D., Y.Y. Chen, Y.H. Lin, *et al*. 2007. The immune response of tilapia Oreochromis mossambicus and its

susceptibility to Streptococcus iniae under stress in low and high temperatures. *Fish Shellfish Immunol.* **22:** 686–694.

127. Demas, G.E. & R.J. Nelson. 1998. Photoperiod, ambient temperature, and food availability interact to affect reproductive and immune function in adult male deer mice (Peromyscus maniculatus). *J. Biol. Rhythms* **13:** 253–262.
128. Ksiazek, A., M. Konarzewski, M. Chadziska & M. Cicho. 2003. Costs of immune response in cold-stressed laboratory mice selected for high and low basal metabolism rates. *Proc. Biol. Sci.* **270:** 2025–2031.
129. Dabbert, C.B., R.L. Lochmiller & R.G. Teeter. 1997. Effects of acute thermal stress on the immune system of the Northern Bobwhite (Colinus virginianus). *Auk* **114:** 103–109.
130. Sinclair, J. & R. Lochmiller. 2000. The winter immunoenhancement hypothesis: associations among immunity, density, and survival in prairie vole (Microtus ochrogaster) populations. *Can. J. Zool.* **78:** 254–264.
131. Zahraa, H. 2008. Effects of commutative heat stress on immunoresponses in broiler chickens reared in closed system. *Int. J. Poultry Sci.* **7:** 964–968.
132. Zulkifli, I., M.T.C. Norma, D.A. Israf & A.R. Omar. 2000. The effect of early age feed restriction on subsequent response to high environmental temperatures in female broiler chickens. *Poult. Sci.* **79:** 1401–1407.
133. Mashaly, M. *et al*. 2004. Effect of heat stress on production parameters and immune responses of commercial laying hens. *Poult. Sci.* **83:** 889–894.
134. Kluger, M.J., W. Kozak, C.A. Conn, *et al*. 1997. The adaptive value of fever. In *Fever: Basic Mechanisms and Management*. P.A. Mackowiak, Ed.: 255–266. Lippincott-Raven. Philadelphia, PA.
135. Martin, L.B., Z.M. Weil & R.J. Nelson. 2008. Fever and sickness behaviour vary among congeneric rodents. *Funct. Ecol.* **22:** 68–77.
136. Hanson, D. 1997. Fever, temperature, and the immune response. *Ann. N. Y. Acad. Sci.* **813:** 453–464.
137. Blatteis, C. 1986. Fever: is it beneficial? *Yale J. Biol. Med.* **59:** 107.
138. Rudaya, A.Y., A.A. Steiner, J.R. Robbins, *et al*. 2005. Thermoregulatory responses to lipopolysaccharide in the mouse: dependence on the dose and ambient temperature. *Am J Physiol Regul Integr Comp Physiol.* **289** R1244–R1252.
139. Carroll, J.A., R.L. Matteri, C.J. Dyer, *et al*. 2001. Impact of environmental temperature on response of neonatal pigs to an endotoxin challenge. *Am J Veterinary Res.* **62:** 561–566.
140. Graener, R. & J. Werner. 1986. Dynamics of endotoxin fever in rabbits. *Appl. Physiol.* **60:** 1504–1510.
141. Blanford, S., M. Thomas & J. Langewald. 2000. Thermal ecology of Zonocerus variegatus and its effects on biocontrol using pathogens. *Agric. Forest Entomol.* **2:** 3–10.
142. Adamo, S. 1998. The specificity of behavioral fever in the cricket Acheta domesticus. *J. Parasitol.* **84:** 529–533.
143. Elliot, S., S. Blanford & M. Thomas. 2002. Host-pathogen interactions in a varying environment: temperature, behavioural fever and fitness. *Proc. R. Soc. B-Biol. Sci.* **269:** 1599.
144. Brown, B.E. 1997. Coral bleaching: causes and consequences. *Coral Reefs* **16:** S129–S138.
145. Bruno, J.F. *et al*. 2007. Thermal stress and coral cover as drivers of coral disease outbreaks. *PLoS. Biol.* **5:** 1220–1227.
146. Harvell, C., C.E. Mitchell, J.R. Ward & S. Altizer. 2002. Climate warming and disease risks for terrestrial and marine biota. *Science*. **296:** 2158–2162.
