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Understanding the interaction between psychosocial stress and immune-related diseases: A stepwise progression

Margaret E. Kemeny [a,*], Manfred Schedlowski [b]

[a] *Health Psychology Program, Department of Psychiatry, University of California, Laurel Heights Campus, 3333 California Street, Suite 465, San Francisco, CA 94143-0848, USA*
[b] *Institute of Medical Psychology & Behavioral Immunobiology, University of Duisburg-Essen, Medical Faculty, 45122 Essen, Germany*

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Abstract

For many years, anecdotal evidence and clinical observations have suggested that exposure to psychosocial stress can affect disease outcomes in immune-related disorders such as viral infections, chronic autoimmune diseases and tumors. Experimental evidence in humans supporting these observations was, however, lacking. Studies published in the last 2 decades in *Brain, Behavior and Immunity* and other journals have demonstrated that acute and chronic psychological stress can induce pronounced changes in innate and adaptive immune responses and that these changes are predominantly mediated via neuroendocrine mediators from the hypothalamic–pituitary–adrenal axis and the sympathetic–adrenal axis. In addition, psychological stress has predicted disease outcomes using sophisticated models such as viral challenge, response to vaccination, tracking of herpesvirus latency, exploration of tumor metastasis and healing of experimental wounds, as well as epidemiological investigations of disease progression and mortality. These studies have contributed significantly to our understanding that the neuroendocrine–immune interaction is disturbed in many pathophysiological conditions, that stress can contribute to this disturbance, and that malfunction in these communication pathways can play a significant role in the progression of disease processes. There are, however, significant gaps in the extant literature. In the coming decade(s), it will be essential to further analyze neuroendocrine–immune communication during disease states and to define the specific pathways linking the central nervous system to the molecular events that control important disease-relevant processes. This knowledge will provide the basis for new therapeutic pharmacological and non-pharmacological behavioral approaches to the treatment of chronic diseases via specific modulation of nervous system–immune system communication.

Keywords: Stress; Leukocytes; Cytokines; Catecholamines; Glucocorticoids; Arthritis; Tumor; HIV; Psychoimmunology; Infection; Autoimmune

1. Introduction

The notion that stressful life experiences and one's psychological state can influence the onset and progression of disease has existed for centuries, despite a paucity of evidence. Research conducted over the past 20 years in the field of psychoneuroimmunology has carefully examined this premise, leading to a much clearer picture of its strengths and weaknesses. The last 2 decades of research in the field of psychoneuroimmunology have been exciting, beginning with rigorous evidence that stress can affect the immune system, followed by intensive investigation of mediating mechanisms and extrapolation to disease processes. This short review focuses on the effects of psychological stress on immune functions and the etiology and progression of immune-mediated diseases since *Brain, Behavior and Immunity* (BBI) was first published in 1987. We will mainly concentrate on human work, in particular on the effects of stressors on viral infections, autoimmune diseases, wound healing and cancer. Since we are limited in the number of citations, we will predominantly cite review articles and apologize to all those colleagues who

* Corresponding author. Fax: +1 415 476 7744.
E-mail address: kemenym@healthpsych.ucsf.edu (M.E. Kemeny).

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contributed to the findings but whose work could unfortunately not be cited due to page and reference limitations.

1.1. Psychosocial stress, neuroendocrine–immune interactions

In response to stressful circumstances, the neuroendocrine system stimulates a series of adaptive responses involving behavioral, cardiovascular, metabolic, and immunological changes. Pituitary hormones such as prolactin and growth hormone, and neuropeptides like corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), neuropeptide Y (NPY) and the opioids can be released during stressor exposure and can affect cellular and humoral immune responses (Malarkey and Mills, 2007; Kelley et al., 2007; Blalock and Smith, 2007; see Fig. 1).

Experimental data in rodents and humans demonstrate that: (1) primary and secondary lymphoid organs are innervated by sympathetic noradrenergic nerve fibers, (2) all lymphoid cells express β-adrenoceptors and some subsets express α-adrenoreceptors, and (3) adrenaline and noradrenaline can alter circulation of leukocyte subpopulations and the functional capacity of immuncompetent cells, including cytokine production and release (Glaser and Kiecolt-Glaser, 2005; Sanders and Kavelaars, 2007).

Increased sympathetic adrenal activity appears to play a major role in immune changes observed after acute psychological stress. Hypothalamic–Pituitary–Adrenal (HPA) axis-activity, resulting in enhanced release of glucocorticoids, together with sympathetic mechanisms are mainly responsible for the inhibition of cellular and humoral immune responses after chronic psychological stress exposure (Glaser and Kiecolt-Glaser, 2005) (Fig. 1).

Glucocorticoids regulate multiple aspects of immune cell functions. For example, they regulate innate immune responses to bacterial and viral infection and can cause a shift in the adaptive immune response from T-helper-1 (Th-1) to T-helper-2 (Th-2) cell activity by inhibiting the production of pro-inflammatory cytokines such as Interleukin 12 (IL-12) and Tumor Necrosis Factor (TNF) or IL-2 and by stimulating the synthesis of the Th-2 cytokines IL-10 or IL-4 (Glaser and Kiecolt-Glaser, 2005).

