A hassle a day may keep the pathogens away: The fight-or-flight stress response and the augmentation of immune function

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Synopsis

Stress is known to suppress or dysregulate immune function and increase susceptibility to disease. Paradoxically, the short-term fight-or-flight stress response is one of nature’s fundamental defense mechanisms that galvanizes the neuroendocrine, cardiovascular, and musculoskeletal systems into action to enable survival. Therefore, it is unlikely that short-term stress would suppress immune function at a time when it may be critically required for survival (e.g., in response to wounding and infection by a predator or aggressor). In fact, studies have shown that stress can enhance immune function under certain conditions. Several factors influence the direction (enhancing versus suppressive) of the effects of stress on immune function: (1) Duration: acute or short-term stress experienced at the time of activation of an immune response enhances innate and adaptive immune responses. Chronic or long-term stress can suppress or dysregulate immune function. (2) Leukocyte distribution: compartments (e.g., skin), that are enriched with immune cells during acute stress show immuno-enhancement, while those that are depleted of leukocytes (e.g., blood), show immuno-suppression. (3) The differential effects of physiologic versus pharmacologic stress hormones: Endogenous hormones in physiological concentrations can have immuno-enhancing effects. Endogenous hormones at pharmacologic concentrations, and synthetic hormones, are immuno-suppressive. (4) Timing: immuno-enhancement is observed when acute stress is experienced during the early stages of an immune response while immuno-suppression may be observed at late stages. The type of immune response (protective, regulatory/inhibitory, or pathological) that is affected determines whether the effects of stress are ultimately beneficial or harmful for the organism. Arguments based on conservation of energy have been invoked to explain potential adaptive benefits of stress-induced immuno-suppression, but generally do not hold true because most mechanisms for immuno-suppression expend, rather than conserve, energy. We propose that it is important to study, and if possible, to clinically harness, the immuno-enhancing effects of the acute stress response that evolution has finely sculpted as a survival mechanism, just as we study its maladaptive ramifications (chronic stress) that evolution has yet to resolve.

Introduction

Numerous studies have demonstrated adverse effects of stress on health (McEwen 1998; Ader 2006; Cohen et al. 2007). These studies show that chronic or long-term stressors can have health-aversive effects, some of which are mediated through immune mechanisms. It is also important, however, to appreciate that a psycho-physiological response to stress is one of nature’s fundamental survival mechanisms. Without a fight-or-flight stress response, a lion has no chance of catching a gazelle, just as the gazelle has no chance of escaping. During such short-term stress responses, physiological systems act in synchrony, thereby enabling survival. It is unlikely that eons of evolution would have finely sculpted organisms to escape the jaws and claws of predators, only to succumb to microscopic pathogens and infected wounds. Therefore, we hypothesized that just as the stress response prepares the cardiovascular, musculoskeletal, and neuroendocrine systems for fight-or-flight, under certain conditions, stress may also prepare the immune system for challenges (from wounding or infection) that may be imposed by a stressor (e.g., predator or surgical procedure) (Dhabhar et al. 1995b; Dhabhar 1996, 2008; Dhabhar and McEwen 2007). Studies have shown that stressors of short duration induce a redistribution of immune cells within the body and that immune function is significantly enhanced in organs like the skin to which leukocytes traffic...
during acute stress. Studies have also identified mechanisms involving dendritic cell, neutrophil, macrophage, and lymphocyte trafficking, maturation, and function through which acute stressors may enhance innate as well as adaptive immunity.

We suggest that the acute stress response may serve as an endogenous psycho-physiological adjuvant that enhances immune responses and may have evolved by virtue of the fact that many stressful situations (aggression and accidents) result in immune activation (wounding and infection) and many situations involving immune activation can stimulate elements of a physiological stress response. Interestingly, in modern times, many situations that launch an immune response (vaccination, surgery, and injury) also induce a psychological stress response. It is important to recognize that while acute stress-induced immuno-enhancement may serve to increase immuno-protection during exposure to infectious agents or wounding, it may also exacerbate immuno-pathology if enhanced immune responses are directed against innocuous antigens or self-antigens, or are dysregulated following prolonged activation as seen during chronic stress.

In contrast to acute stress, chronic stress has been shown to dysregulate immune responses (Glaser and Kiecolt-Glaser 2005; Chrousos and Kino 2007) by altering the cytokine balance from Type-1 to Type-2 cytokine-driven responses (Glaser et al. 2001) and accelerating immunosenescence (Epel et al. 2004), and to suppresses immunity by decreasing numbers (Dhabhar and McEwen 1997), trafficking (Dhabhar and McEwen 1997) and function of protective immune cells while increasing regulatory/suppressor T cells (Saul et al. 2005). This article focuses on acute stress-induced enhancement of immune responses.

**Stress: definition and categories**

Although the word “stress” generally has negative connotations, stress is a familiar and ubiquitous aspect of life, being a stimulant for some, but a burden for many others. Numerous definitions have been proposed for the concept of stress. Each definition focuses on aspects of an internal or external challenge, disturbance, or stimulus; on perception of a stimulus by an organism; or on a physiological response of the organism to the stimulus (Goldstein and McEwen 2002; McEwen 2002; Sapolsky 2004). Physical stressors have been defined as external challenges to homeostasis and psychological stressors as the “anticipation justified or not, that a challenge to homeostasis looms” (Sapolsky 2005). An integrated definition states that stress is a constellation of events, consisting of a stimulus (stressor), that precipitates a reaction in the brain (stress perception and evaluation), that in turn activates physiological fight-or-flight systems in the body (stress response) (Dhabhar and McEwen 1997). It is important to understand that the only way a stressor can affect the brain or body is by inducing biological changes. Therefore, the physiological stress response is critical for mediating the effects of stress. This response results in the release of neurotransmitters, hormones, peptides and other factors into the circulation or locally within tissues. Even cytokines, factors that were traditionally thought to be the domain of the immune system, have relatively recently been shown to be released into the systemic circulation during psychological stress (Altemus et al. 2001; Pace et al. 2006). The major mediators of stress effects are norepinephrine and epinephrine that are released by the sympathetic nervous system, and corticotrophin-releasing hormone, adrenocorticotropic, and cortisol, that make up the hypothalamic–pituitary–adrenal (HPA) axis (Lundberg 2005). Since virtually every cell in the body expresses receptors for one or more of these factors, stress-related mediators can induce changes in almost all cells and tissues and, as a result, “inform/warn” all the cells and tissues of an organism about the presence of a stressor.

Although stress can be harmful when it is chronic or long lasting (Irwin et al. 1990; McEwen 1998; Sapolsky 2004; Glaser and Kiecolt-Glaser 2005; Chrousos and Kino 2007), it is often overlooked that a stress response has salubrious adaptive effects in the short run (Dhabhar and Viswanathan 2005; Dhabhar and McEwen 2007). Therefore, a major distinguishing characteristic of stress, in terms of its biological effects, is the duration of elevation of the physiological stress response. *Acute stress* has been defined as stress that lasts for a period of minutes to hours, and *chronic stress* as stress that persists for several hours per day for weeks or months (Dhabhar and McEwen 1997). For most organisms, including humans, life consists of a series of repeated acute stress responses that occur at different frequencies and last for different durations. It is important to recognize that repeated exposure to acute stress is not necessarily detrimental as long as the physiological mediators that are elevated during stress return to baseline/resting levels soon after the cessation of stress, and as long as the frequency or duration of repeated stress responses is not such that it results in a constant increased exposure to stress-related...
hormones and neurotransmitters. Psychological and physiological resilience mechanisms (Fig. 1) are crucial for determining how quickly an organism’s physiological returns to baseline/resting conditions following the activation of a stress response. Importantly, dysregulation of the circadian cortisol rhythm, and a decrease in resting state lymphocyte and monocyte numbers, appear to be two crucial biomarkers for the deleterious effects of stress (Dhabhar and McEwen 1997; Sephton et al. 2000; Sephton and Spiegel 2003; Saul et al. 2005).