147. Harvell, D. *et al*. 2007. Coral disease, environmental drivers, and the balance between coral and microbial associates. *Oceanography* **20:** 172–195.
148. McClanahan, T.R., E. Weil & J. Maina. 2009. Strong relationship between coral bleaching and growth anomalies in massive Porites. *Glob. Change Biol.* **15:** 1804–1816.
149. Miller, J., R. Waara, E. Muller & C. Rogers. 2006. Coral bleaching and disease combine to cause extensive mortality on reefs in US Virgin Islands. *Coral Reefs* **25:** 418.
150. Croquer, A. & E. Weil. 2009. Changes in Caribbean coral disease prevalence after the 2005 bleaching event. *Dis. Aquat. Organ.* **87:** 33–43.
151. Petes, L.E., C.D. Harvell, E.C. Peters, *et al*. 2003. Pathogens compromise reproduction and induce melanization in Caribbean Sea fans. *Mar. Ecol. Prog. Ser.* **264:** 167–171.
152. Kim, K., C.D. Harvell, P.D. Kim, *et al*. 2000. Fungal disease resistance of Caribbean Sea fan corals (Gorgonia spp.). *Marine Biol.* **136:** 259–267.
153. Mydlarz, L., S. Holthouse, E. Peters & C. Harvell. 2008. Cellular responses in sea fan corals: granular amoebocytes react to pathogen and climate stressors. *PLoS ONE* **3:** e1811.
154. Palmer, C.V., L.D. Mydlarz & B.L. Willis. 2008. Evidence of an inflammatory-like response in non-normally pigmented tissues of two scleractinian corals. *Proc. R. Soc. B-Biol. Sci.* **275:** 2687–2693.
155. Ward, J.R., K. Kim & C.D. Harvell. 2007. Temperature affects coral disease resistance and pathogen growth. *Mar. Ecol.-Prog. Ser.* **329:** 115–121.

156. Mydlarz, L.D., C.S. Couch, E. Weil, *et al*. Immune defenses of healthy, bleached and diseased Montastraea faveolata during a natural bleaching event. *Dis. Aquat. Organ.* **87:** 67–78.
157. Ritchie, K.B. 2006. Regulation of microbial populations by coral surface mucus and mucus-associated bacteria. *Mar. Ecol.-Prog. Ser.* **322:** 1–14.
158. Chisholm, J. & V. Smith. 1994. Variation of antibacterial activity in the haemocytes of the shore crab, Carcinus maenas, with temperature. *J. Marine Biol. Assoc. UK* **74:** 979–982.
159. Brockton, V., J. Hammond & V. Smith. 2007. Gene characterisation, isoforms and recombinant expression of carcinin, an antibacterial protein from the shore crab, Carcinus maenas. *Mol. Immunol.* **44:** 943–949.
160. Travers, M.A., N. Le Goic, S. Huchette, *et al*. 2008. Summer immune depression associated with increased susceptibility of the European abalone, Haliotis tuberculata to Vibrio harveyi infection. *Fish Shellfish Immunol.* **25:** 800–808.
161. Paillard, C., B. Allam & R. Oubella. 2004. Effect of temperature on defense parameters in Manila clam Ruditapes philippinarum challenged with Vibrio tapetis. *Dis. Aquat. Org.* **59:** 249–262.
162. Mydlarz, L.D., C.S. Couch, E. Weil, *et al*. 2009. Immune defenses of healthy, bleached and diseased *Montastrea faveolata* during a natural bleaching event. *Dis. Aquat. Org.* **87:** 67–78.
163. Brockton, V., J.A. Hammond & V.J. Smith. 2007. Gene characterisation, isoforms and recombinant expression of carcinin, an antibacterial protein from the shore crab, Carcinus maenas. *Mol. Immunol.* **44:** 943–949.
164. Mydlarz, L., L.E. Jones & C. Harvell. 2006. Innate immunity, environmental drivers, and disease ecology of marine and freshwater invertebrates. *Annu. Rev. Ecol.* **37:** 251–288.
165. Cook, T., M. Folli, J. Klinck, *et al*. 1998. The relationship between increasing sea-surface temperature and the northward spread of Perkinsus marinus (Dermo) disease epizootics in oysters. *Estuarine Coast. & Shelf Sci.* **46:** 587–598.
166. Ford, S. 1996. Range extension by the oyster parasite Perkinsus marinus into the northeastern United States: response to climate change? *J. Shellfish Res.* **15:** 45–56.