Sensory peptides, such as Substance P (SP), also interact with the immune system and may play a role in the link between stress and inflammatory processes. The primary role of SP in the periphery is to promote inflammation in order to protect tissue from irritants and pathogens. Many immune cell types express receptors for SP and SP afferents innervate immune organs. Binding of SP to its receptor upregulates pro-inflammatory cytokines, and influences a variety of other immunological processes that support inflammation. SP also plays a role in moderating stress pathways, such as the HPA-axis (see Rosenkranz, in press).

Glaser et al. (1987) published the first study on stress and immune functions in humans in BBI, demonstrating an inhibition of cellular immune functions and poorer cellular immune control of herpesvirus latency during examination stress in medical students. This first report in BBI confirmed earlier studies of this group and others demonstrating a suppression of humoral and cellular immune responses in individuals exposed to psychological stress. Over the last 20 years, the concept of immunosuppression following prolonged psychological stress has been demonstrated by numerous studies employing different stress models (e.g., examination, caregiving, marital conflict, bereavement) and parameters of the innate and adaptive immune response (e.g., circulation of leukocyte subpopulations, lymphocyte activity, cytokine production; Glaser and Kiecolt-Glaser, 2005).

At approximately the time that BBI was first published, an increasing number of publications reported effects of acute psychological stress on human peripheral immune functions. These studies, using public speech, mental arithmetic or naturalistic stressors such as a parachute jump, demonstrated a transient activation in innate immune responses, such as an increase in natural killer (NK) cell activity and NK cell and granulocyte numbers.

Over the last 2 decades we have learned a remarkable amount about how immune responses change during and after stressful events. However, there is still considerable debate over the normal versus pathological nature of these shifts in immunity. In healthy individuals, the changes in immune response following exposure to an acute psychological stressor are generally evaluated as an evolutionary adaptive process, indicating that immune responses are highly sensitive and quickly responsive to environmental stimuli, such as stressful or threatening circumstances. And the healthy immune system is capable of compensating for prolonged exposure to psychosocial stress-induced immune inhibition. However, experimental data in humans clearly indicate that the risk for illness due to the adverse effects of stress on the immune system can be increased.

Not only from animal experiments but also from human studies, we recognize today, however, that even exposure to acute stressors can have prolonged effects on the immune response to pathogens (Edwards et al., 2006). In addition, numerous studies demonstrate that maladaptive neuroendocrine hyper- or hypoactive responses of the HPA or the sympathetic nervous system (SNS) to stress, including glucocorticoid resistance, can function as risk factors for the initiation and progression of specific diseases, in particular viral infection and chronic, inflammatory autoimmune diseases.

2. The first decade 1987–1996

2.1. Stress and chronic inflammatory diseases

The etiology of chronic inflammatory diseases such as *rheumatoid arthritis* (RA) or *systemic lupus erythematosus* (SLE) has been and remains unclear. Clinical observations suggest that stressful life events are associated with the onset and aggravation of symptoms in these autoimmune