Another important characteristic of a stress response is its intensity, which can be gauged by the peak levels of stress hormones, neurotransmitters, and other physiological changes such as increases in heart rate and blood pressure, and by the amount of time over which these changes persist during stress and following the cessation of stress. It is important to note that there are significant differences among individuals in perceiving, processing, and coping with stress (Marsland et al. 2002; Abbott et al. 2003; Dhabhar and McEwen 2007; Gunnar and Quevedo 2007; Taylor and Stanton 2007). Individual differences become particularly relevant while studying human subjects because mechanisms for perceiving, processing, and coping with stress can have significant effects on the kinetics and peak levels of circulating stress hormones and on the duration for which these hormone levels are elevated. Studies show significant differences among different genetic strains in reactivity to stress, peak hormone levels attained during stress (Sternberg et al. 1989a; Dhabhar et al. 1993), adaptation of the physiological response to stress (Dhabhar et al. 1997), distribution and activation of adrenal steroid receptors during stress, and in corticosteroid binding globulin levels that could buffer an organism from some chronic physiological activation (neurotransmitters, hormones, and their molecular, cellular, organ-level and systemic effects) that results in PSYCHO-PHYSIOLOGICAL STATES that have different effects on health. Acute stress generally results in activation of mechanisms that include enhancement of immune function while chronic stress results in health-aversive conditions that result in dysregulation or suppression of immune function. The molecular mechanisms mediating conversion from positive to negative effects of stress on immune function and health are slowly beginning to emerge, and merit further investigation. Figure reprinted from Dhabhar and McEwen (2007). This figure was reprinted with permission from: Dhabhar FS, McEwen BS. 2007. Bidirectional effects of stress on immune function: possible explanations for salubrious as well as harmful effects. In: Ader R, editor. Psychoneuroimmunology IV. San Diego: Elsevier. p. 723–60. Copyright Elsevier.
of the biological effects of stress hormones (Dhabhar et al. 1993, 1995a). These studies suggest that genetic as well as environmental factors, i.e., nature and nurture, play a role in establishing individual differences in the psychophysiological response to stress and in the effects that response can have on an organism or individual (Dhabhar et al. 1993, 1995a, 1997; Gomez-Serrano et al. 2001). The ability of humans to generate and experience internal psychological stressors in the absence of external stressors can result in long-term activation of the physiological stress response that often has deleterious effects. The magnitude and duration of stress-induced elevations in catecholamine and glucocorticoid hormones can have significant effects on the distribution and function of immune cells (Benshop et al. 1996; Dhabhar and McEwen 2001; Pruett 2001; Schwab et al. 2005).

**Immune responses defined in terms of their immuno-protective, immuno-pathological, and immuno-regulatory/inhibitory end-effects**

While discussing immune responses, it is useful to classify them in terms of their principal cellular and molecular components. For example, innate, adaptive, Type-1 and Type-2 cytokine-driven immune responses are all defined in terms of their cellular and cytokine components. In addition to these categorizations, it is also useful to define immune responses in terms of their end-effects. Therefore, we suggest that immune responses can be classified as being immuno-protective, immuno-pathological, and immuno-regulatory/inhibitory. It is important to bear in mind that while all these classifications provide useful constructs for organizing ideas, concepts, and models, an overall in vivo immune response is likely to consist of several types of responses with varying amounts of predominance from each category. For example, combination of innate and adaptive responses work together to promote protective immune function following exposure to a pathogen. The contribution of innate immunity is larger in proportion during primary exposure to a novel pathogen, while the contribution of adaptive immunity is larger during exposure to a pathogen that has previously been encountered by the immune system.

We define immuno-protective responses as those that promote efficient healing of wounds and repair of tissues, eliminate infections and cancer, and mediate vaccine-induced immunological memory. Key characteristics of immuno-protection involve strong immune surveillance, a rapid and robust response upon immune activation, efficient clearance of the activating agent or pathogen, followed by rapid resolution of inflammation. Immuno-protective responses are also critical for completion of the proliferative and remodeling phases of wound healing, which is important not only for frank wounds where the initiating event is tissue damage itself, but also for tissue-intrinsic “wounds” where the initiating event is an immune response precipitated by intracellular infection during which there can be collateral damage to tissue. Innate and/or adaptive Type-1 or Type-2 immune responses can all confer immuno-protection. Specific responses are more effective for specific types of pathogens (viral, bacterial, protozoan, fungal, and helminthic), for intra-cellular versus extra-cellular pathogens, and for specific types of wounds (e.g., sterile, infected, external, or internal).

We define immuno-pathological responses as those that are directed against self (autoimmune disease like multiple sclerosis, arthritis, and lupus) or innocuous antigens (asthma and allergies) and responses that involve chronic, nonresolving inflammation. Immuno-pathology may also be reflected in low-level, long-term elevations in local and/or systemic inflammatory mediators that are thought to contribute to disorders like cardiovascular disease (Van Gaal et al. 2006; Aronne and Isoldi 2007), obesity (Van Gaal et al. 2006; Aronne and Isoldi 2007), and depression (Maes 1993; Dantzer et al. 2008).

We define immuno-regulatory/suppressive responses as those that involve immune cells and factors that inhibit or suppress the function of other immune cells. Although the previous concept of suppressor T cells was mired in controversy (Germain 2008), recent studies show that there is an arm of the immune system that functions to inhibit immune responses (Lehner 2008). Regulatory CD4+CD25+FoxP3+ T cells (Germain 2008), interleukin-10 (IL-10) (Taylor et al. 2006), and TGF-β (Taylor et al. 2006) have been shown to have immuno-regulatory/inhibitory functions. The physiological function of these factors is to keep pro-inflammatory, allergic, and autoimmune responses in check (Bluestone and Tang 2005; Raghavan and Holmgren 2005; Akdis et al. 2006). However, it has also been suggested that immuno-regulatory/inhibitory factors may suppress antitumor immunity and be indicative of negative prognosis for cancer (Saul et al. 2005; Finn 2008).
Acute stress-induced enhancement of immune function: an adaptive response

Dhabhar et al. initially suggested that an acute stress-induced enhancement of immune function may be an adaptive psycho-physiological mechanism that confers increased immune protection following wounding or infection (Dhabhar et al. 1994, 1995b; Dhabhar and McEwen 1996). When viewed from an evolutionary perspective, immuno-suppression under all stress conditions would not be adaptive because stress is an intrinsic part of life for most organisms, and dealing successfully with stressors enables survival. Moreover, most selection pressures, the chisels of evolution, are stressors. The brain perceives stressors, warns the body of danger, and promotes survival (e.g., when a gazelle sees a charging lion, the gazelle’s brain detects a threat and orchestrates a physiological response that enables the gazelle to flee). Since stressful experiences often result in wounding or infection, immuno-enhancement, rather than immuno-suppression, would be adaptive during acute stress since it is unlikely that eons of evolution would select for a system exquisitely designed to escape the jaws and claws of a lion only to succumb to wounds and pathogens (Dhabhar et al. 1994, 1995b; Dhabhar and McEwen 1996). In other words, just as an acute stress response prepares the cardiovascular, musculoskeletal, and neuroendocrine systems for fight-or-flight, it should also prepare the immune system for challenges (wounding or infection) that are likely to result from stressful encounters (attack by a predator).

In contrast to the above discussion, it was previously believed that stress-induced suppression of immune function may be adaptive because immuno-suppression may conserve energy that is required to deal with the immediate demands imposed by the stressor. However, most mechanisms of immuno-suppression are likely to expend, rather than conserve, energy. Moreover, the immune system may often be critically needed for responding immediately to the actions of the stress-inducing agent (e.g., wounding by a predator). Thus, while ovulation, copulation, or digestion can wait for the cessation of stress, the immune response may not be similarly dispensable during times of stress. Immune activation may be critical for responding to the immediate demands of a stressful situation, especially if the situation results in wounding or infection. Furthermore, the time course for many proposed mechanisms for stress-induced immuno-suppression, such as inhibition of prostaglandin synthesis, cytokine production, or leukocyte proliferation (Schleimer et al. 1989) is significantly longer than that seen during acute stress. Thus, while conservation of energy may play a role in stress-induced immuno-suppression under some conditions, it would not do so under all conditions of stress.

The energy-conservation hypothesis has also been invoked to suggest that adaptive immunity is suppressed and that only innate immunity is enhanced during acute stress (Dopp et al. 2000; Segerstrom and Miller 2004). The underlying assumption for this hypothesis is that only innate immune responses are required for, and capable of, effective immunoprotection on a short time scale, and that suppressing adaptive immune function would make more energy available to the innate immune system. There are several reasons for considering a revision of these assumptions and hypothesis: First, while classifications such as “innate” and “adaptive” are useful for conceptualization of different types of immune responses, it is now increasingly apparent that in vivo immune responses consist of intricate and synchronous interactions among numerous proteins, cytokines, and cell types that include components of what were traditionally thought to be separate “innate” versus “adaptive” systems (Vivier and Malissen 2005). In general, most, if not all, components of an immune response are galvanized following immune activation although different components may predominate during different phases of the response. Second, it must be appreciated that suppressing an immune response does not necessarily conserve energy and, in fact, may even require additional expenditure of energy (e.g., energy is consumed during synthesis and/or release of immuno-suppressive factors or during apoptosis). Third, the “adaptive” immune system is not designed solely to fight challenges that the “innate” system fails to overcome. An important function of adaptive immunity is to “memorize” previously encountered antigens/pathogens and to increase the overall efficiency with which a total, in vivo immune response is mounted against the antigen/pathogen upon subsequent exposure. In many instances, antigens and pathogens that activate an immune response may be those that the organism has previously encountered. In such cases, surveillance-memory T cells may play a critical role in conferring protection by initiating the immune-response cascade and the sooner they are activated the more robust the protection. It would make no sense from an evolutionary standpoint to specifically waste energy resources during stress to suppress the specific and powerful adaptive immune responses that are driven by memory lymphocytes that the organism...
has invested considerable amounts of energy to acquire in the first place, and then to maintain for most if not all of its life span.