167. Ford, S. & R. Smolowitz. 2007. Infection dynamics of an oyster parasite in its newly expanded range. *Mar. Biol.* **151:** 119–133.
168. Wegner, K.M., M. Kalbe, M. Milinski & T.B.H. Reusch. 2008. Mortality selection during the 2003 European heat wave in three-spined sticklebacks: effects of parasites and MHC genotype. *BMC Evol. Biol.* **8:** 1–12.
169. Eggset, G., A. Mortensen, L.H. Johansen & A.I. Sommer. 1997. Susceptibility to furunculosis, cold water vibriosis, and infectious pancreatic necrosis (IPN) in post-smolt Atlantic salmon (Salmo salar L.) as a function of smolt status by seawater transfer. *Aquaculture* **158:** 179–191.
170. Shephard, R. & P. Shek. 1998. Cold exposure and immune function. *Can. J. Physiol. Pharmacol.* **76:** 828–836.
171. Raffel, T.R., J.R. Rohr, J.M. Kiesecker & P.J. Hudson. 2006. Negative effects of changing temperature on amphibian immunity under field conditions. *Funct. Ecol.* **20:** 819–828.
172. Munson, L. *et al*. 2008. Climate extremes promote fatal co-infections during canine distemper epidemics in African Lions. *PLoS ONE* **3:** e2545.
173. Wilcove, D.S., D. Rothstein, J. Dubow, *et al*. 1998. Quantifying threats to imperiled species in the United States. *Bioscience* **48:** 607–615.
174. Bakker, J.D. & S.D. Wilson. 2004. Using ecological restoration to constrain biological invasion. *J. Appl. Ecol.* **41:** 1058–1064.
175. Human, K.G. & D.M. Gordon. 1996. Exploitation and interference competition between the invasive Argentine ant, Linepithema humile, and native ant species. *Oecologia* **105:** 405–412.
176. Mooney, H.A. & E.E. Cleland. 2001. The evolutionary impact of invasive species. *Proc. Natl. Acad. Sci. USA* **98:** 5446–5451.
177. Mack, R.N. *et al*. 2000. Biotic invasions: causes, epidemiology, global consequences, and control. *Ecol. Appl.* **10:** 689–710.
178. Levine, J.M. & C.M. D'Antonio. 2003. Forecasting biological invasions with increasing international trade. *Conservation Biol.* **17:** 322–326.
179. Raberg, L. *et al*. 2006. The role of immune-mediated apparent competition in genetically diverse malaria infections. *Am. Nat.* **168:** 41–53.
180. de Roode, J.C., M.E.H. Helinski, M.A. Anwar & A.F. Read. 2005. Dynamics of multiple infection and within-host competition in genetically diverse malaria infections. *Am. Nat.* **166:** 531–542.
181. Berger, S., M. Wikelski, L.M. Romero, *et al*. 2007. Behavioral and physiological adjustments to new predators in an endemic island species, the Galapagos marine iguana. *Hormones Behav.* **52:** 653–663.
182. Lee, K.A. & K.C. Klasing. 2004. A role for immunology in invasion biology. *Trends Ecol. Evol.* **19:** 523–529.

183. Lee, K.A. 2006. Linking immune defenses and life history at the levels of the individual and the species. *Integr. Comp. Biol.* **46:** 1000–1015.
184. Wingfield, J.C. *et al*. 1998. Ecological bases of hormone-behavior interactions: the "emergency life history stage." *Am. Zool.* **38:** 191–206.
185. Avitsur, R., J.L. Stark & J.F. Sheridan. 2001. Social stress induces glucocorticoid resistance in subordinate animals. *Hormones Behav.* **39:** 247–257.
186. Goujon, E., P. Parnet, S. Cremona & R. Dantzer. 1995. Endogenous glucocorticoids down-regulate central effects of interleukin-1-Beta on body-temperature and behavior in mice. *Brain Res.* **702:** 173–180.
187. Partecke, J., I. Schwabl & E. Gwinner. 2006. Stress and the city: urbanization and its effects on the stress physiology in European blackbirds. *Ecology* **87:** 1945–1952.
188. Fokidis, H.B., M. Orchinik & P. Deviche. 2009. Corticosterone and corticosteroid binding globulin in birds: relation to urbanization in a desert city. *Gen. Comp. Endocrinol.* **160:** 259–270.
