Enhancing versus Suppressive Effects of Stress on Immune Function: Implications for Immunoprotection and Immunopathology

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Key Words

Acute stress-induced enhancement • Fight-or-flight stress • Immune cell distribution • Immune function, effects of stress • Immune function, enhancing vs. suppressive effects • Immunoprotection vs. immunopathology • Innate/primary immune responses • Leukocyte trafficking • Adaptive/secondary immune responses

Abstract

Stress is known to suppress immune function and increase susceptibility to infections and cancer. Paradoxically, stress is also known to exacerbate asthma, and allergic, autoimmune and inflammatory diseases, although such diseases should be ameliorated by immunosuppression. Moreover, the short-term fight-or-flight stress response is one of nature's fundamental defense mechanisms that enables the cardiovascular and musculoskeletal systems to promote survival, and it is unlikely that this response would suppress immune function at a time when it is most required for survival (e.g. in response to wounding and infection by a predator or aggressor). These observations suggest that stress may suppress immune function under some conditions while enhancing it under others. The effects of stress are likely to be beneficial or harmful depending on the type (immunoprotective, immunoregulatory/inhibitory, or immunopathological) of immune response that is affected. Studies have

shown that several critical factors influence the direction (enhancing vs. suppressive) of the effects of stress or stress hormones on immune function: (1) *Duration (acute vs. chronic) of stress*: Acute or short-term stress experienced at the time of immune activation can enhance innate and adaptive immune responses. Chronic or long-term stress can suppress immunity by decreasing immune cell numbers and function and/or increasing active immunosuppressive mechanisms (e.g. regulatory T cells). Chronic stress can also dysregulate immune function by promoting proinflammatory and type-2 cytokine-driven responses. (2) *Effects of stress on leukocyte distribution*: Compartments that are enriched with immune cells during acute stress show immunoenhancement, while those that are depleted of leukocytes, show immunosuppression. (3) *The differential effects of physiologic versus pharmacologic concentrations of glucocorticoids, and the differential effects of endogenous versus synthetic glucocorticoids*: Endogenous hormones in physiological concentrations can have immunoenhancing effects. Endogenous hormones at pharmacologic concentrations, and synthetic hormones, are immunosuppressive. (4) *The timing of stressor or stress hormone exposure relative to the time of activation and time course of the immune response*: Immunoenhancement is observed when acute stress is experienced at early stages of immune activation, while immunosuppression may be observed at late stages of the immune response. We propose that it is important to study and, if

possible, to clinically harness the immunoenhancing 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. In view of the ubiquitous nature of stress and its significant effects on immunoprotection as well as immunopathology, it is important to further elucidate the mechanisms mediating stress-immune interactions and to meaningfully translate findings from bench to bedside.

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Introduction

Numerous studies have demonstrated adverse effects of stress on health [1, 2]. These studies show that chronic or long-term stressors can have health-aversive effects, some of which are mediated through immune mechanisms. However, it is also important to appreciate that a psychophysiological stress response 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 escape. During such short-term stress responses observed in nature, physiological systems act in synchrony to enable survival. 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 (e.g. wounding or infection) that may be imposed by a stressor (e.g. predator or surgical procedure) [3, 4]. Studies have shown that short duration stressors 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 psychophysiological adjuvant that enhances immune responses and may have evolved by virtue of the fact that many stressful situations (aggression, accident) result in immune activation (wounding, infection) and vice versa. Interestingly, in modern times, many situations involving immune activation (vaccination, surgery, injury) also induce a stress response. It is also important to recognize that while acute stress-induced immunoenhancement may serve to increase immunoprotection during exposure to infectious agents or wounding, it may also

exacerbate immunopathology if the enhanced immune response is directed against innocuous or self-antigens, or dysregulated following prolonged activation as seen during chronic stress.

In contrast to acute stress, chronic stress has been shown to dysregulate immune responses [5, 6] by altering the cytokine balance from type-1 to type-2 cytokine-driven responses [7] and accelerating immunosenescence [8], and to suppress immunity by decreasing numbers [9], trafficking [9], and function of protective immune cells while increasing regulatory/suppressor T cells [10]. This paper discusses the effects of stress on immune function and implications of these effects for immunoprotection versus immunopathology.

Stress: Definition, Mediators, and Individual Differences

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 [11–13]. 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' [13]. 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), that activates physiological fight-or-flight systems in the body (stress response) [9]. It is important to understand that the only way that a stressor can affect the brain or body is by inducing biological changes in the organism. Therefore, the physiological stress response is critical for mediating the effects of stress on health. 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 in the systemic circulation during psychological stress [14]. The major mediators of stress effects are norepinephrine and epinephrine that are released by the sympathetic nervous system, and corticotropin-releasing hormone, adrenocorticotropin (ACTH), and cortisol, that make up the hypothalamic-pituitary-adrenal (HPA)

axis. Since virtually every cell in the body expresses receptors for one or more of these factors, they can induce changes in almost all cells and tissues and inform them about the presence of a stressor.