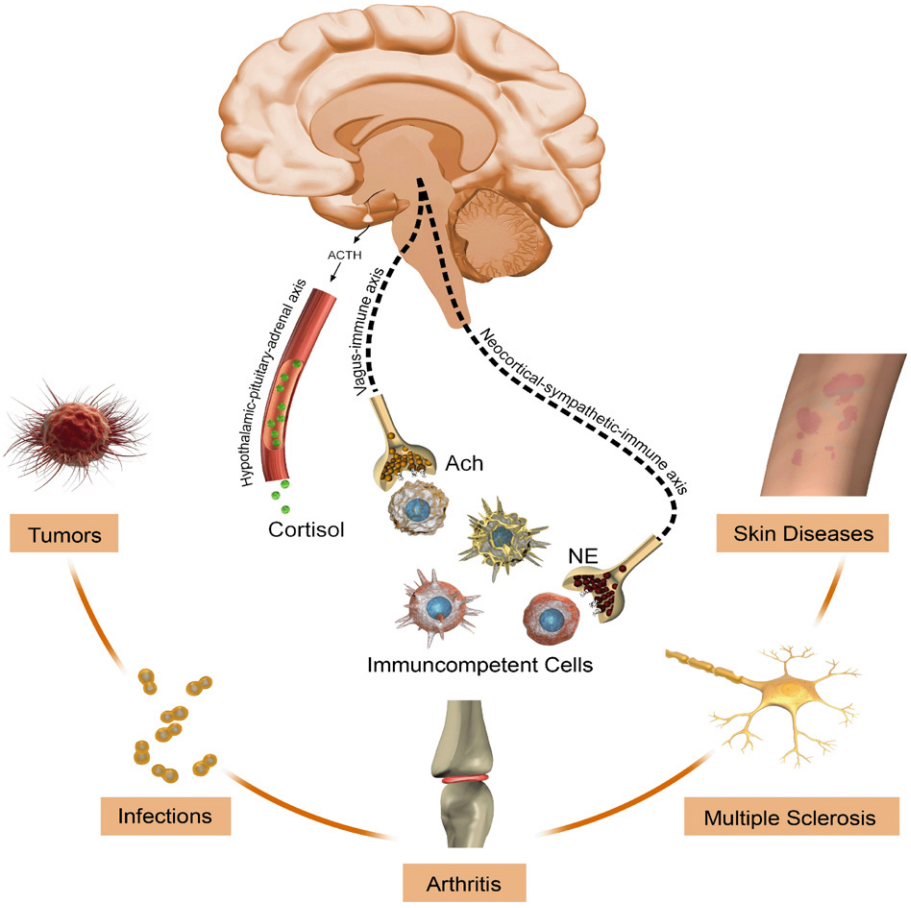

Fig. 1. Acute and sustained psychosocial stress affects the circulation and activity of immuncompetent cells via the release of neuroendocrine mediators. The major neural efferent pathways, through which stress can affect peripheral immune functions, are the neocortical–sympathetic–immune axis, the hypothalamus–pituitary–adrenal immune axis, and the brain stem–vagus–cholinergic pathway with the release of the major mediators noradrenaline, cortisol and acetylcholine. These hormones and neurotransmitters can subsequently modulate the inflammatory process in autoimmune diseases such as rheumatoid arthritis, multiple sclerosis or skin disease, affect the immune response during infection and may influence tumor development and progression. ACTH, adrenocorticotropic hormone; Ach, acetylcholine; NE, noradrenaline.

disorders. Twenty years ago, however, experimental data investigating the effects of stress on neuroendocrine and immunological responses and disease outcome in patients with RA or SLE were rare. Most of our knowledge came from work with experimental animals demonstrating that stress effects on these inflammatory processes seem to be predominantly mediated via two neuroendocrine communication pathways. Chronic inflammatory processes appeared to be associated with a dysfunction of the HPA-axis, resulting in an altered secretion pattern of CRH, ACTH and glucocorticoids, which in turn modulated immune functions in the autoimmune process. In addition, animal data clearly showed an involvement of the SNS and adrenoceptor mediated mechanisms, in particular in chronic inflammatory processes. Treatment with β-adrenoceptor antagonists in experimentally induced arthritis in rats significantly decreased disease symptoms. In contrast, the application of adrenaline exacerbated arthritis in rats via β_2-adrenergic mechanisms (Wilder, 1995).

Most of the studies in humans on the effects of stress and disease outcomes were retrospective. However these studies suggested that stress can be a disease permissive and aggravating factor in particular in *juvenile idiopathic arthritis* (JIA) and less so in RA. These findings were experimentally confirmed in studies demonstrating a disturbed, β_2-adrenoceptor mediated SNS–immune system interaction in JIA patients in response to stress (Kuis et al., 1996).

Researchers investigated the effects of stress on the exacerbation and the subsequent development of brain lesions in patients with *multiple sclerosis* (MS). Also here, a number of clinical, mainly retrospective studies indicated that critical life events preceded the onset or exacerbation of MS (Grant et al., 1989). Again, 20 years ago, experimental data on the effects of stress in MS patients were lacking and hypotheses regarding these effects and possible underlying mechanisms could only be generated from animal experiments. These data in *experimental allergic encephalomyelitis* (EAE), an animal model of MS, showed that exposure to stress such as restraint stress or maternal deprivation influenced the development of EAE in rats. However, these data also underscored the importance of effects of sex, strain, time of the onset of the stressor and subsequent

kinetics of the immune response on disease exacerbation (Griffin et al., 1993).

Although clinical evidence suggested an association between psychosocial stressors, immunological functions and other chronic inflammatory diseases such as skin diseases (*psoriasis* or *atopic dermatitis;* Gaston et al., 1987) or *inflammatory bowel diseases* (IBD), no systematic approach to investigation in these areas had been undertaken during the first decade of BBI.

A number of human studies also published in BBI during the first decade demonstrated that acute psychological stress induced a transient activation in particular innate immune responses such as increased natural killer and granulocyte numbers. In contrast, sustained psychosocial stress was documented to suppress humoral and cellular immune responses and inflammatory reactions. Against the background of inconclusive results from retrospective studies on the effects of stress on the onset or aggravation of symptoms in patients with chronic inflammatory diseases however, the mechanisms underlying effects of stress on inflammatory processes in these conditions were largely unknown during this first decade.

2.2. Stress and infectious disease

A number of paradigms have been utilized to examine the effects of stressful life experience on infectious disease outcomes. The most rigorous of these have involved viral challenge, response to vaccinations, and a focus on reactivation of latent viruses. *Viral challenge* studies involve inoculating healthy individuals with a virus under controlled conditions and quarantine and then examining individuals for evidence of infection and symptoms on a daily basis. The advantages of this approach are its ability to control viral exposure, verify effects observed in naturalistic studies and test for physiological mediators. In this early period, Cohen et al. (1991) found that greater levels of stress (defined on the basis of stressful life events, perceived stress and negative affect) predicted greater susceptibility to rhinovirus infection, lower neutralizing antibody titers and higher cold symptoms. During this same time period, Stone and colleagues found that stressful events, but not perceived stress, predicted rhinovirus virus infection using a similar paradigm.