A variant of the energy-conservation hypothesis has been proposed to explain a transient acute stress-induced decline in immune function observed in some invertebrate species like crickets (e.g., Gryllus texensis) (Adamo 2008). It has been suggested that high-intensity short-term stressors (e.g., flying while being tethered to a stick) lead to immuno-suppression in G. texensis because of octopamine (the insect analog of norepinephrine)-driven competition for specific factors that are required for both lipid-derived mobilization of energy as well as for immune activation. However, octopamine suppresses immune function in crickets, but enhances immunity in the tobacco hornworm and in cockroaches (Baines and Downer 1994), suggesting that the relationship between octopamine and immune function in insects is diverse and complex. It is important to recognize that stress-induced immuno-suppression in some organisms may simply reflect the fact that these organisms have not experienced selection pressures for long-term survival following wounding or infection (this may be due to their very short life spans), and therefore have not evolved independent mechanisms to simultaneously support both the mobilization of energy and immune function. However, organisms have not experienced selection pressures for long-term survival following wounding or infection (this may be due to their very short life spans), and therefore have not evolved independent mechanisms to simultaneously support both the mobilization of energy and immune function.

**Factors that are important for examining the effects of acute stress on immune function**

It is important to consider several factors while examining acute stress-induced immuno-enhancement (Table 1). Stress-induced changes in distribution of immune cells between different compartments of the body can critically affect immune responses measured *in vivo* and *in vitro* and hence need to be carefully taken into account. We have proposed that the short-term stress response may prepare the immune system for immune challenges that occur through the natural route of exposure and involve ecologically relevant concentrations/numbers of pathogens or immune-activating agents (Dhabhar et al. 1995b; Dhabhar and McEwen 1996). For example, most natural pathogens do not get injected directly into the blood stream (or hemolymph in invertebrates). Yet, many experimental paradigms involve direct administration of pathogens or tumor cells into the blood (or hemolymph). Given that acute stress induces a rapid and significant decrease in numbers of immune cells in the blood (Dhabhar et al. 1995b), it is likely that relatively unnatural experimental paradigms that involve administration of immune challenge directly into the circulatory system, will show acute stress-induced immuno-suppression and miss the point that immune function may actually be enhanced in those compartments through which the pathogen is likely to naturally enter the organism. Similarly, inoculating numbers of pathogens that are orders of magnitude higher than those to which an organism would be naturally exposed, can indicate acute stress-induced immuno-suppression simply by overwhelming the natural dynamics for which acute stress-induced activation of immune function may have evolved. Thus, it is important to bear in mind that experimentally, one is likely to observe acute stress-induced immuno-enhancement if the antigen/pathogen is administered to the natural site of exposure, and the appropriate immune parameter is measured in the relevant immune compartment at the relevant time.

Multiple components of an immune response have the potential to be enhanced by acute stress. The antigen, pathogen, chemoattractants, and initially responding cells and leukocytes, present at the site of immune activation determine which specific components are recruited in greater numbers and respond more vigorously (Dhabhar and McEwen 1996; Dhabhar and Viswanathan 2005; Viswanathan and Dhabhar 2005; Viswanathan et al. 2005). Exposure to novel antigens during, or following, acute stress will enhance innate immune mechanisms that respond to the initial encounter with an antigen (Saint-Mezard et al. 2003; Dhabhar and Viswanathan 2005; Viswanathan and Dhabhar 2005; Viswanathan et al. 2005). Such immuno-enhancement during primary exposure to the antigen can also induce long-lasting increases in immunological memory (Dhabhar and Viswanathan 2005). Similarly, exposure to previously encountered antigens during, or following, stress is likely to enhance adaptive immune mechanisms (Dhabhar and McEwen 1996; Dhabhar et al. 2000). Both Type-1 cytokine-driven cell-mediated immunity (CMI) (Dhabhar and McEwen 1996, 1999; Dhabhar et al. 2000; Saint-Mezard et al. 2003; Dhabhar and Viswanathan 2005; Viswanathan et al. 2005) and Type-2 cytokine-driven humoral immunity (Carr et al. 1992; Cocke et al. 1993; Wood et al. 1993; Persoons et al. 1995) can be enhanced by acute stress. The predominance of one type of response over the other is determined by the antigen/pathogen, and the antigen presentation milieu during the initiation of immune response cascades. Importantly, it appears that acute stress significantly
Accurately determining resting baseline conditions is critical. For wild-caught animals, capture is likely to induce a rapid and significant stress. Acute stress (minutes to hours in duration) should be induced on, and compared to, a background of resting baseline conditions. The heterogeneity of acute stress-induced changes in leukocyte redistribution means that changes in leukocyte distribution can affect functional assays even if immune cell numbers are “normalized” for in vitro assays.

Pathogens or immune activating agents, should be administered through their natural routes of entry. If pathogens naturally enter an organism through the skin during natural infection, they must also be administered to skin experimentally and not inoculated into blood or hemolymph. Unnatural inoculation of pathogens (or tumor cells) into the circulation may indicate acute stress-induced suppression of immune function, when immune function may actually have been enhanced if the challenge had been administered through the natural route.

The type and magnitude of pathogen challenge should be physiologically and ecologically relevant. The type and number of pathogens that are inoculated should approximate the type and number encountered during natural infection. Some experimental models inoculate number of pathogens that are orders of magnitude higher than those encountered naturally. Such inoculations suppress of immune function, when immune function may actually have been enhanced if the challenge had been administered through the natural route.

Acute stress (minutes to hours in duration) should be induced on, and compared to, a background of resting baseline conditions. Accurately determining resting baseline conditions is critical. For wild-caught animals, capture is likely to induce a rapid and significant stress response. Subsequent housing in captivity is likely to prolong this response and induce chronic stress. For laboratory animals, unintended disturbances in holding rooms can disrupt resting baseline and inadvertently induce stress.

The stage of development (early versus late) of the immune response should be considered. Immuno-enhancement is generally observed when acute stress is experienced during early stages of immune activation while suppression may be observed at late stages. This difference in stress or stress hormone-induced up- versus down-regulation of early- versus late-stage immune reactions may mediate the negative feedback suppression of pro-inflammatory and autoimmune responses by endogenous glucocorticoid hormones whose release is stimulated by pro-inflammatory cytokine activation of the HPA axis.

Influence of evolutionary selection pressures for long-term survival following wounding or infection. Some organisms (e.g., those with very short life spans) may not have experienced selection pressures that favor long-term survival following wounding or infection and hence may not show acute stress-induced immuno-enhancement.

Enhances the trafficking, maturation and function of dendritic cells and macrophages (Viswanathan and Dhabhar 2005; Viswanathan et al. 2005). Therefore, macrophages and dendritic cells, which form the nexus between innate and adaptive immune responses, may be critical mediators of acute stress-induced enhancement of in vivo immune responses. Other cells such as keratinocytes, endothelial cells, and mast cells may also be important and their roles need to be investigated further. It is important to recognize that a stress-induced enhancement of immune function is likely to be beneficial in the context of wound healing, vaccination, or resistance to infection (Dhabhar and McEwen 1996, 1997; Dhabhar et al. 2000; Dhabhar and Viswanathan 2005; Viswanathan and Dhabhar 2005; Viswanathan et al. 2005). However, such immuno-enhancement is likely to be harmful if it exacerbates inflammatory (cardiovascular disease and gingivitis) or autoimmune (psoriasis, arthritis, multiple, and sclerosis) diseases (Folks and Kinney 1992; Al’Abadie et al. 1994; Weigl 2000; Ackerman et al. 2002). Therefore, the overall focus of our research has been the elucidation of cellular and molecular mechanisms mediating the beneficial versus harmful effects of stress on the health of an organism because understanding these mechanisms may lead to the development of interventions designed to maximize endogenous immuno-enhancement in the case of infections, vaccination, and some types of cancer, and to minimize/eliminate stress-induced exacerbation of pro-inflammatory and autoimmune diseases (Dhabhar and McEwen 2007; Dhabhar 2008).