Although stress can be harmful when it is chronic or long-lasting [1, 5, 6, 15], it is often overlooked that a stress response has salubrious adaptive effects in the short run [16, 17]. Therefore, major distinguishing characteristics of stress are duration and intensity. *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 [9]. Dysregulation of the circadian cortisol rhythm is one marker that appears to coincide with the deleterious effects of chronic stress [9, 10, 18]. The intensity of stress may 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 for which these changes persist during stress and following the cessation of stress. It is important to note that significant individual differences in stress perception, processing, and coping have been observed [17, 19]. Individual differences become particularly relevant while studying human subjects because stress perception, processing, and coping mechanisms 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. Animal studies showing significant strain differences in stress reactivity and peak hormone levels [20, 21], adaptation to stress [22], and in distribution and activation of adrenal steroid receptors and corticosteroid-binding globulin levels [20, 23], suggest that genetic as well as environmental factors play a role in establishing individual differences [20, 22–24]. 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 immune cell distribution and function [4, 25, 26].

Immune Responses Defined in Terms of Their End Effects: Immunoprotective, Immunopathological, and Immunoregulatory/Inhibitory

While discussing immune responses, it is useful to categorize 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 categorized as being immunoprotective, immunopathological, and immunoregulatory/inhibitory. It is important to bear in mind that while all these categories provide useful constructs with which to organize ideas, concepts and models, an overall *in vivo* immune response is likely to consist of several types of responses with varying amounts of dominance from each category. Each of the proposed end-effect-based categories is defined below:

Immunoprotective responses are defined as responses that promote efficient wound healing, eliminate viral infections and cancer, and mediate vaccine-induced immunological memory. Key characteristics of immunoprotection involve active immune surveillance, a rapid and robust response upon immune activation, efficient clearance of the activating agent or pathogen, followed by rapid resolution of inflammation. Immunoprotective responses are critical for completion of the proliferative and remodeling phases of wound healing. Wound healing 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 tissue damage. Innate and/or adaptive type-1 or type-2 immune responses can all confer immunoprotection depending on the type of the pathogen (viral, bacterial, protozoan, fungal, helminthic), on whether it is intra- or extracellular, and on the accompanying wounding conditions (e.g. sterile, infected, external or internal).

Immunopathological responses are defined as those that are directed against self- (autoimmune disease like multiple sclerosis, arthritis, lupus) or innocuous antigens (asthma, allergies) and responses that involve chronic, non-resolving inflammation. Immunopathology is also involved during low-level, long-term elevations in local and/or systemic inflammatory mediators that are thought to contribute to disorders like cardiovascular disease, obesity, and depression [27–29].

Immunoregulatory/inhibitory responses are defined as those that involve immune cells and factors that inhibit the function of other immune cells. Although the previous concept of suppressor T cells became mired in controversy, recent studies suggest that there is an arm of the immune system that functions to inhibit immune

responses. Regulatory CD4+CD25+FoxP3+ T cells, interleukin (IL)-10, and TGF- β have been shown to have immunoregulatory/inhibitory functions. The physiological function of these factors is to keep proinflammatory, allergic, and autoimmune responses in check [30]. However, it has also been suggested that immunoregulatory/inhibitory factors may suppress antitumor immunity and be indicative of negative prognosis for cancer [31].

Factors That May Determine Whether Stress Will Enhance or Suppress Immune Function and the Potential Health Consequences of These Effects of Stress

Several critical factors are likely to influence the direction (enhancing vs. suppressive) of the effects of stress or stress hormones, and the nature of the immune response (immunoprotective, immunoregulatory/inhibitory, or immunopathological) that is affected. These include: (1) the effects of stress on leukocyte distribution in the body; (2) the duration (short-term/acute vs. 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, corticosterone) versus synthetic (e.g. dexamethasone) glucocorticoids, and (4) the timing of stressor or stress hormone exposure 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 affects the health of the organism or individual (fig. 1). Given the definitions in the preceding section, stress-induced enhancement of immunoprotection is likely to have beneficial effects while stress-induced suppression of immunoprotection is likely to be harmful. Similarly, stress-induced enhancement of immunopathology or long-term proinflammation is also likely to be harmful. Finally, stress-induced enhancement of active immunoregulation/inhibition is likely to be beneficial in case of autoimmune and proinflammatory disorders and harmful in case of infections and cancer.

Stress-Induced Changes in Immune Cell Distribution

Effective immunoprotection requires rapid recruitment of leukocytes into 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 [32]. The numbers and proportions of leukocytes in the blood provide an important representation of the state of distribution of leukocytes in the body and of the state of activation of the immune system. The ability of acute stress to induce changes in leukocyte distribution within different body compartments is perhaps one of the most underappreciated effects of stress and stress hormones on the immune system [3].