Another excellent model involves measuring the immune response to *vaccinations* against influenza or Hepatitis B, since there is important variability in the extent to which individuals develop protective immunity following vaccination. Antibody titers following vaccination with Hepatitis B and/or influenza were predicted by acute stress (medical student exams), chronic stress (caregiving for a family member with Alzheimer's Disease), as well as perceived stress (Glaser, 2005). Other relevant immune processes in this context, such as virus-specific IL-2 and IL-1β levels, were also related to chronic stress.

A third important model is *reactivation of latent herpesviruses*, such as the Epstein–Barr virus (EBV), capable of causing mononucleosis, the herpes simplex virus (HSV), and the cytomegalovirus (CMV). Early work examined predictors of EBV infection and illness in West Point cadets and found that psychological factors such as a high motivation to achieve and poor academic performance predicted seroconversion, EBV titers and length of hospitalization. Glaser and colleagues reported effects of examination stress on herpesvirus latency beginning in 1984. Subsequent studies showed that academic exam stress and other stressors were capable of reactivating latent EBV as well as HSV-1 and CMV (see Glaser, 2005).

Another latent virus, *HIV-1*, has been a focus for a number of studies in PNI. HIV-1 infection is an important model for understanding the potential impact of stressors on disease because immune and virologic processes that play a significant role in disease pathogenesis are known and easily accessible to investigation. In addition, there is a great deal of unexplained variability in disease course even in those on an adequate medical regimen, suggesting that factors such as stress may be capable of affecting disease course. HIV positive individuals are exposed to profoundly stressful circumstances (e.g., death of loved ones to HIV, stigma) which can be a focus for investigation. While there were a few studies documenting a link between exposure to AIDS-related bereavement and markers of HIV progression, the data demonstrating a relationship between stressful life events more generally and indices of HIV progression was limited during this period (see Cole and Kemeny, 2001). However, those stress studies that incorporated measures of stressor context so that the stressfulness of the event could be more readily assessed were better able to predict CD4 T cell decline and time to onset of AIDS, controlling for relevant alternative explanations (see Leserman et al., 2000). Particular psychological responses to the risk of HIV progression, such as HIV-specific pessimism about one's future health, have been shown to predict onset of HIV-related symptoms and mortality, particularly among those who experienced the death of a close other to AIDS (e.g., Reed et al., 1994).

2.3. Stress and cancer

There is a long history of interest in whether psychological factors can affect the etiology and progression of cancer. Very early studies suggested links between personality types and cancer etiology; however, interpretation of these findings has been significantly hampered by methodological problems in many of these studies. A great deal of important work has taken place in this area over the past 2 decades with a tremendous acceleration of studies demonstrating potential effects of stress on tumor metastasis, the tumor microenvironment, and regulation of cell growth.

2.3.1. Cancer etiology

During this decade and before, the data linking stressor exposure to cancer etiology was quite inconsistent and

most reviews failed to find a relationship (Reiche et al., 2004), although evidence may have been stronger for severe life events, such as death of a child or spouse (see Lutgendorf et al., 2007). Also, depression and other psychological factors were not found to be consistent predictors (see Lutgendorf et al., 2007).

2.3.2. Cancer progression

The strongest relations with course of cancer were found for social support and emotional expression (see Sephton and Spiegel, 2003). For example, higher levels of social support (e.g., emotional support, presence of supportive persons, marriage) have been associated with survival time in breast, colorectal and lung cancer. Important studies were conducted on the effects of psychological interventions and cancer prognosis during this early period. Spiegel and colleagues utilized a supportive–expressive group therapy approach in studies of women with metastatic breast cancer. This therapeutic approach involves expressing and dealing with negative emotions in a supportive group environment. They found that participation in this intervention predicted longer survival time, with support group members surviving an average of 18 months longer than those assigned to the control condition (Spiegel et al., 1989). The impact of a psychoeducational group intervention for patients with malignant melanoma was evaluated in relation to mood, the natural killer cell system, recurrence and survival over a 6-year period (Fawzy et al., 1993). The intervention involved health education, training in problem-solving skills, stress management, and social support. Those randomly assigned to the 6-week intervention showed improved mood relative to the controls, as well as increases in the number of NK cells and in IFN-α augmentation of NK cell activity at 6 months. Most importantly, the intervention group had fewer deaths than controls at 6 years post treatment.