Factors that determine whether stress will enhance or suppress immune function, and the potential consequences of these effects of stress upon health. Several critical factors are likely to influence the direction (enhancing versus suppressive) of the effects of...
stress or stress hormones, and the nature of the 
immune response (immuno-protective, immuno-
regulatory/inhibitory, or immuno-pathological) that 
is affected (Table 1). These include: (1) the effects of 
stress on the distribution of leukocytes in the body. 
(2) The duration (short-term/acute versus long-term/
chronic) of stress. (3) The differential effects of 
physiologic versus pharmacologic concentrations 
of glucocorticoids, and the differential effects of 
endogenous (e.g., cortisol and corticosterone) 
versus synthetic (e.g., dexamethasone) glucocorti-
coids. (4) The timing of exposure to stressors or 
stress hormones relative to the time of activation 
and ensuing time-course of the immune response. 
It is important to recognize that factors such as 
gender, genetics, age, the route of administration 
and nature of the immunizing antigen, and time of 
day, may additionally affect the relationship between 
stress and immune function.

It is also important to bear in mind that whether 
a stressor enhances or suppresses immune function, 
it is the end-effect of the affected immune response 
that influences the health of the organism or individ-
ual. Given the definitions in the preceding section, 
stress-induced enhancement of immuno-protection 
is likely to have beneficial effects while stress-induced 
suppression of immuno-protection is likely to be 
harmful. Similarly, stress-induced enhancement of 
immuno-pathology or long-term pro-inflammation 
is also likely to be harmful. Finally, stress-induced 
enhancement of active immuno-regulation/inhibition 
is likely to be beneficial in the case of autoimmune 
and pro-inflammatory disorders and harmful in the 
case of infections and cancer.

**Stress-induced changes in the 
distribution of immune cells**

Effective immuno-protection requires rapid recruit-
ment of leukocytes to sites of surgery, wounding, 
infection, or vaccination. Immune cells circulate 
continuously on surveillance pathways that take 
them from the blood, through various organs, and 
back into the blood. This circulation is essential for 
the maintenance of an effective immune defense 
network (Sprent and Tough 1994). The numbers 
and proportions of leukocytes in the blood provide 
an important representation of the state of distribu-
tion of leukocytes in the body and of the state 
of activation of the immune system. The ability of acute 
stress to induce changes in the distribution of 
leukocytes within different compartments of the 
body is perhaps one of the most under-appreciated 
effects of stress and stress hormones on the immune 
system (Dhabhar et al. 1995b).

Numerous studies have shown that stress and 
stress hormones induce significant changes in 
absolute numbers and in relative proportions of 
leukocytes in the blood. In fact, changes in leukocyte 
numbers in the blood were used as a measure of 
stress before methods were available to directly 
assay the hormone (Hoagland et al. 1946). Studies 
have also shown that glucocorticoid (Fauci and Dale 
1974, 1975; Dhabhar et al. 1996) and catecholamine 
hormones (Benschop et al. 1993, 1996; Carlson et al. 
1997; Mills et al. 1998, 2001; Redwine et al. 2003) 
induce rapid and significant changes in leukocyte 
distribution and that these hormones are the major 
mediators of the effects of stress. Stress-induced 
changes in numbers of leukocytes in the blood 
have been reported in fish (Pickford et al. 1971), 
hamsters (Bilbo et al. 2002), mice (Jensen 1969), 
rats (Dhabhar et al. 1994, 1995b, 1996; Rinder et al. 1997), rabbits (Toft et al. 1993), horses 
(Snow et al. 1983), nonhuman primates (Morrow-
Tesch et al. 1993), and humans (Herbert and 
Cohen 1993; Schedlowski et al. 1993; Mills et al. 
1998; Bosch et al. 2003; Redwine et al. 2004). This 
suggests that the phenomenon of stress-induced 
redistribution of leukocytes has a long evolutionary 
lineage, and that perhaps it has important functional 
significance.

Studies have shown that stress-induced changes in 
leukocyte numbers in the blood are characterized by 
a significant decrease in numbers and percentages 
of lymphocytes and monocytes, and by an increase in 
numbers and percentages of neutrophils (Dhabhar 
that absolute numbers of peripheral blood T cells, B 
cells, NK cells, and monocytes all show a rapid and 
significant decrease (40–70% lower than baseline) 
during stress (Dhabhar et al. 1995b). Moreover, it 
has been shown that stress-induced changes in 
leukocyte numbers are rapidly reversed upon the 
cessation of stress (Dhabhar et al. 1995b). In appar-
ent contrast to studies in animals, studies of humans 
have shown that stress increases, rather than 
decreases, numbers of blood leukocytes (Naliboff 
et al. 1991; Schedlowski et al. 1993; Brosschot et al. 
1994; Mills et al. 1995; Bosch et al. 2003). This 
apparent contradiction may be resolved by taking 
the following factors into consideration: First, 
stress-induced increases in the number of leukocytes 
in the blood in humans have been studied using 
stressful conditions that result in the activation 
primarily of the sympathetic nervous system. These 
stressors are often of a short duration (few minutes)
or relatively mild (Naliboff et al. 1991; Schedlowski et al. 1993; Brosschot et al. 1994; Mills et al. 1995). Second, the increase in total leukocyte numbers may be accounted for mainly by stress-induced or catecholamine-induced increases in granulocytes and NK cells (Naliboff et al. 1991; Schedlowski et al. 1993; Brosschot et al. 1994; Mills et al. 1995; Benschop et al. 1996). Third, stress or pharmacologically induced increases in glucocorticoid hormones induce a significant decrease in the numbers of lymphocytes and monocytes in the blood (Hoagland et al. 1946; Stein et al. 1951; Schedlowski et al. 1993; Dhabhar et al. 1996). Thus, stressful conditions that result in a significant and sustained activation of the HPA axis result in a decrease in blood leukocyte numbers.

It has been proposed that acute stress induces an initial increase, followed by a decrease, in numbers of blood leukocytes (Dhabhar and McEwen 2001). Stressful conditions that result in activation of the sympathetic nervous system, especially conditions that induce high levels of norepinephrine, may induce an increase in numbers of circulating leukocytes. These conditions may occur during the beginning of a stress response, during very short-duration stress (order of minutes), during mild psychological stress, or during exercise. In contrast, stressful conditions that result in the activation of the HPA axis induce a decrease in numbers of circulating leukocytes. These conditions often occur during the later stages of a stress response, under acute stress of long duration (order of hours), or during severe psychological, physical, or physiological stress. An elegant and interesting example in support of this hypothesis comes from a study by Schedlowski et al. (1993) who measured changes in the numbers of T cells and natural killer (NK) cells in the blood, as well as levels of catecholamine and cortisol in the plasma of parachutists. Measurements were made 2 h before, immediately after, and 1 h following the jump. Results showed a significant increase in numbers of T cells and NK cells immediately (minutes) after the jump that was followed by a significant decrease 1 h after the jump. An early increase in plasma catecholamines preceded early increases in lymphocyte numbers whereas the more delayed rise in plasma cortisol preceded the late decrease in lymphocyte numbers (Schedlowski et al. 1993). Importantly, changes in NK cell activity and antibody-dependent cell-mediated cytotoxicity closely paralleled changes in the number of NK cells in the blood, thus suggesting that changes in leukocyte numbers may be an important mediator of apparent changes in leukocyte “activity.” Similarly, Rinner et al. (1992) have shown that a short stressor (1 min of handling) induced an increase in mitogen-induced proliferation of T- and B-cells obtained from peripheral blood, while a longer stressor (2 h immobilization) induced a decrease in the same proliferative responses. In another example, Manuck et al. (1991) showed that acute psychological stress induced a significant increase in cytolytic T cell numbers in the blood only in those subjects who showed heightened catecholamine and cardiovascular reactions to stress.

Thus, an acute stress response may induce biphasic changes in blood leukocyte numbers. Soon after the beginning of stress (order of minutes) or during mild acute stress, or exercise, catecholamine hormones and neurotransmitters induce the body’s “soldiers” (leukocytes), to exit their “barracks” (spleen, lung, marginated pool, and other organs) and enter the “boulevards” (blood vessels and lymphatics). This results in an increase in numbers of blood leukocyte, the effect being most prominent for NK cells and granulocytes. As the stress response continues, activation of the HPA axis results in the release of glucocorticoid hormones which induce leukocytes to exit the blood and take position at potential “battle stations” (such as the skin, lung, gastro-intestinal and urinary-genital tracts, mucosal surfaces, and lymph nodes) in preparation for immune challenges which may be imposed by the actions of the stressor (Dhabhar and McEwen 1996, 2001; Dhabhar et al. 1995b). Such a redistribution of leukocytes results in a decrease in leukocyte numbers in the blood. Thus, acute stress may result in a redistribution of leukocytes from the barracks, through the boulevards, and to potential battle stations within the body.