Numerous studies have shown that stress and stress hormones induce significant changes in absolute numbers and relative proportions of leukocytes in the blood. In fact, changes in blood leukocyte numbers were used as a measure of stress before methods were available to directly assay the hormone [33]. Studies have also shown that glucocorticoid [34, 35] and catecholamine hormones [26] 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 blood leukocyte numbers have been reported in numerous species including humans [3, 36–40]. This suggests that the phenomenon of stress-induced leukocyte redistribution has a long evolutionary lineage, and that perhaps it has important functional significance.

Studies have shown that stress-induced changes in blood leukocyte numbers are characterized by a significant decrease in numbers and percentages of lymphocytes and monocytes, and by an increase in numbers and percentages of neutrophils [3, 37]. Flow cytometric analyses revealed 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 [3]. Moreover, it has been shown that stress-induced changes in leukocyte numbers are rapidly reversed upon the cessation of stress [3]. In apparent contrast to animal studies, human studies have shown that stress increases rather than decreases blood leukocyte numbers [39, 41, 42]. This apparent contradiction may be resolved by taking the following factors into consideration: First, stress-induced increases in blood leukocyte numbers in humans have been studied using stress conditions which result in the activation of primarily the sympathetic nervous system. These stressors are often of

Fig. 1. The relationship among stress, immune function, and health outcomes. Acute stress experienced during vaccination, wounding, or infection may enhance immunoprotective responses. Acute stress experienced during immune activation in response to self/innocuous antigens or allergens may exacerbate proinflammatory and autoimmune disorders. Chronic stress-in-

duced increases in proinflammatory or type-2 cytokine-mediated immune responses may also exacerbate inflammatory and autoimmune disease. Chronic stress-induced suppression of immune responses may decrease the efficacy of vaccination and wound healing and decrease resistance to infection and cancer.

a short duration (few minutes) or relatively mild (e.g. public speaking) [39, 41, 42]. Second, the increase in total leukocyte numbers may be accounted for mainly by stress- or catecholamine-induced increases in granulocytes and NK cells [26, 39, 41, 42]. Third, stress or pharmacologically-induced increases in glucocorticoid hormones induce a significant decrease in blood lymphocyte and monocyte numbers [33, 35, 39]. Thus, stress 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 blood leukocyte numbers [4]. Stress conditions that result in activation of the sympathetic nervous system, especially conditions that induce high levels of norepinephrine, may induce an

increase in circulating leukocyte numbers. These conditions may occur during the beginning of a stress response, very-short-duration stress (order of minutes), mild psychological stress, or during exercise. In contrast, stress conditions that result in the activation of the HPA axis induce a decrease in circulating leukocyte numbers. These conditions often occur during the later stages of a stress response, long-duration acute stressors (order of hours), or during severe psychological, physical or physiological stress. An elegant and interesting example in support of this hypothesis comes from Schedlowski et al. [39] who measured changes in blood T-cell and NK cell numbers as well as plasma catecholamine and cortisol levels in parachutists. Measurements were made 2 h before, immediately after, and 1 h after the jump. Results showed a significant increase in T-cell and NK cell num-

bers 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 [39]. Importantly, changes in NK cell activity and antibody-dependent cell-mediated cytotoxicity closely paralleled changes in blood NK cell numbers, thus suggesting that changes in leukocyte numbers may be an important mediator of apparent changes in leukocyte 'activity'. Similarly, Rinner et al. [43] have shown that a short stressor (1 min 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. [44] showed that acute psychological stress induced a significant increase in blood CTL numbers 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, margined pool and other organs) and enter the 'boulevards' (blood vessels and lymphatics). This results in an increase in blood leukocyte numbers, 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, gastrointestinal and urinary-genital tracts, mucosal surfaces, and lymph nodes) in preparation for immune challenges which may be imposed by the actions of the stressor [3, 4, 45]. Such a redistribution of leukocytes results in a decrease in blood leukocyte numbers. 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 blood immune parameters might reflect in vivo immune function in the context of the specific experiments or study at hand. Moreover, since most blood collection procedures 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 blood leukocyte distribution become a factor of considerable importance.

Dhabhar et al. [37, 46] were the first to propose that stress-induced changes in blood leukocyte distribution may represent an adaptive response. They suggested that acute stress-induced changes in blood leukocyte numbers represent a redistribution of leukocytes from the blood to organs such as the skin, draining sentinel lymph nodes, and other compartments [4, 45]. They hypothesized that such a leukocyte redistribution 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 [45–47].

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. 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 cell-mediated immunity (CMI) [16, 45]. In what might at first glance appear to be contradicting results, acute stress has been shown to suppress splenic and peripheral blood responses to T-cell mitogens [48] and splenic IgM production [49]. 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 [50]. This stress-induced decrease in blood and spleen leukocyte numbers 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 immunosuppressive effect of chronic stress [9]. Again, in what might appear to be contradicting results, chronic stress has been shown to enhance mitogen-induced proliferation of splenocytes [51] and splenic IgM production

[49]. 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 [52], 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 [3] 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, antibody production) and/or through leukocyte redistribution 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 and Dhabhar [53] 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 or the surgical sponge showed a two- to threefold higher neutrophil, macrophage, NK cell and T-cell infiltration than non-stressed animals. Leukocyte infiltration was evident as early as 6 h and peaked between 24 and 48 h. Importantly, at 72 h, sponges from non-stressed 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 proinflammatory cytokine, tumor necrosis factor- α (TNF- α), and lymphocyte-specific chemokine, lymphotactin (LTN). Acute stress significantly increased infiltration of macro-

phages, 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-, or pathogen-driven chemoattractants synergizing with acute stress to further determine the specific subpopulations that are recruited [53]. 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 by which acute stressors alter the course of different (innate vs. adaptive, early vs. late, acute vs. 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 [16]. 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 immunoenhancement 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 γ -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 psychologi-

cally and/or pharmacologically manipulated to safely increase vaccine efficacy.