3. The second decade 1997–2007

3.1. Stress and chronic inflammatory diseases

Based on knowledge of the kinetics and potential mechanisms of the way stress affects the immune response in the healthy individual, further research activities demonstrated that leukocytes from individuals with chronic inflammatory diseases such as RA or SLE differ in their response to acute psychological stress or adrenergic and corticoid stimulation in comparison to immuncompetent cells from healthy subjects (Straub et al., 2005). This can be explained by a disturbed neuroendocrine–immune interaction in these chronic inflammatory states based on an inadequate HPA-axis and SNS response to stress. For example, RA patients with a recent diagnosis showed a significantly impaired stress- or dexametasone-induced ACTH or cortisol increase, with this insensitivity apparently located both at a hypothalamic/pituitary and at an adrenal level (Dekkers et al., 2001). Similarly, the SNS response to acute psychological stress seemed to differ in RA and SLE patients in comparison to healthy controls. The expression of β-adrenoceptors on peripheral and synovial immune cells appeared to be decreased in patients and the numbers of β-adrenoceptors on peripheral blood mononuclear cells (PBMC) significantly increased in healthy subjects but not in SLE patients after stress exposure (Pawlak et al., 1999). In addition, an up-regulation of α-adrenoceptors on monocytes of patients with JIA has been reported. Due to this shift from β- to α-adrenoceptors, the immunosuppressive effect of noradrenaline by activation of β-adrenoceptors might be prevented in these patients (Kuis et al., 1996; Straub et al., 2005). In addition, patients with SLE or RA react differently in terms of leukocyte numbers in circulation, activity and cytokine release to acute psychological stress in comparison to healthy controls, underscoring the disturbed communication pathway between the brain, the neuroendocrine system and the immune system (Pawlak et al., 1999). In particular, the disturbed SNS–immune pathway seemed to be partly due to an altered receptor sensitivity mediated by the activity of G-protein-coupled receptor kinases (GRK) and protein expression. For example, in RA patients, the pro-inflammatory signaling pathway mediated through G-protein coupled receptors (i.e., β_2-adrenoceptors) are less efficiently turned off by the GRK/β-arrestin desensitization machinery (Lombardi et al., 1999). Moreover, the inflammatory process *in vivo* induces a tissue-specific down-regulation of GRKs in lymphocyte subpopulations in these patients (Lombardi et al., 2001).

All together, these data demonstrate that, in the healthy individual, acute psychological stress leads to various forms of immune system activation, whereas sustained stress exposure inhibits key immune responses. In conditions of chronic inflammation such as in the rheumatoid diseases (RA, JIA or SLE) however, experimental evidence in humans demonstrates disturbed neuroendocrine–immune communication during stress exposure. These data show an inadequate secretion of cortisol as well as increased sympathetic tone at rest but an inadequate response during stress exposure, a functional loss of synovial sympathetic nerve fibers, a local β- to α- adrenergic shift, and a disturbed adrenoceptor intracellular signaling cascade in leukocytes, which seemed to generate the basis for stress-induced aggravation of these chronic inflammatory rheumatoid diseases (Straub et al., 2005).

Similar to inflammatory rheumatoid diseases, the pathogenesis of MS remains unclear and is most likely heterogeneous. However, there is increasing evidence during the last decade that stressful life events correlate with exacerbations in MS. Also, here we see the disruption in the communication between the peripheral immune system and the two major stress response systems, the HPA and the SNS. Disturbed glucocorticoid and β-adrenergic modulation of immune responses during stress exposure may be mainly responsible for the overshooting inflammatory process in MS. In addition, hyperreactivity of the HPA-axis in

MS might be responsible, in part, for the neurodegenerative process and increased disability (Gold et al., 2005). It has been recently suggested that the impact of stress on disease outcome in MS may be related to the temporal relationship of the stressor, the stress response and the disease outcome. This may include the onset of the stressor and the temporal course from acute to chronic and the resolution of the stress response with a unique neuroendocrine–immune interaction influencing the exacerbation process in MS (Mohr and Pelletier, 2006).

During the last decade, increasing experimental evidence indicated that patients with inflammatory skin diseases such as psoriasis or atopic dermatitis also differ in their response to psychological stress (Buske-Kirschbaum et al., 2007) and that stress exposure can trigger or aggravate the inflammatory skin process (Paus et al., 2006). Although the mechanisms underlying the impact of stress on the inflammatory process in the skin are still largely unknown, the activity of mast cells, NK cells or dendritic cells in the skin are regulated by neuroendocrine mediators such as CRH, Substance P, ACTH, glucocorticoids and catecholamines, mediating the brain–skin cross talk (Paus et al., 2006).

Psychological stress has long been suggested to increase the likelihood of relapse in patients with inflammatory bowl diseases (IBD) such as Crohn's disease or ulcerative colitis. However, experimental data in humans providing evidence of a causal link between stress exposure, and neuroendocrine and immune responses in these patients are rare. However, preliminary evidence also indicates disturbed adrenoceptor-mediated cytokine production in these patients.

3.2. Stress and infectious disease

The relations between stress and response to *viral challenge* were replicated and extended in the second decade by Cohen and colleagues (see Cohen, 2005). In a viral challenge study including 276 individuals, for example, Cohen and colleagues found that exposure to chronically stressful life events (of one month or longer duration) predicted greater susceptibility to infection. Extending this paradigm to influenza virus, they found that greater levels of psychological stress were associated with greater symptom scores and mucus weights, as well as higher levels of IL-6. In addition, the greater the diversity of one's social network (defined by types of social groups) the lower the susceptibility to viral infection using this model. Thus far, little is known about the physiological mediators of these effects since attempts to link hormonal and immunologic processes to viral outcomes in this paradigm have been largely unsuccessful. However, animal studies conducted by Sheridan and colleagues suggest three major pathways linking stress exposure to natural resistance to influenza viral infection—the response of pro-inflammatory cytokines, β-chemokines, and natural killer cells. In addition, the adaptive immune response, involving antigen-specific T cell activation, also plays a role in this process (see Bailey et al., 2007). These may be important targets for future influenza viral challenge studies in humans.