Since the blood is the most accessible and commonly used compartment for human studies, it is important to carefully evaluate how changes in immune parameters in the blood might reflect in vivo immune function in the context of the specific experiments or study at hand. Moreover, since most procedures for the collection of blood involve a certain amount of stress, since all patients or subjects will have experienced acute and chronic stress, and since many studies of psychophysiological effects on immune function focus on stress, the effects of stress on the distribution of blood leukocytes become a factor of considerable importance.

Dhabhar and colleagues were the first to propose that stress-induced changes in the distribution of blood leukocytes may represent an adaptive response (Dhabhar et al. 1994; Dhabhar and McEwen 1999).
They suggested that acute stress-induced changes in numbers of blood leukocytes represent a redistribution of leukocytes from the blood to organs such as the skin, draining sentinel lymph nodes, and other compartments (Dhabhar and McEwen 1996, 2001). They hypothesized that such a redistribution of leukocytes may enhance immune function in compartments to which immune cells traffic during stress. In agreement with this hypothesis, it was demonstrated that a stress-induced redistribution of leukocytes from the blood to the skin is accompanied by a significant enhancement of skin immunity (Dhabhar and McEwen 1996, 1999; Dhabhar et al. 2000).

**Functional consequences of stress-induced changes in immune cell distribution**

When interpreting data showing stress-induced changes in functional assays such as lymphocyte proliferation or NK activity it may be important to bear in mind the effects of stress on the leukocyte composition of the compartment in which an immune parameter is being measured (Table 1). For example, it has been shown that acute stress induces a redistribution of leukocytes from the blood to the skin and that this redistribution is accompanied by a significant enhancement of skin CMI (Dhabhar and McEwen 1996; Dhabhar and Viswanathan 2005). In what might, at first glance, appear to be contradicting results, acute stress has been shown to suppress splenic responses and peripheral blood responses to T cell mitogens (Cunnick et al. 1990) and antibody production by splenocytes (Zalcman and Anisman 1993). However, it is important to note that in contrast to the skin that is enriched in leukocytes during acute stress, peripheral blood and spleen, are relatively depleted of leukocytes during acute stress (Dhabhar 1998). Thus, the stress-induced decrease in leukocyte numbers in the blood and spleen may contribute to the acute stress-induced suppression of immune function in these compartments.

Moreover, in contrast to acute stress, chronic stress has been shown to suppress skin CMI and a chronic stress-induced suppression of blood leukocyte redistribution is thought to be one of the factors mediating the immuno-suppressive effect of chronic stress (Dhabhar and McEwen 1997). Again, in what might appear to be contradicting results, chronic stress has been shown to enhance mitogen-induced proliferation of splenocytes (Monjan and Collector 1977) and splenic IgM production (Zalcman and Anisman 1993). However, the spleen is relatively enriched in T cells during chronic glucocorticoid administration, suggesting that it may also be relatively enriched in T cells during chronic stress (Miller et al. 1994), and this increase in spleen leukocyte numbers may contribute to the chronic stress-induced enhancement of immune parameters measured in the spleen.

It is also important to bear in mind that the heterogeneity of the stress-induced changes in leukocyte distribution (Dhabhar et al. 1995b) suggests that using equal numbers of leukocytes in a functional assay may not account for stress-induced changes in relative percentages of different leukocyte subpopulations in the cell suspension being assayed. For example, samples that have been equalized for absolute numbers of total blood leukocytes from control versus stressed animals may still contain different numbers of specific leukocyte subpopulations (e.g., T cells, B cells, or NK cells). Such changes in leukocyte composition may contribute to the effects of stress even in functional assays using equalized numbers of leukocytes from different treatment groups. Therefore, stress may affect immune function at a cellular level (e.g., phagocytosis, antigen presentation, killing, and antibody production) and/or through a redistribution of leukocytes that could increase or decrease the number of cells with a specific functional capacity in the compartment being studied.

**Effects of acute stress on leukocyte trafficking to a site of surgery or immune activation**

Viswanathan et al. (2005) used a subcutaneously implanted surgical sponge model to elucidate the effects of stress on the kinetics, magnitude, subpopulation, and chemoattractant specificity of leukocyte trafficking to a site of immune activation or surgery. Mice that were acutely stressed before subcutaneous implantation of the surgical sponge showed a two- to three-fold higher neutrophil, macrophage, NK cell, and T cell infiltration than did nonstressed animals. Leukocyte infiltration was evident as early as 6 h and peaked between 24 h and 48 h. Importantly at 72 h, sponges from nonstressed and acutely stressed mice had comparable and significantly lower leukocyte numbers, indicating effective resolution of inflammation in both groups. These authors also examined the effects of stress on early (6 h) leukocyte infiltration in response to a predominantly pro-inflammatory cytokine, tumor necrosis factor (TNF)-α, and
lymphocyte-specific chemokine, lymphotactin (LTN). Acute stress significantly increased infiltration of macrophages, in response to saline, LTN or TNF-α; neutrophils, only in response to TNF-α; and NK and T cells only in response to LTN. These results showed that acute stress significantly enhances the kinetics and magnitude of leukocyte infiltration into a site of immune activation or surgery in a subpopulation and chemoattractant-specific manner, with tissue damage, antigen-driven, or pathogen-driven chemoattractants synergizing with acute stress to further determine the specific subpopulations that are recruited (Viswanathan and Dhabhar 2005). Thus, depending on the primary chemoattractants driving an immune response, acute stress may selectively mobilize specific leukocyte subpopulations into sites of surgery, wounding, or inflammation. Such a stress-induced increase in leukocyte trafficking may be an important mechanism whereby acute stressors alter the course of different (innate versus adaptive, early versus late, acute versus chronic) protective or pathological immune responses.

**Acute stress-induced enhancement of innate/primary immune responses**

In view of the skin being one of the target organs to which leukocytes traffic during stress, studies were conducted to examine whether skin immunity is enhanced when immune activation/antigen exposure occurs following a stressful experience. Studies showed that acute stress experienced at the time of novel or primary antigen exposure results in a significant enhancement of the ensuing skin immune response (Dhabhar and Viswanathan 2005). Compared to controls, mice restrained for 2.5 h before primary immunization with keyhole limpet hemocyanin (KLH) showed a significantly enhanced immune response when re-exposed to KLH 9 months later. This immuno-enhancement was mediated by an increase in numbers of memory and effector helper T cells in sentinel lymph nodes at the time of primary immunization. Further analyses showed that the early stress-induced increase in T cell memory may have stimulated the robust increase in infiltrating lymphocyte and macrophage numbers observed months later at a novel site of antigen re-exposure. Enhanced leukocyte infiltration was driven by increased levels of the Type-1 cytokines, IL-2 and gamma interferon (IFN-γ), and TNF-α, observed at the site of antigen re-exposure in animals that had been stressed at the time of primary immunization. Given the importance of inducing long-lasting increases in immunological memory during vaccination, it has been suggested that the neuroendocrine stress response is nature’s adjuvant that could be psychologically and/or pharmacologically manipulated to safely increase vaccine efficacy.

In a series of elegant experiments, Saint-Mezard et al. (2003) similarly showed that acute stress, experienced at the time of sensitization, resulted in a significant increase in the contact hypersensitivity (CHS) response. These investigators showed that acute stress experienced during sensitization enhanced dendritic cell migration from skin to sentinel lymph nodes and also enhanced priming of lymph node CD8+ T cells. These CD8+ T cells responded in greater numbers at the site of antigen re-exposure during the recall phase of the CHS response. These studies also suggested that in this case the effects of acute stress were mediated primarily by norepinephrine. Other investigators have similarly reported stress-induced enhancement of Type-1 cytokine-driven CMI (Blecha et al. 1982; Coe et al. 1989; Wood et al. 1993) and Type-2 cytokine-driven humoral immunity (Carr et al. 1992; Cocke et al. 1993; Wood et al. 1993; Persoons et al. 1995).

Viswanathan et al. further elucidated the molecular and cellular mediators of the immuno-enhancing effects of acute stress (Viswanathan et al. 2005). They showed that compared to nonstressed mice, acutely stressed animals showed significantly greater pinna swelling, leukocyte infiltration, and upregulated macrophage chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-3α (MIP-3α), IL-1α, IL-1β, IL-6, TNF-α, and IFN-γ gene expression at the site of primary antigen exposure. Stressed animals also showed enhanced maturation and trafficking of dendritic cells from skin to lymph nodes, higher numbers of activated macrophages in skin and lymph nodes, increased T cell activation in lymph nodes, and enhanced recruitment of surveillance T cells to skin. These findings showed that important interactive components of innate (dendritic cells and macrophages) and adaptive (surveillance T cells) immunity are mediators of the stress-induced enhancement of a primary immune response. Such immuno-enhancement during primary immunization may induce a long-term increase immunologic memory resulting in subsequent augmentation of the immune response during secondary antigen exposure.