In a series of elegant experiments, Saint-Mezard et al. [54] 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 the effects of acute stress in this case were mediated primarily by norepinephrine [54]. Other investigators have similarly reported stress-induced enhancement of type-1 cytokine-driven CMI [55–57] and type-2 cytokine-driven humoral immunity [57, 58].

Viswanathan et al. [59] further elucidated the molecular and cellular mediators of the immunoenhancing effects of acute stress. They showed that compared to non-stressed mice, acutely stressed animals showed significantly greater pinna swelling, leukocyte infiltration, and upregulated macrophage chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-3 α (MIP-3 α), IL-1 α , IL-1 β , 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 immunoenhancement 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 proinflammatory reactions, the above-mentioned studies provide further support for the idea 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.

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 antigen re-exposure can also enhance secondary or recall responses in skin [45]. Compared to non-stressed controls, mice that were acutely stressed at the time of antigen re-exposure 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. [55] reported a similar stress-induced enhancement of CHS reactions in mice, and Flint et al. [60] showed that acute stress enhanced CHS responses in both male and female mice and that immunoenhancement was partially dependent on glucocorticoid hormones, and a stress-induced enhancement of the elicitation phase of skin CMI has also been reported in hamsters [36]. Taken together, studies show that acute stress can significantly enhance the immunization/sensitization/induction 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, immunoenhancing 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 immunoenhancement [46]. Adrenalectomy, which eliminates the glucocorticoid and epinephrine stress response, eliminated the stress-induced enhancement of skin CMI. Low-dose corticosterone or epinephrine administration significantly enhanced skin CMI [46]. In contrast, high-dose corticosterone, chronic corticosterone, or low-dose dexamethasone administration significantly suppressed skin CMI. These results suggested a novel role for adrenal stress hormones as endogenous immunoenhancing agents. They also showed that stress hormones released during a circumscribed or acute 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. Studies by Flint et al. [60] have also suggested that corticosterone is a mediator of the stress-induced enhancement of skin CHS, while Saint-Mezard et al. [54] have suggested that the adjuvant-like effects of stress on dendritic cell and CD8⁺ T-cell migration and function are mediated by norepinephrine.

Studies have also examined the immunological mediators of an acute stress-induced enhancement of skin immunity. Since IFN- γ is a critical cytokine mediator of CMI and delayed as well as CHS, studies were conducted to examine its role as a local mediator of the stress-induced enhancement of skin CMI [47]. The effect of acute stress on skin CMI was examined in wild-type and IFN- γ receptor gene knockout mice (IFN- γ R^{-/-}) that had been sensitized with 2,4-dinitro-1-fluorobenzene (DNFB). Acutely stressed wild-type mice showed a significantly larger CMI response than non-stressed mice. In contrast, IFN- γ R^{-/-} mice failed to show a stress-induced enhancement of skin CMI. Immunoneutralization of IFN- γ in wild-type mice significantly reduced the stress-induced enhancement of skin CMI. In addition, an inflammatory response to direct IFN- γ administration was significantly enhanced by acute stress. These results showed that IFN- γ is an important local mediator of a stress-induced enhancement of skin CMI [47]. In addition to IFN- γ , TNF- α , MCP-1, MIP-3 α , IL-1, and IL-6 have also been associated with a stress-induced enhancement of the immunization/sensitization phase of skin CMI [16, 59]. 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.

Acute Stress Psychophysiology 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) [45, 50]. 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 [16]. In keeping with this hypothesis, studies conducted by our group have shown that patients undergoing knee surgery, who show a robust and adaptive immune cell redistribution profile during the acute stress of surgery, also show significantly enhanced recovery. Similarly, studies conducted by Edwards et al. [61, 62] have shown that acute stressors can enhance vaccine-induced humoral and CMI in human subjects. 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 vaccine efficacy. 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.