In the second decade, the chronic stress of caregiving, other stressors and certain psychological factors continued to demonstrate relationships to response to *vaccination* (in most but not all studies; Glaser, 2005). An interesting study published in BBI found that an acute laboratory stress followed by influenza vaccination increased antibody titers at 4 and 20 weeks (Edwards et al, 2006), but only in women. On the other hand, distress on the days *after* the vaccination but not before may contribute to an inadequate response to vaccination (Miller et al., 2004). It is interesting to note that the antibody response to a Hepatitis B vaccination can be enhanced by a brief psychological intervention provided after the vaccination.

Following on the findings in the first decade on stress effects on EBV in West Point cadets, Glaser et al. (1999) published a paper in BBI, examining effects of West Point training and final exam stress during training on *herpesvirus latency*. They found that exam stress was associated with increases in EBV-titer but not HSV-1 or human herpesvirus 6 (HHV)-6 titers. Based on a recent meta-analytic review of the research on the effects of stress on the immune system, there appear to be relatively consistent effects of stress on antibody titer to the EBV virus (Segerstrom and Miller, 2004). Overall, about seven studies of brief naturalistic stressors, primarily examination stress, demonstrated a significant relationship between stress exposure and elevated EBV antibody titers.

In the second decade of research on predictors of *HIV progression*, a number of studies utilized measures of stressful events that incorporated measures of subjective experience and found that stress predicted a more rapid loss of the CD4 T cells, and onset of AIDS-related conditions (see Sloan et al., 2007). These studies have been bolstered by studies of Rhesus macaques inoculated with the Simian immunodeficiency virus (SIV), showing that social stressors such as housing changes and separation predict accelerated disease progression and alterations in relevant immune processes (e.g., Capitanio and Lerche, 1998). Depression has also been shown to predict accelerated disease course in some, but not all studies, and effects appear to depend on stage of disease. A wide range of other psychological responses to the presence of HIV infection have been examined as predictors of disease course. For example, cognitive and emotional reactions associated with negative views of the self, stigmatization or rejection predicted virologic and immunologic evidence of disease progression and mortality as well as a weaker response to anti-viral therapy in terms of HIV viral load (e.g., Cole et al., 2003). Effects were not explained by health behavior, demographics, medication regimen or general levels of stress or depression.

Higher levels of distress have also been associated with alterations in HIV-relevant immune parameters, such as CD4 and CD8 T cells, and NKCA. While HPA activity has been invoked as a potential mediator of such effects since corticosteroids can enhance viral replication and

may prolong viral gene expression and HPA activity has predicted disease progression in both the HIV and SIV models, cortisol levels have not been found to mediate the relations between stress and disease progression noted above. An alternative proposed pathway is via SNS reactivity. Cole and colleagues have conducted intensive investigation of the role of the SNS in HIV replication and disease progression, taking these studies from the epidemiological to the molecular (see Sloan et al., 2007). They have found that SNS activity predicts viral load and CD4 responses to anti-retroviral therapy and mediates some of the effects of psychological factors on disease course. In vitro studies showed that NE can enhance HIV replication in a dose–response relationship. This relationship involves the cyclic AMP/protein kinase A signaling pathway.

In terms of interventions, both short and longer term psychological interventions have been associated with immunologic or virologic benefit in HIV positive individuals. The intervention program Cognitive Behavioral Stress Management (CBSM) has undergone intensive investigation by a team of researchers including Antoni, Schneiderman, Ironson, Esterling and others. CBSM focuses on modifying stress-related cognitive appraisals and teaching effective coping skills (Antoni, 1997). For example, in HIV positive individuals, CBSM has been shown to result in a decrease in antibody titers to herpesviruses EBV and HSV-2 along with reductions in negative mood. Also, CBSM + adherence training versus adherence training alone reduced HIV viral load in gay men treated with HAART (Antoni et al., 2007). Goodkin and colleagues found that a 10 week supportive–expressive program combined with coping skills training was associated with decreased cortisol, increased CD4 counts, and decreased viral load relative to controls in recently bereaved HIV infected gay men (see Antoni et al., 2007). At the same time, there have been many intervention studies with HIV+ samples that have not found effects on relevant virologic or immune processes (Carrico and Antoni, in press). No studies have reported intervention effects on mortality outcomes.

3.3. Stress and cancer

3.3.1. Cancer etiology

A few recent studies suggest a relationship between stress and the onset of cancer (e.g., a 20 year longitudinal study of a very large sample of Isrealis who experienced the death of an adult son due to accidents or related to war). However, overall, the relationship between stressor exposure and the etiology of cancer in humans is weak (Reiche et al., 2004). If there is such a relationship, it is highly likely that it will only be detectable if considered in conjunction with known risk factors such as genetics, gender, site of cancer, age and health behaviors, such as smoking.

3.3.2. Cancer progression

In the second decade, a few well conducted studies do support a relation between stress and cancer progression. For example, one interesting model involved examining effects on human papilomavirus (HPV)-associated cervical intraepithelial neoplasia (CIN), a precursor to cervical cancer. Stress and pessimism have predicted greater severity of CIN (see Antoni et al., 2007). In women coinfected with HIV and HPV, greater negative life events predicted declines in NK number, greater risk of outbreak of genital herpes, as well as persisting CIN over a year follow-up. However, overall, the relationship between stress and cancer prognosis has not been strengthened by the recent evidence. For example, some of the effects of interventions on cancer progression found during the first decade were not replicated in more recent studies. One study, using the Spiegel supportive–expressive intervention, did not show effects on breast cancer survival despite psychological benefits. Overall, the potential benefit of psychological interventions for slowing cancer progression and increasing survival is unknown, since there are well designed studies that demonstrate effects on survival and those that do not (see Spiegel, 2002).