189. Bonier, F. *et al.* 2007. Sex-specific consequences of life in the city. *Behav. Ecol.* **18:** 121–129.
190. Lee, K.A., L.B. Martin & M.C. Wikelski. 2005. Responding to inflammatory challenges is less costly for a successful avian invader, the house sparrow (*Passer domesticus*), than its less-invasive congener. *Oecologia* **145:** 244–251.
191. Lee, K.A., L.B. Martin, D. Hasselquist, *et al*. 2006. Contrasting adaptive immune defenses and blood parasite prevalence in closely related *Passer* species. *Oecologia* **150:** 383–392.
192. Torchin, M.E., K.D. Lafferty, A.P. Dobson, *et al*. 2003. Introduced species and their missing parasites. *Nature* **421:** 628–630.
193. Blossey, B. & R. Notzold. 1995. Evolution of increased competitive ability in invasive nonindigenous plants – a hypothesis. *J. Ecol.* **83:** 887–889.
194. Colautti, R.I., J.R. Muirhead, R.N. Biswas & H.J. MacIsaac. 2005. Realized vs apparent reduction in enemies of the European starling. *Biol. Invasions* **7:** 723–732.
195. Dobson, A.P. & R.M. May. 1986. Disease and conservation. In *Conservation Biology: Science of Rarity*. M. Soule, Ed.: 345–365. Sinauer. Sunderland, MA.
196. Lively, C.M. & M.F. Dybdahl. 2000. Parasite adaptation to locally common host genotypes. *Nature* **405:** 679–681.
197. Klasing, K.C. 2004. The costs of immunity. *Acta Zoologica Sinica* **50:** 961–969.
198. Jeschke, J.M. & D.L. Strayer. 2005. Invasion success of vertebrates in Europe and North America. *Proc. Natl. Acad. Sci. USA* **102:** 7198–7202.
199. Jeschke, J.M. & D.L. Strayer. 2006. Determinants of vertebrate invasion success in Europe and North America. *Glob. Change Biol.* **12:** 1608–1619.
200. Kobasa, D. *et al*. 2007. Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. *Nature* **445:** 319–323.
201. Klein, R.S. & M.S. Diamond. 2008. Immunological headgear: antiviral immune responses protect against neuroinvasive West Nile virus. *Trends Mol. Med.* **14:** 286–294.
202. Brown, G.P., C. Shilton, B.L. Phillips & R. Shine. 2007. Invasion, stress, and spinal arthritis in cane toads. *Proc. Natl. Acad. Sci. USA* **104:** 17698–17700.
203. Marr, S.R., W.J. Mautz & A.H. Hara. 2008. Parasite loss and introduced species: a comparison of the parasites of the Puerto Rican tree frog, (Eleutherodactylus coqui), in its native and introduced ranges. *Biol. Invasions* **10:** 1289–1298.
204. Pasternak, Z., A. Diamant & A. Abelson. 2007. Co-invasion of a Red Sea fish and its ectoparasitic monogenean, Polylabris cf. mamaevi into the Mediterranean: observations on oncomiracidium behavior and infection levels in both seas. *Parasitology Res.* **100:** 721–727.
205. Torchin, M.E. & C.E. Mitchell. 2004. Parasites, pathogens, and invasions by plants and animals. *Front. Ecol. Environ.* **2:** 183–190.
206. Raberg, L., A.L. Graham & A.F. Read. 2009. Decomposing health: tolerance and resistance to parasites in animals. *Phil. Trans. R. Soc. B-Biol. Sci.* **364:** 37–49.
207. Schneider, D.S. & J.S. Ayres. 2008. Two ways to survive infection: what resistance and tolerance can teach us about treating infectious diseases. *Nat. Rev. Immunol.* **8:** 889–895.
208. Raberg, L., D. Sim & A.F. Read. 2007. Disentangling genetic variation for resistance and tolerance to infectious diseases in animals. *Science* **318:** 812–814.
209. Wikel, S.K. 1996. Host immunity to ticks. *Annu. Rev. Entomol.* **41:** 1–22.
210. Dobson, A.P. & P.J. Hudson. 1986. Parasites, disease and the structure of ecological communities. *Trends Ecol. Evol.* **1:** 11–15.
211. Dunn, A.M. 2009. Parasites and biological invasions. *Adv. Parasitol.* **68:** 161–184.
212. Prenter, J., C. MacNeil, J.T.A. Dick & A.M. Dunn. 2004. Roles of parasites in animal invasions. *Trends Ecol. Evol.* **19:** 385–390.