Chronic Stress Can Suppress Immunoprotection, While Enhancing Immunopathological and Immunoregulatory/Suppressive Responses

In contrast to acute stressors, chronic stress has been shown to suppress type-1 cytokine-driven protective immune responses while enhancing proinflammatory and type-2 cytokine-driven immune responses [5]. Chronic stress also appears to mobilize immunoregulatory/inhibitory mechanisms [10]. Therefore, chronic stress is likely to exacerbate proinflammatory diseases and increase susceptibility to infections and cancer. Dhabhar and McEwen [9] conducted studies designed to examine 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. These studies showed that acute stress administered for 2 h prior to antigenic challenge significantly enhanced skin CMI [9]. Increasing the duration of stress from 2 to 5 h produced the same magnitude immunoenhancement. 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, or continued an additional week until challenge, or extended for 1 week after challenge [9]. Interestingly, acute stress-induced redistribution of peripheral blood lymphocytes was attenuated with increas-

ing duration of stressor exposure and correlated with attenuated glucocorticoid responsivity. These results suggested that stress-induced alterations in lymphocyte redeployment may play an important role in mediating the bidirectional effects of stress on cutaneous CMI [9]. An association between chronic stress and reduced skin CMI has also been reported in human subjects [63].

Given the importance of cutaneous CMI in elimination of immunoresponsive tumors like squamous cell carcinoma (SCC) [64, 65], Saul et al. [10] examined the effects of chronic stress on susceptibility to ultraviolet (UV) radiation-induced SCC. Mice were exposed to a minimal erythral dose of UVB three times a week for 10 weeks. Half of the UVB-exposed mice were left non-stressed (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. mRNA expression of IL-12p40, IFN- γ , IL-4, IL-10, CD3 ϵ , and CCL27/CTACK, the skin T-cell-homing chemokine, 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 vs. 16.5 weeks) and reached 50% incidence earlier than controls (15 vs. 21 weeks). Stressed mice also had lower IFN- γ , CCL27/CTACK, and CD3 ϵ gene expression and lower CD4+ and CD8+ T cells infiltrating within and around tumors than non-stressed mice. In addition, stressed mice had higher numbers of tumor infiltrating and circulating CD4+CD25+ suppressor cells than non-stressed 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 immunosuppression through regulatory/suppressor T cells [10]. In addition, chronic stress has also been shown to suppress several other indices of immunoprotection [15, 66] and to enhance proinflammatory and type-2 cytokine-driven conditions and disorders [7, 67].

Bidirectional Effects of Glucocorticoid Hormones on Immune Function

In contrast to the well-known immunosuppressive effects of glucocorticoids, several studies have revealed that glucocorticoid hormones also exert immunomodulating [68] and immunoenhancing effects [17, 69]. In general,

pharmacological concentrations of glucocorticoids exert immunosuppressive effects, whereas under different conditions, physiologic concentrations may exert immuno-modulatory, immunoenhancing, or immunosuppressive effects. It is important to recognize that the source (natural vs. synthetic) and concentration (physiologic vs. pharmacologic) of glucocorticoid hormones, the effects of other physiologic factors (hormones, cytokines, and neurotransmitters), and the state of activation of an immune parameter (naive vs. activated leukocyte, early vs. late activation, etc.) are all important factors which ultimately determine the nature of the effects of glucocorticoids on a given immune response. Immunoenhancing effects of glucocorticoids are discussed below, whereas immunosuppressive effects are discussed in the following section.

Acute stress-induced enhancement of skin CMI is mediated by adrenal stress hormones [46]. Adrenalectomy, which eliminates the glucocorticoid and epinephrine stress response, eliminated the stress-induced enhancement of skin CMI. Low-dose corticosterone or epinephrine administration significantly enhanced skin CMI and produced a significant increase in T-cell numbers in lymph nodes draining the site of the CMI reaction [46]. Moreover, simultaneous administration of these two stress hormones produced an additive increase in the skin CMI response. These results showed that hormones released during an acute 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 [46].

A permissive role for glucocorticoids in antibody production was described over 30 years ago. Several investigators reported that low levels of cortisol were a necessary factor in cell culture media in order to obtain in vitro antibody production [70]. Moreover, glucocorticoids were determined to be the critical permissive component present in serum supplements of culture media, and it was suggested that variability in antibody production assays may be the result of variability of glucocorticoid content in different batches of serum [70]. Under some conditions, glucocorticoids have been shown to shift the balance of an immune response towards humoral immunity [71–73]. Physiological doses of glucocorticoids have been shown to enhance immunoglobulin production by mitogen-stimulated human lymphocytes in culture [74], and glucocorticoids have been shown to stimulate B-cell number and antibody production in vitro and in vivo [75].

Studies examining the effects of corticosterone on T-lymphocyte proliferation *in vitro* demonstrate an important mechanism by which corticosterone may mediate the enhancement of immune function [76]. These studies have shown that during the early stages of T-cell activation, low levels of corticosterone potentially enhance anti-T-cell receptor (TCR)-induced lymphocyte proliferation. Furthermore, they showed that corticosterone had to be present during the process of TCR activation in order to enhance the proliferative response. Other studies have suggested that low concentration corticosterone-induced enhancement of concanavalin A-stimulated mitogenesis of splenocytes from ADX animals may be mediated by the type-1 or mineralocorticoid receptor [77]. Finally, it was shown that corticosterone increases T-cell responsiveness to IL-2 and proliferation under conditions of high cell densities *in vitro*, that mimic conditions that are likely to be found in lymph nodes *in vivo* [78]. Thus, these *in vitro* studies indicate a possible mechanism by which stress and stress hormones may enhance immune function *in vivo*.