In addition to elucidating mechanisms that could be targeted to reduce stress-induced exacerbation of allergic, autoimmune, and pro-inflammatory
reactions, the above-mentioned studies provide further support for the idea that a psycho-physiological stress response is nature’s fundamental survival mechanism that could be therapeutically harnessed to augment immune function during vaccination, wound healing, or infection.

**Acute stress-induced enhancement of adaptive/secondary immune responses**

Studies have shown that in addition to enhancing primary cutaneous immune responses, acute stress experienced at the time of re-exposure to antigens can also enhance secondary or recall responses in skin (Dhabhar and McEwen 1996). Compared to nonstressed controls, mice that were acutely stressed at the time of re-exposure to antigens showed a significantly larger number of infiltrating leukocytes at the site of the immune reaction. These results demonstrated that a relatively mild behavioral manipulation can enhance an important class of immune responses that mediate harmful (allergic dermatitis) as well as beneficial (resistance to certain viruses, bacteria, and tumors) aspects of immune function.

Blecha et al. (1982) reported a similar stress-induced enhancement of CHS reactions in mice; and Flint et al. (2000) showed that acute stress-enhanced CHS responses both in male and female mice and that immuno-enhancement was partially dependent on glucocorticoid hormones (Flint et al. 2000), and a stress-induced enhancement of the elicitation phase of skin CMI has also been reported in hamsters (Bilbo et al. 2002). Taken together, studies show that acute stress can significantly enhance the immunization/sensitization/induction phases as well as the re-exposure/elicitation/recall phases of skin CMI.

**Hormone and cytokine mediators of stress-induced enhancement of immune function**

Although much work remains to be done, to identify molecular, cellular, and physiological mechanisms mediating the adjuvant-like, immuno-enhancing effects of acute stress, several studies have begun to identify endocrine and immune mediators of these effects. Studies have shown that corticosterone and epinephrine are important mediators of an acute stress-induced immuno-enhancement (Dhabhar and McEwen 1999). Adrenalectomy, which eliminates the stress-induced enhancement of cutaneous CMI. Administration of low doses of corticosterone or epinephrine significantly enhanced cutaneous CMI (Dhabhar and McEwen 1999). In contrast, administration of high doses of corticosterone, chronic corticosterone, or low doses of dexamethasone, significantly suppressed cutaneous CMI. These results suggested a novel role for adrenal stress hormones as endogenous immuno-enhancing agents. They also showed that stress hormones released during a circumscribed or short-term stress response may help prepare the immune system for potential challenges (e.g., wounding or infection) for which stress perception by the brain may serve as an early warning signal. Flint et al. (2000) have also suggested that corticosterone is a mediator of the stress-induced enhancement of skin CHS while Saint-Mezard et al. (2003) suggested that the adjuvant-like effects of stress on the migration and function of dendritic cells and CD8+ T cells are mediated by norepinephrine. Although it is beyond the scope of this review, the potential roles of the mineralocorticoid or Type-1 and the glucocorticoid or Type-2 adrenal steroid receptors in mediating the differential effects of low-dose physiological versus high-dose pharmacological concentrations of corticosterone, and the effects on the early versus late stages of an immune response merit further investigation.

The immunological mediators of an acute stress-induced enhancement of skin immunity also have been examined. Since IFN-γ is a critical cytokine mediator of CMI delayed as well as CHS (Abe et al. 1996), studies were conducted to examine its role as a local mediator of the stress-induced enhancement of cutaneous CMI (Dhabhar et al. 2000). The effect of acute stress on cutaneous CMI was examined in wild-type and IFN-γ receptor-gene-knockout mice (IFN-γR−/−) that had been sensitized with 2,4-dinitro-1-fluorobenzene. Acutely stressed wild-type mice showed a significantly larger CMI than did nonstressed mice. In contrast, IFN-γR−/− mice failed to show a stress-induced enhancement of cutaneous CMI. Immunoneutralization of IFN-γ in wild-type mice significantly reduced the stress-induced enhancement of cutaneous CMI. In addition, an inflammatory response to direct administration of IFN-γ was significantly enhanced by acute stress. These results showed that IFN-γ is an important local mediator of a stress-induced enhancement of cutaneous CMI (Dhabhar et al. 2000). In addition to IFN-γ, TNF-α, MCP-1, MIP-3α, IL-1, and IL-6 have been associated with a
stress-induced enhancement of the immunization/sensitization phase of CMI (Dhabhar and Viswanathan 2005; Viswanathan et al. 2005). It is clear that further investigation is necessary in order to identify the most important molecular, cellular and physiological mediators of a stress-induced enhancement of skin immunity.

The psychophysiology of short-term/acute stress as an endogenous adjuvant

We initially suggested that just as the acute stress response prepares the cardiovascular, musculoskeletal, and neuroendocrine systems for flight-or-flight, it may also prepare the immune system for challenges, such as wounding and infection, that are likely to result due to the actions of the stressor (predator, or process of undergoing surgery) (Dhabhar and McEwen 1996; Dhabhar 1998). Upon seeing the evidence in support of the above hypothesis, we put forth the novel hypothesis that a psychophysiological stress response is nature’s fundamental survival mechanism that could be therapeutically harnessed to augment immune function during vaccination, wound healing, or infection (Dhabhar and Viswanathan 2005). In keeping with this hypothesis, studies conducted by our group have shown that among patients undergoing knee surgery, those who show a robust and adaptive immune-cell-redistribution profile during the acute stress of surgery, also show significantly enhanced recovery. Similarly, other studies have shown that acute stressors can enhance vaccine-induced humoral-mediated immunity and CMI in human subjects (Edwards et al. 2006, 2007, 2008). Further research is required to test the hypothesis that behavioral and/or pharmacological induction of the acute psychophysiological stress response can be used therapeutically to enhance protective immunity during wound healing, infection, and cancer, and to enhance the efficacy of vaccines. Such intervention is likely to allow for safe and effective enhancement of protective immunity because it would tap into the body’s natural, endogenous, adjuvant mechanisms to enhance immune function.

The skin and subcutaneous tissue are compartments in which the adjuvant-like effects of acute or short-term stress have thus far been demonstrated. This makes sense from an evolutionary perspective because the physiological stress response may have evolved to enhance immune function in these compartments that are the ones that are most likely to encounter immune challenges (e.g., wounding and infection) during stressful conditions (e.g., attack by a predator). However, in future studies, it may useful and interesting to examine the effects of acute stress on immune responses in other compartments like the lung. Moreover, it would also be interesting to examine the effects of acute stress on pathogens that are inoculated by vectors (e.g., Plasmodium inoculation by mosquitoes) as such inoculations often take place in the absence of directly coupled stressors.

Chronic stress can suppress immuno-protection while enhancing immuno-pathological and immuno-regulatory/suppressive responses

In contrast to acute stressors, chronic stress has been shown to suppress Type-1 cytokine-driven protective immune responses while enhancing pro-inflammatory and Type-2 cytokine-driven immune responses (Marshall and Agarwal 2000; Glaser and Kiecolt-Glaser 2005). Chronic stress also appears to mobilize immuno-regulatory/inhibitory mechanisms (Saul et al. 2005). Therefore, chronic stress is likely to exacerbate pro-inflammatory diseases and increase susceptibility to infections and cancer. Studies of the effects of increasing the intensity and duration of acute stress as well as the transition from acute to chronic stress on skin immune function have shown that acute stress, administered for 2 h prior to antigenic challenge, significantly enhanced cutaneous CMI (Dhabhar and McEwen 1997). Increasing the duration of stress from 2 h to 5 h produced immuno-enhancement of the same magnitude. Interestingly, increasing the intensity of acute stress produced a significantly larger enhancement of the CMI response that was accompanied by increasing magnitudes of leukocyte redeployment. In contrast, these studies found suppression of the skin immune response when chronic stress exposure was begun 3 weeks before sensitization and either discontinued upon sensitization, continued an additional week until challenge, or extended for 1 week after challenge (Dhabhar and McEwen 1997). Interestingly, acute stress-induced redistribution of peripheral blood lymphocytes was attenuated with increasing chronicity of stress and correlated with attenuated glucocorticoid responsivity. These results suggested that stress-induced alterations in lymphocyte redeployment may play an important role in mediating the bi-directional effects of stress on cutaneous CMI (Dhabhar and McEwen 1997). An association between chronic stress and reduced cutaneous CMI
has also been reported in human subjects (Smith et al. 2004).