A promising area of current research evaluates the relationship between stress and immune function in cancer patients, including in the tumor microenvironment (see Lutgendorf et al., 2005). Lutgendorf and colleagues have found stress to be associated with lower NKCA in tumor-infiltrating lymphocytes from patients with ovarian cancer, while social support has been associated with higher NKCA. Impaired NKCA has been linked with progression of this tumor in previous research. In a study reported in BBI, TNF-α, which is associated with tumor regression and survival time, was found to be decreased in breast cancer patients with social disruption at cancer diagnosis (Marucha et al., 2005). A number of studies have found that interventions can influence important immune parameters relevant to cancer progression in cancer patients, for example, the lymphocyte proliferative response. Studies of stress effects in healthy humans on processes important to cancer also support potential mechanistic pathways. For example, acute stress has been shown to alter the response of leukocytes to factors that induce apoptosis, a process that plays an important role in defense against the development of malignant cells. In addition, Kiecolt-Glaser and colleagues found greater impairment of DNA repair mechanisms in those with psychiatric illness compared to healthy controls (see Reiche et al., 2004) suggesting that this critically important cancer-relevant process may be amenable to influence by psychological factors.

The animal literature appears to show a more robust and consistent relation between stress, tumor growth and metastases. Animal studies have demonstrated effects of stress on tumor growth or metastasis, with stressors such as restraint, forced swim and social isolation (see Reiche et al., 2004). For example, Ben-Eliyahu and colleagues have demonstrated that surgical and psychological stress can suppress NK activity in rats, and this suppression compromises resistance to tumor progression. NK effects in this tumor model can be mediated by catecholamines, which

suppress NK activity by elevating cAMP levels. More recently, in BBI, these researchers report on a successful method for preventing the negative effects of stressors on metastasis utilizing a product that causes NK cells to be partially resistant to suppression by agents that increase cAMP. These findings may have clinical utility in humans.

Studies of human cancer cell lines have also provided an important opportunity to investigate potential pathways between stress and tumor cell outcomes. Intriguing findings demonstrate that noradrenaline can promote processes related to metastases in vitro, such as cancer cell migration. NE acts on the β-adrenergic receptor-cyclic AMP–protein kinase A pathway in ovarian cancer cell lines, with effects abolished by a β blocker. Also HPA effects on apoptosis of lymphocytes, survival genes that protect cancer cells from chemotherapy effects, oncogenic viruses, and immune responses to tumors may play a role in tumor initiation, growth and survival (Antoni et al., 2006).

In BBI, Sephton and Spiegel (2003) proposed an interesting hypothesis that stress-related alterations in hormonal and immunological circadian rhythms could play a role in cancer progression. Stressful life experiences, depression and other psychiatric disorders have been shown to disrupt circadian rhythms of the HPA. There is some evidence of abnormal circadian rhythms in individuals at high risk for breast cancer and predicting cancer outcomes. For example, a flattened cortisol rhythm has predicted early mortality up to 7 years after assessment as well as decrements in number and activity of NK cells, which also predicted mortality. These HPA alterations were associated with poor sleep and prior marital disruption. In addition, animals with mutations in circadian clock genes are at increased risk for tumor development and shortened survival.

Clearly, animal studies and in vitro work are pointing to mechanisms that would allow stress and psychological factors to affect tumor progression, at least with certain forms of cancer. Future directions in this area may include an attempt to integrate the molecular level investigation with the human experimental study paradigms in order to begin to define the pathway from stress to the molecular events controlling tumor progression.

3.4. Stress and wound healing

Wound healing became a very important outcome in PNI research in this second decade (see Marucha and Engeland, 2007). The initial study in this area conducted by Kiecolt-Glaser, Marucha and colleagues showed that the chronic stress of caregiving for a person with Alzheimer's Disease was associated with a delay in wound healing. Punch biopsy wounds healed about 25% more slowly in the chronically stressed group, and these individuals also produced lower blood levels of IL-1β, which may have played a role in the wound healing effect. These investigators have also examined the impact of examination stress on wound healing, and found that oral wounds placed 3 days before exams healed 40% more slowly on average when compared to those placed during the less stressful summer vacation. In addition, higher perceived stress and cortisol levels have been associated with slower wound healing, consistent with the evidence that glucocorticoids have an inhibitory effect on wound healing via effects on recruitment and bacterial killing. Physiological processes taking place within the wound, for example, levels of IL-1β, IL-8, and MMP-9, have also been found to be associated with level of perceived stress. The role of pro-inflammatory cytokines as mediators of effects of stress on wound healing is supported by animal studies. For example, in a study published in BBI, Padgett et al. (1998) demonstrated that restraint stress lowers levels of pro-inflammatory cytokines, such as IL-1β in wounds with effects due to glucocorticoids. However, evidence also published in BBI by these investigators suggests that HPA induced effects on pro-inflammatory cytokines are not the sole mediators. In another paper published in BBI, these researchers show that stress effects on iNOS gene expression in mice have also been implicated in dermal wound healing effects, suggesting a role for stress induced SNS effects on tissue oxygen levels. Overall, these results provide strong support for a link between stressor exposure and physiological processes that regulate the wound healing process (see Marucha and Engeland, 2007).