Several lines of evidence indicate that glucocorticoid stress hormones may act synergistically with cytokines to enhance specific immune reactions. Thus, while glucocorticoids inhibit the synthesis of cytokines under some conditions, they have also been shown to induce the release and potentiate the actions of cytokines under other conditions. For example, acute psychological stress has been shown to increase circulating TNF- α , IL-1 β and IL-10 levels in human subjects [14] and acute stress increases circulating IL-1 β and IL-6 in rodents [79, 80]. Glucocorticoids have been shown to induce the production of migration inhibitory factor [81]. Moreover, glucocorticoids synergistically enhance the induction of acute-phase proteins by IL-1 and IL-6 [82]. Glucocorticoids similarly enhance the biological responses of other cytokines such as IL-2, IFN- γ , granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, and oncostatin M [for review, see 83].

Synergistic interactions between glucocorticoids and cytokines may be mediated by glucocorticoid-induced upregulation of cytokine receptors on target cells as determined by increased cytokine binding or cytokine receptor mRNA expression. For example, glucocorticoid-induced TNF receptor has been shown to promote survival and serve as a costimulatory receptor for T cells [84, 85], and glucocorticoids increase IL-1 binding to human peripheral blood B cells [86]. Glucocorticoids also act synergistically with IFN- γ to induce high-affinity Fc γ receptors on human monocytic cell lines [87] and stress-

induced increases in endogenous glucocorticoids also appear to facilitate the expression of low-affinity Fc γ receptors on peritoneal macrophages [88]. While some studies have reported that glucocorticoids inhibit IL-2 receptor (IL-2R) expression in leukocytes [89], a recent study indicates that the reduced IL-2R expression is secondary to glucocorticoid suppression of IL-2 [90]. In contrast, studies have found a stimulating effect of glucocorticoids on IL-2 induction of IL-2R mRNA levels in several T-cell lines [91].

Several books and articles have extensively reviewed the anti-inflammatory or immunosuppressive effects of glucocorticoid hormones [92–94]. It is apparent from these reviews that under specific conditions, glucocorticoids have been shown to suppress immunoglobulin, prostaglandin, leukotriene, histamine, and cytokine production, neutrophil superoxide production, macrophage function, mitogen- and antigen-induced lymphocyte proliferation, lymphocyte differentiation, NK cell activity and leukocyte migration and activation. Due to their potentially immunosuppressive actions, glucocorticoids are widely used in the clinic as anti-inflammatory agents [93].

It has been hypothesized that an important physiologic role of endogenous glucocorticoids might be to suppress an ongoing immune response so as to prevent it from reaching levels of reactivity which might cause damage to self [21, 92, 95, 96]. Strong support for this hypothesis comes from studies that show that adrenalectomized rats die within 24–48 h after being immunized with horse serum or Freund's complete adjuvant, but they can be rescued by corticosterone replacement therapy [97]. A number of studies involving animal models of inflammatory disorders and autoimmune disease also lend support for this hypothesis [73]. These studies have demonstrated the existence of a negative feedback loop between the immune system and the HPA axis, such that proinflammatory mediators arising from an ongoing immune reaction stimulate the HPA axis [92, 98, 99], which in turn results in the secretion of corticosterone which suppresses the immune response and prevents it from potentially damaging the host. The protective effects of immunosuppression by endogenous glucocorticoids are discussed below.

Immunomodulatory Effects of Timing of Stress or Stress Hormone Administration 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 immunoenhancing 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 very 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 immunoenhancement. In contrast, at a later, more advanced stage of an immune response these components may be more receptive to glucocorticoid-mediated immunosuppression. 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 [76]. 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. Furthermore, Wiegers et al. [76] 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 more than 2 h after the initiation of TCR activation, the enhancement of lymphoproliferation was not observed.

Interestingly, Wiegers and Reul [for review, see 83] have shown that these bidirectional effects of corticosterone on different stages of T-lymphocyte proliferation are mediated by opposing effects of corticosterone on IL-2R versus the cytokine itself. Thus, during the early stages of lymphocyte proliferation, corticosterone induces an increase in IL-2R α expression. This increases the IL-2 receptivity of lymphocytes and is reflected by an increase in lymphocyte proliferation [76]. Although corticoste-

rone 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, the enhancement in IL-2R expression is absent, while the suppression of IL-2 production is still present. Under these conditions, the availability of IL-2 does become rate-limiting and hence corticosterone suppresses the lymphoproliferative response. Thus, these studies indicate an important mechanism mediating an endogenous glucocorticoid-induced immunoenhancement during the early stages, and an endogenous glucocorticoid-induced immunosuppression during the later stages of an immune response.