Given the importance of cutaneous CMI in elimination of immuno-responsive tumors like squamous cell carcinoma (SCC) (Kripke 1994; Granstein and Matsui 2004), Saul et al. (2005) examined the effects of chronic stress on susceptibility to ultraviolet (UV) radiation-induced SCC. Mice were exposed to a minimal erythematous dose of UVB three times a week for 10 weeks. Half of the UVB-exposed mice were left nonstressed (i.e., they remained in their home cages) and the other half were chronically stressed (i.e., restrained during Weeks 4–6). UV-induced tumors were measured weekly from Week 11 through Week 34, blood was collected at Week 34, and tissues were collected at Week 35. IL-12p40, IFN-γ, IL-4, IL-10, CD3ε, and CCL27/CTACK (the skin T cell-homing chemokine) gene expression in dorsal skin was quantified using real-time polymerase chain reaction. CD4+, CD8+, and CD25+ leukocytes were counted using immunohistochemistry and flow cytometry. Stressed mice had a shorter median time to first tumor (15 weeks versus 16.5 weeks) and reached 50% incidence earlier than did controls (15 weeks versus 21 weeks). Stressed mice also had lower IFN-γ, CCL27/CTACK, and CD3ε gene expression and lower numbers of CD4+ and CD8+ T cells infiltrating within and around tumors than did nonstressed mice. In addition, stressed mice had higher numbers of tumor infiltrating and circulating CD4+CD25+ regulatory/suppressor T cells than did nonstressed mice. These studies showed that chronic stress increased susceptibility to UV-induced SCC by suppressing skin immunity, Type 1 cytokines, and protective T cells, and increasing active immuno-suppression through regulatory/suppressor T cells (Saul et al. 2005).

Chronic stress has also been shown to suppress immuno-protective parameters such as: CMI (Kelley et al. 1982; Basso et al. 1993), antibody production (Edwards and Dean 1977; Fleschner et al. 1989), NK activity (Bartrop et al. 1977; Kiecolt-Glaser et al. 1984; Cheng et al. 1990; Irwin et al. 1990), leukocyte proliferation (Bartrop et al. 1977; Regnier and Kelley 1981; Cheng et al. 1990), skin homograft rejection (Wistar and Hildemann 1960), virus-specific T cell and NK cell activity (Bonneau et al. 1991), vaccine-induced immune responses (Glaser et al. 1998, 2000), and antimycobacterial activity of macrophages from susceptible mouse strains (Brown and Zwilling 1994), and to enhance pro-inflammatory and Type-2 cytokine-driven conditions and disorders (Marshall and Agarwal 2000; Glaser et al. 2001; Elenkov 2004).

**Immunomodulatory effects of timing of exposure to stress or stress hormones relative to the timing of immune activation and the time course of the ensuing immune response**

Under certain conditions, physiological levels of endogenous glucocorticoids have immuno-enhancing effects while under other conditions similar hormone levels suppress autoimmune and inflammatory reactions. We hypothesize that these differential effects are achieved by differences in overall glucocorticoid sensitivity or receptivity of the immune response being affected. At the beginning of an immune response, certain components such as leukocyte trafficking, antigen presentation, helper T cell function, leukocyte proliferation, cytokine and chemokine function, and effector cell function may all be receptive to glucocorticoid-mediated immuno-enhancement (Table 1). In contrast, at a later, more advanced stage of an immune response these components may be more receptive to glucocorticoid-mediated immuno-suppression. While this hypothesis needs to be tested through further experiments, examples from studies showing temporal differences in the sensitivity of immune reactions to the effects of physiologic concentrations of glucocorticoid hormones are presented below.

Studies examining the effects of corticosterone on T lymphocyte proliferation *in vitro*, support the hypothesis that there may be temporal differences in the receptivity of an immune response to the enhancing versus suppressive effects of endogenous glucocorticoid hormones (Wiegers et al. 1995). These studies have shown that during the early stages of T cell activation, low levels of corticosterone potently enhance anti-TCR-induced lymphocyte proliferation. However, during later stages of culture, the same levels of corticosterone suppress T lymphocyte proliferation (Wiegers et al. 1995). Furthermore, Wiegers et al. showed that corticosterone had to be present during the process of TCR activation in order to enhance the proliferative response. If corticosterone was added to the culture system >2h after the initiation of TCR activation, the enhancement of lympho-proliferation was not observed.

Interestingly, Weigers et al. have shown that these bidirectional effects of corticosterone on different stages of T lymphocyte proliferation are mediated...
by opposing effects of corticosterone on IL-2 receptor (IL-2R) versus the cytokine itself (for review, see Wiegers and Reul 1998). Thus, during the early stages of lymphocyte proliferation, corticosterone induces an increase in IL-2Rα expression. This increases the IL-2 receptivity of lymphocytes and is reflected by an increase in lymphocyte proliferation (Wiegers et al. 1995). Although corticosterone reduces the production of IL-2 under these conditions, this decrease is not rate limiting at this stage since exogenously added IL-2 fails to increase proliferation. However, if corticosterone is administered at later stages, there is no enhancement in IL-2R expression, although suppression of the production of IL-2 still occurs. Under these conditions, the availability of IL-2 does become rate-limiting and hence corticosterone suppress the lymphoproliferative response. Thus, these studies indicate an important mechanism mediating an endogenous glucocorticoid-induced immuno-enhancement during the early stages of an immune response, and an endogenous glucocorticoid-induced immuno-suppression during the later stages.

In a series of seminal studies, Sternberg et al. (1989a) showed that decreased reactivity of the HPA axis to inflammatory stimuli results in increased susceptibility to experimental arthritis (Sternberg et al. 1989a, 1989b, 1992). A similar role for HPA axis-mediated endogenous immunoregulation has been shown for development of autoimmune thyroiditis, lupus erythematosus, and avian sclerderma in Obese strain (OS) chickens (Wick et al. 1998) and experimental autoimmune encephalomyelitis in rats (Whitacre et al. 1998). Sternberg and co-workers investigated the influence of the HPA axis on the development of streptococcal cell wall (SCW)-induced arthritis in female rats belonging to the genetically related Lewis/N (LEW/N) and Fischer 344/N (F344/N) strains (Sternberg and Wilder 1989; Sternberg et al. 1989a, 1989b; Webster et al. 2002). The F344/N strain is resistant to the development of SCW-induced arthritis whereas the LEW/N strain is susceptible. Interestingly, the F344/N strain mounts a significantly greater corticosterone response and adrenocorticotropic hormone (ACTH) response than does the LEW/N strain when challenged with a variety of stressors or with inflammatory mediators like SCW, peptidoglycan polysaccharide, or IL-1α (Sternberg et al. 1989a, 1989b; Dhabhar et al. 1993, 1995a), and compared to the F344 strain, the LEW strain shows a significantly greater habituation or adaptation to an acute or chronic stressor (Dhabhar et al. 1997). F344/N rats treated with the glucocorticoid receptor antagonist, RU486, are rendered susceptible to SCW-induced arthritis indicating that they do carry the immune-response genes with potential for triggering autoimmunity (Sternberg et al. 1989a, 1989b). Conversely, LEW rats treated with pharmacologic doses of dexamethasone, become completely resistant to the development of SCW-induced arthritis (Sternberg et al. 1989a, 1989b). Furthermore, compared to F344 rats, adrenal steroid receptors in neural and immune tissues of LEW rats show a significantly lower magnitude of activation in response to stress-induced increases in plasma corticosterone (Dhabhar et al. 1993, 1995a). Thus, differences in levels of plasma corticosterone among strains are also manifest as significant differences in the extent of activation of corticosterone receptors in target tissues.

Experimental allergic encephalomyelitis (EAE) is another animal model of an autoimmune disease in which a similar immuno-suppressive role for the HPA axis has been proposed (Mason et al. 1990; Mason 1991; Whitacre et al. 1998). The LEW strain shows a greater susceptibility to EAE (Mason 1991). MacKenzie et al. (1989) suggested that during the preclinical phase of EAE, elevations in plasma corticosterone may regulate the lymphoproliferative stage of the disease, and that during the clinical phase of the disease, elevations in plasma corticosterone as well as in splenic norepinephrine may regulate other recovery-oriented immune mechanisms (MacKenzie et al. 1989). Similar correlations between hyporeactivity of the HPA axis and susceptibility to autoimmune disease have been observed for autoimmune conditions in chickens (Wick et al. 1998), and mice (Lechner et al. 1996). In an elegant series of studies using an EAE model, del Rey et al. (1998) demonstrated that a pro-inflammatory/autoimmune response itself stimulates the HPA axis primarily through cytokines like IL-1, and that activation of the HPA axis is independent of the stress and discomfort associated with EAE-induced paralysis.