213. Tompkins, D.M., A.W. Sainsbury, P. Nettleton, *et al*. 2002. Parapoxvirus causes a deleterious disease in red

squirrels associated with UK population declines. *Proc. R. Soc. Lond. B-Biol. Sci.* **269:** 529–533.
214. Tompkins, D.M., A.R. White & M. Boots. 2003. Ecological replacement of native red squirrels by invasive greys driven by disease. *Ecol. Lett.* **6:** 189–196.
215. Holdich, D.M. 2003. *Ecology of the White-Clawed Crayfish.* Nature. Peterborough, UK.
216. Ley, R.E., D.A. Peterson & J.I. Gordon. 2006. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell* **124:** 837–848.
217. Ayres, J.S. & D.S. Schneider. 2008. A signaling protease required for melanization in drosophila affects resistance and tolerance of infections. *PLoS Biol.* **6:** 2764–2773.
218. Kelly, D.W., R.A. Paterson, C.R. Townsend, *et al*. 2009. Parasite spillback: a neglected concept in invasion ecology? *Ecology* **90:** 2047–2056.
219. Garner, T.W.J. *et al*. 2006. The emerging amphibian pathogen Batrachochytrium dendrobatidis globally infects introduced populations of the North American bullfrog, Rana catesbeiana. *Biol. Lett.* **2:** 455–459.
220. Kopp, K. & J. Jokela. 2007. Resistant invaders can convey benefits to native species. *Oikos* **116:** 295–301.
221. Telfer, S. *et al*. 2005. Disruption of a host-parasite system following the introduction of an exotic host species. *Parasitology* **130:** 661–668.
222. Graham, A.L., J.E. Allen & A.F. Read. 2005. Evolutionary causes and consequences of immunopathology. *Annu. Rev. Ecol. Evol. Syst.* **36:** 373–397.
223. Rolff, J. & M.T. Siva-Jothy. 2003. Invertebrate ecological immunology. *Science* **301:** 472–475.
224. Medzhitov, R. & C.A. Janeway Jr. 1998. An ancient system of host defense. *Curr. Opin. Immunol.* **10:** 12–15.
225. Schnare, M., M. Rollinghoff & S. Qureshi. 2006. Toll-like receptors: sentinels of host defence against bacterial infection. *Int. Arch. Allergy Immunol.* **139:** 75–85.
226. Ausubel, F.M. 2005. Are innate immune signaling pathways in plants and animals conserved? *Nat. Immunol.* **6:** 973–979.
227. Noyes, P.D. *et al*. 2009. The toxicology of climate change: environmental contaminants in a warming world. *Environ. Int.* **35:** 971–986.
228. McKinney, M.L. 2002. Urbanization, biodiversity, and conservation. *Bioscience* **52:** 883–890.
229. Bradley, C.A. & S. Altizer. 2007. Urbanization and the ecology of wildlife diseases. *Trends Ecol. Evol.* **22:** 95–102.
230. Patz, J.A., P.R. Epstein, T.A. Burke & J.M. Balbus. 1996. Global climate change and emerging infectious diseases. *JAMA* **275:** 217–223.
231. Bradley, C.A., S.E.J. Gibbs & S. Altizer. 2008. Urban land use predicts West Nile virus exposure in songbirds. *Ecol. Appl.* **18:** 1083–1092.
232. Blair, R.B. 2001. Birds and butterflies along urban gradients in two ecoregions of the U.S. In *Biotic Homogenizations*. J. L. Lockwood & M. L. McKinney, Eds.: Kluwer. Norwell, MA.
233. Robb, G.N., R.A. McDonald, D.E. Chamberlain & S. Bearhop. 2008. Food for thought: supplementary feeding as a driver of ecological change in avian populations. *Front. Ecol. Environ.* **6:** 476–484.
234. Easterbrook, J.D. *et al*. 2007. A survey of zoonotic pathogens carried by Norway rats in Baltimore, Maryland, USA. *Epidemiol. Infect.* **135:** 1192–1199.
235. Klein, S.L., B.H. Bird, R.J. Nelson & G.E. Glass. 2002. Environmental and physiological factors associated with Seoul virus infection among urban populations of Norway rats. *J. Mammal.* **83:** 478–488.