In a series of seminal studies, Sternberg et al. [21, 100, 101] showed that decreased HPA axis reactivity to inflammatory stimuli results in increased susceptibility to experimental arthritis. A similar role for HPA axis-mediated endogenous immunoregulation has been shown for development of autoimmune thyroiditis, lupus erythematosus, and avian scleroderma in obese-strain (OS) chickens [102]. Sternberg et al. [21, 95, 96, 100] 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. 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 and ACTH response than the LEW/N strain when challenged with a variety of stressors or with inflammatory mediators like SCW peptidoglycan polysaccharide, or IL-1 α [20, 21, 23, 100], and compared to the F344 strain, the LEW strain shows a significantly greater habituation or adaptation to an acute or chronic stressor [22]. F344/N rats treated with the glucocorticoid receptor antagonist, RU-486, are rendered susceptible to SCW-induced arthritis indicating that they do carry the immune response genes with potential for triggering autoimmunity [21, 100]. Conversely, LEW rats treated with pharmacologic doses of dexamethasone become completely resistant to the development of SCW-induced arthritis [21, 100]. 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 [20, 23]. Thus, strain differences in plasma corticosterone levels 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 immunosuppressive role for the HPA axis has been proposed [for review, see 73]. The LEW strain shows a greater susceptibility to EAE [73]. MacKenzie et al. [103] have 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 splenic norepinephrine may regulate other recovery-oriented immune mechanisms. Similar correlations between HPA axis hyporeactivity and susceptibility to autoimmune disease have been observed for autoimmune conditions in chickens [102]. In an elegant series of studies using an EAE model, del Rey et al. [104] demonstrated that a proinflammatory/autoimmune response itself stimulates the HPA axis primarily through cytokines like IL-1, and that HPA axis activation is independent of the stress and discomfort associated with EAE-induced paralysis.

Complementing these preclinical studies, a series of elegantly conducted clinical studies [105, 106] have shown that patients with atopic dermatitis [107] and asthma [108] show decreased reactivity of their HPA axis [109]. A more complex role for sympathetic nervous system involvement in autoimmune disease has also been proposed [110].

Glucocorticoid hormones may exert their protective immunosuppressive effects by inhibiting the production or actions of proinflammatory molecules as discussed previously. In addition, it has been hypothesized that glucocorticoids may suppress certain autoimmune reactions by inducing a shift towards a Th2 or humoral immune response [67, 73, 111]. For example, stimulation of the HPA axis by inflammatory mediators released during the initiation of an autoimmune response results in increased plasma corticosterone. Increased corticosterone levels may shift the balance of the ongoing immune reaction from a Th1-directed (cell-mediated) response towards a Th2-directed (antibody-mediated) response, by promoting the production of IL-4 and suppressing the production of IL-2 [71].

The Stress-Immune Spectrum

It is often overlooked that a stress response has salubrious adaptive effects in the short run [3, 16, 17, 45, 46, 53, 69], although stress can be harmful when it is long-lasting [1, 5, 9]. In order to reconcile these seemingly contradic-

tory effects of stress, we proposed that a stress response and its effects on immune function be viewed in the context of a *stress spectrum* [4, 9] (fig. 2). One region of this spectrum is characterized by *acute stress* or *eustress*, i.e., conditions of short-duration stress that may result in immunopreparatory or immunoenhancing physiological conditions. An important characteristic of acute stress is a rapid physiological stress response mounted in the presence of the stressor, followed by a rapid shutdown of the response upon cessation of the stressor. The other region of the stress spectrum is characterized by *chronic stress* or *distress*, i.e., repeated or prolonged stress which 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 1, 12]. We suggest that conditions of high allostatic load would 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 [9]. The *stress spectrum* also proposes that acute or chronic stress is generally superimposed on a psychophysiological *health maintenance equilibrium* (fig. 2). The extent and efficiency with which an organism returns to its health maintenance equilibrium after stress depends on *resilience*, which we define as reserve capacity of psychophysiological systems to recover from challenging conditions (fig. 2). Factors such as coping mechanisms, sense of control, optimism, social support, early life experiences, learning, genetics, and sleep may be important mediators of *psychological resilience* (fig. 2). Factors such as neuroendocrine reactivity, genetics, environment, nutrition, and sleep may be important mediators of *physiological resilience* (fig. 2). The psychophysiological basis of resilience and reserve capacity are underinvestigated 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

Fig. 2. The stress spectrum model. We have proposed a definition of stress as a constellation of events, consisting of a stimulus (*stressor*), that precipitates a reaction in the brain (*stress perception & processing*), that activates physiologic fight-or-flight systems in the body (*physiological stress response*) [9]. The duration of a physiological stress response is the critical determinant of its effects on immune function and health. The *stressor* itself may be acute (e.g. narrowly missing being hit by a car) or chronic (e.g. caring for a chronically ill child, spouse or parent). *Stress perception and processing* by the brain are critical for determining the duration and magnitude of the *physiological stress response* stimulated by any given stressor. Acute or chronic stress is generally superimposed on a psychophysiological *health maintenance steady state*. The extent and efficiency with which an organism returns to its health maintenance steady state after stress depends on *resilience*, which we define as the capacity of psychological and interacting physiological systems to recover from challenging conditions. Factors such as coping mechanisms, sense of control, optimism, social support, early life experiences, learning, genetics, and sleep are important mediators of *psychological resilience*. Factors such as neuroendocrine reactivity,