Complementing these preclinical studies, a series of elegantly conducted clinical studies (Torpy and Chrousos 1996; Buske-Kirschbaum and Hellhammer 2003) have shown that patients with atopic dermatitis (Buske-Kirschbaum et al. 1997, 1998, 2001), and asthma (Buske-Kirschbaum et al. 2003) show decreased reactivity of their HPA axis (Priftis et al. 2008). Studies of pediatric rheumatic diseases suggest a similar deficiency of the HPA axis coupled with other pro-inflammatory hormonal biases (Chikanza et al. 2000). Differences in reactivity of NK cells to stress and upregulation of β (2)-adrenoreceptors on
conditions of high allostatic load are likely to result in dysregulation or suppression of immune function. Importantly, a disruption of the circadian corticosterone/cortisol rhythm may be an indicator and/or mediator of distress or high allostatic load (Dhabhar and McEwen 1997; Sephton et al. 2000). The Stress Spectrum also proposes that acute or chronic stress occur on a background psycho-physiological HEALTH MAINTENANCE EQUILIBRIUM (Fig. 1). We define RESILIENCE as the extent and efficiency with which an organism returns to its health-maintenance equilibrium after experiencing stress, i.e., the capacity of psychophysiological systems to recover from challenging conditions (Fig. 1). Factors such as coping mechanisms, sense of control, optimism, social support, early life experiences, learning, genetics, and sleep may be important contributors to PSYCHOLOGICAL RESILIENCE (Fig. 1). Factors such as neuro-endocrine reactivity, genetics, environment, nutrition, and sleep may be important components of PHYSIOLOGICAL RESILIENCE (Fig. 1). The psychophysiological basis of resilience (Charney 2004) and reserve capacity are under-investigated and provide an important opportunity for future research.

The Stress Spectrum, taken together with the preceding discussion, shows that the duration, intensity/concentration, and timing of exposure to stressor-induced physiological activation (neurotransmitters, hormones, and their molecular, cellular, organ-level, and systemic effects) are critical for determining whether stress will enhance or suppress/dysregulate immune function. The model shows that the stressor itself can be acute or chronic (Fig. 1). Perception and evaluation of stress by the brain, and mechanisms mediating psychological and physiological resilience are critical for determining the duration and magnitude of physiological responses to stress (Fig. 1). Mechanisms of psychological resilience are especially important for humans because these mechanisms can limit the duration and magnitude, and potentially, the deleterious effects, of chronic stress. Psychogenic stressors are also very important in human subjects because such stressors can generate physiological responses to stress long after exposure to the stressor (e.g., posttraumatic stress disorder following a severe traumatic experience, or in a milder form, lingering anger/mood disturbance following a social altercation) or even in the absence of a physical stressor or salient threat (e.g., worrying about whether one’s romantic feelings will be reciprocated). Therefore, following exposure to a stressor and stress perception and processing by the brain, there ensues a PHYSIOLOGICAL STRESS RESPONSE. This response may consist of acute or chronic physiological

The stress-immune spectrum

It is often overlooked that a psycho-physiological response to stress has salubrious adaptive effects in the short run (Dhabhar et al. 1995b; Dhabhar and McEwen 1996, 1999, 2006; Dhabhar and Viswanathan 2005; Viswanathan and Dhabhar 2005; Dhabhar 2008) although stress can be harmful when it is long-lasting (Dhabhar and McEwen 1997; McEwen 1998; Sapolsky et al. 2000; Glaser and Kiecolt-Glaser 2005). In order to reconcile these seemingly contradictory effects of stress, we proposed that a stress response and its effects on immune function be viewed in the context of a STRESS SPECTRUM (Dhabhar and McEwen 1997, 2001) (Fig. 1). One region of this spectrum is characterized by ACUTE STRESS or EUSTRESS, i.e., conditions of short-duration stress that activate the survival-promoting aspects of the fight-or-flight response, and result in immuno-preparatory, or immuno-enhancing physiological conditions. An important characteristic of acute stress is a rapid physiological response mounted in the presence of the stressor, followed by a rapid shut-down of the response upon cessation of the stressor. The opposite region of the stress spectrum is characterized by CHRONIC STRESS or DISTRESS, i.e., repeated or prolonged stress that may result in dysregulation or suppression of immune function. An important characteristic of chronic stress is that the physiological response either persists long after the stressor has ceased, or is activated repeatedly to result in an overall integrated increase in exposure of the organism to stress hormones. The concept of “allostatic load” has been proposed to define the “psychophysiological wear and tear” that takes place while different biological systems work to stay within a range of equilibrium (allostasis) in response to demands placed by internal or external chronic stressors (for review see McEwen 1998, 2002) We suggest that conditions of high allostatic load are likely to result

peripheral blood mononuclear cell have been observed in patients with systemic lupus erythematosus (Pawlak et al. 1999). A more complex role for involvement of the sympathetic nervous system in autoimmune disease has also been proposed (Kuis et al. 1996; Kavelaars et al. 1998). It has also been hypothesized that under certain conditions, glucocorticoid hormones may suppress certain autoimmune reactions by inducing a shift toward a TH2 or humoral immune response (Mason et al. 1990; Mason 1991; Chrousos 2000; Elenkov 2004; Elenkov and Chrousos 2006).
activation (neurotransmitters, hormones, and their molecular, cellular, organ-level, and systemic effects) that results in PSYCHO-PHYSIOLOGICAL STATES that have different effects on overall health and immune function (Fig. 1). While there is significant supporting evidence from animal studies, this model needs to be further examined and tested in studies involving human subjects.

**Summary and implications**

Due to a host of psycho-socio-political and environmental factors, stress has become an increasing and inevitable part of the lives of most living organisms. Stress is also a major factor during the diagnosis, treatment, and follow-up, for most diseases. Chronic stress has been shown to dysregulate immune function and is thought to play a role in the etiology of many diseases. In contrast, it has been shown that activation of acute stress physiology may enhance protective immune responses (Dhabhar et al. 1995b; Dhabhar and McEwen 1996; Dhabhar and Viswanathan 2005; Viswanathan et al. 2005).

It is important to recognize that humans, as well as animals, experience stress as an intrinsic part of life, and in conjunction with many standard diagnostic, clinical, and experimental manipulations. Unintended stressors may significantly affect experimental and clinical measurements, as well as overall health outcomes. Thus, when conducting clinical, diagnostic, or experimental procedures, it is important to account for the effects of acute and chronic stress on the specific physiologic parameter or health outcome being measured. For example, it is critical to elucidate and account for the effects of stress and/or stress hormones on changes in the distribution of leukocytes within different compartments of the body. Where possible, redistribution needs to be monitored in terms of changes in absolute numbers of specific sub-populations of leukocytes as these changes can significantly affect results (in the case of experiments), diagnosis (in the case of medical tests), or outcome (in the case of treatments and surgery).

Accurately assessing the resting-state baseline and the activated acute and/or chronic states of stress, is also important for psycho-neuro-endocrine-immune studies in wild- or free-ranging animals because such animals are likely to mount a tremendous acute stress response when they are initially trapped and captured, followed by a chronic stress response if retained in captivity. As a result, the true baseline state of a wild-caught animal is fleeting, and may only be determined if it is accurately assessed within a few minutes of the animal being disturbed from a resting state (e.g., sleeping or grooming under relatively sedentary conditions). Yet, accurately determining baseline physiological, endocrine, and immune parameters is critical for subsequently understanding the effects of acute or chronic stress. Ensuring that wild- or free-ranging animals habituate or acclimatize to captive conditions and regain states that approximate resting baselines, although difficult, is important for long-term studies.

**Conclusion**

It is critically important to further study, and attempt to positively harness, the adaptive effects of the fight-or-flight response (that evolution has finely sculpted into a survival mechanism) to acute stress, just as it is to understand and counter the maladaptive effects of chronic stress (that evolution has yet to resolve). An integrative and comparative approach directed toward elucidating the mechanisms whereby stress can enhance or suppress immune responses may be crucial for understanding and countering the negative effects of environmental stressors on numerous organisms. In the clinical setting, increased understanding of mechanisms used in coping with stress, and/or buffering the effects of stress, may be crucial for elucidating risk, and developing preventative and therapeutic interventions designed to harness an individual’s psychophysiology to selectively enhance (during vaccination, wounding, infections, or cancer) or suppress (during autoimmune or inflammatory disorders) the immune response, depending on the intended outcome that would be most beneficial for the patient.

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