genetics, environment, nutrition, and sleep are important mediators of *physiological resilience*. Psychological resilience mechanisms are especially important in humans because they can limit the duration and magnitude of chronic stress responses. By the same token, psychogenic stressors can be particularly detrimental in human subjects because they may generate stress responses long after stressor exposure or even in the absence of physical stressors or salient threats. The *physiological stress response* is the ultimate effector arm of the stress spectrum. It may consist of acute or chronic physiological activation (neurotransmitters, hormones, and their molecular, cellular, organ-level and systemic effects) that results in *psychophysiological 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-averse 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. Reprinted from Dhabhar and McEwen [17], with permission.

or suppress/dysregulate immune function. The model shows that the stressor itself can be acute or chronic (fig. 2). Stress perception and processing by the brain and mechanisms mediating psychological and physiological resilience are critical for determining the duration and magnitude of the physiological stress response (fig. 2). Psychological resilience mechanisms are especially important in humans because they can limit the duration and magnitude of chronic stress responses. Psychogenic stressors are also very important in human subjects because they can generate stress responses long after stressor exposure (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 stressor exposure and its processing by the brain, there ensues a *physiological stress response*. This response may consist of acute or chronic physiological activation (neurotransmitters, hormones, and their molecular, cellular, organ-level and systemic effects) which results in *psychophysiological states* that have different effects on overall health and immune function as shown in figure 2. While there is significant evidence from animal studies to support this model, it needs to be further examined in studies involving human subjects.

Conclusion

Stress has long been suspected to play a role in the etiology of many diseases, and numerous studies have shown that stress can be immunosuppressive and hence may be detrimental to health. Moreover, glucocorticoid stress hormones are widely regarded as being immunosuppressive, and are used clinically as anti-inflammatory agents. However, studies have shown that the acute stress response may play a critical adaptive and protective role, with stress hormones and neurotransmitters preparing the immune system for potential challenges (e.g. wounding or infection) that are perceived by the brain (e.g. the detection of predator or attacker) [9, 16, 37, 45, 53]. It may be useful to further study, and clinically harness, the acute stress response that evolution has finely sculpted to be one of nature's crucial survival mechanisms, at least as much as we study its maladaptive ramifications (chronic stress) that evolution yet has to catch up with.

This paper illustrates the complex role that stress and stress hormones play as modulators and regulators of an

immune response. Stress and glucocorticoid hormones can either enhance or suppress immune function depending on the following factors: (1) The duration (acute vs. chronic) of stress. (2) Changes in leukocyte distribution within the body, and the compartments in which the immune response occurs. (3) The concentration (physiologic vs. pharmacologic), duration (acute vs. chronic) and nature (endogenous vs. synthetic) of glucocorticoid hormone exposure. (4) The timing of stress or stress hormone exposure relative to the stage (early vs. late) of an immune response. Further elucidation of the interactions among the above-mentioned factors and other nervous, endocrine, and genetic factors in mediating the effects of stress on immune function is necessary. Importantly, whether a stressor enhances or suppresses immune function, it is the end-effect of the affected immune response that affects the health of the organism or individual. For example, stress-induced enhancement of immunoprotective responses is likely to be beneficial while stress-induced enhancement of immunopathology is harmful. These findings need to be explored and investigated further and translated from bench to bedside.

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 these measures and overall health outcomes. Thus, when conducting clinical, diagnostic, or experimental procedures, it may be important to account for the effects of 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 leukocyte distribution within different body compartments. Where possible, redistribution needs to be monitored in terms of changes in absolute numbers of specific subpopulations of leukocytes. Stress-induced changes in immune cell numbers and/or function could significantly affect results (in case of experiments), diagnosis (in case of medical tests), or outcome (in case of treatment procedures and surgery).

Due to a host of psycho-sociopolitical factors, stress has unfortunately become an increasing and inevitable part of people's lives. 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 [3, 16, 45, 59]. We propose that it is

important to further study, and clinically harness the immunological 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. A determination of the physiologic mechanisms through which stress and stress hormones enhance or suppress immune responses is critically important for elucidating risk, developing preventative and therapeutic interventions, and optimizing a patient's response to treatment. The elucidation of such mechanisms would facilitate development of biomedical treatments designed to harness an individual's physiology to selectively enhance (during vaccination, wound-

ing, infections, or cancer) or suppress (during autoimmune or inflammatory disorders) the immune response depending on the outcome most beneficial for the patient.

Acknowledgments

I wish to thank current and previous members of my laboratory, particularly, Jean Tillie, Dr. Kavitha Viswanathan, Dr. Alison Saul, Kanika Ghai, and Christine Daugherty, whose work and publications are among those discussed in this chapter. The work described here was supported by grants from the NIH (AI48995 and CA107498) and The Dana Foundation.

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