3.5. Future directions for the next decade(s)

Overall, research conducted in the decade encompassing 1987–1996 laid down a research foundation indicating a relationship between stress and specific diseases and disease-related processes, such as infectious disease, antibody response to vaccinations, and latent virus reactivation. Results of such studies in the area of autoimmune disease and cancer were weaker. In the second decade, 1997–2007, neuroendocrine and immunologic mechanisms were more carefully specified and the complexities of these relationships began to be revealed. Important mechanistic work was conduced in cancer (including a focus on the tumor microenvironment, and in vitro studies of cancer cell lines), autoimmune disease, wound healing, HIV-1 and other latent viruses. These data clearly indicate that neuroendocrine and immune system interactions are relevant to the etiology and course of many immunological diseases. It is interesting to note that epidemiological evidence remains weak is some of these areas (e.g., autoimmune disease, cancer) probably as a result of the multiple, interacting factors controlling disease etiology and progression (genetics, lifestyle and environmental factors, etc.).

One of the major challenges for future research activities is to elucidate the hierarchical, temporal and spatial communication patterns linking the brain, our stress-perceiving system, and the neuroendocrine and peripheral immune responses to acute and chronic psychosocial stress in the different diseases. We must understand in more detail how, where and when the brain–immune axis is disturbed

in the different, immune-related diseases. It is important to identify the basic psychological mechanisms that are associated with the relevant brain structures and signaling that are subsequently processed via neuroendocrine efferent pathways to immuncompetent cells in the periphery. Thus far, we know very little about the role of the CNS in orchestrating these neuro-immune responses to emotionally provocative circumstances. Borrowing concepts and tools from affective and cognitive neuroscience would facilitate the integration of neuroscience into these investigations. In addition, it is important to focus on how these stress-induced neuroendocrine signals alter downstream receptor physiology, intracellular signaling cascades and gene expression in normal physiological states and in pathophysiological conditions. Based on this knowledge, new pharmacological and non-pharmacological diagnostic and treatment options can be developed that result in a specific modulation of the nervous system–immune system communication. On a behavioral level in particular, this knowledge will provide the basis for new specific behavioral intervention strategies for the treatment of chronic diseases (Pacheco-Lopez et al. 2006).

References

Antoni, M.H., 1997. Cognitive behavioral stress management for gay men learning of their HIV-1 antibody test results. In: Spira, J. (Ed.), Group Therapy for Patients with Chronic Medical Diseases. Guildford Press, New York, pp. 55–91.

Antoni, M.H., Lutgendorf, S.K., Cole, S.W., Dhabhar, F.S., Sephton, S.E., McDonald, P.G., Stefanek, M., Sood, A.K., 2006. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. Nat. Rev. Cancer 6, 240–248.

Antoni, M.H., Schneiderman, N., Penedo, F., 2007. Behavioral interventions: immunologic mediators and disease outcomes. In: Ader, R. (Ed.), Psychoneuroimmunology. Academic Press, San Diego, pp. 675–703.

Bailey, M.T., Padgett, D.A., Sheridan, J.F., 2007. Stress-induced modulation of innate resistance and adaptive immunity to influenza viral infection. In: Ader, R. (Ed.), Psychoneuroimmunology. Academic Press, San Diego, pp. 1097–1124.

Blalock, J.E., Smith, E.M., 2007. Conceptual development of the immune system as a sixth sense. Brain Behav. Immun. 21, 23–33.

Buske-Kirschbaum, A., Kern, S., Ebrecht, M., Hellhammer, D.H., 2007. Altered distribution of leukocyte subsets and cytokine production in response to acute psychosocial stress in patients with psoriasis vulgaris. Brain Behav. Immun. 21, 92–99.

Capitanio, J.P., Lerche, N.W., 1998. Social separation, housing relocation, and survival in simian AIDS: a retrospective analysis. Psychosomatic Med. 60, 235–244.

Carrico, A.W., Antoni, M.H., in press. The effects of psychological interventions on neuroendocrine hormone regulation and immune status in HIV-positive persons: a review of randomized controlled trials. Psychosom. Med.

Cohen, S., 2005. Keynote presentation at the eight international congress of behavioral medicine: the Pittsburgh common cold studies: psychosocial predictors of susceptibility to respiratory infectious illness. Int. J. Behav. Med. 12, 123–131.

Cohen, S., Tyrrel, D.A.G., Smith, A.P., 1991. Psychological stress and susceptibility to the common cold. N. Eng. J. Med. 325, 606–612.

Cole, S.W., Kemeny, M.E., 2001. Psychological influences on the progression of HIV infection. In: Ader, R., Felten, D.L., Cohen, N. (Eds.), Psychoneuroimmunology. Academic Press, New York, pp. 583–612.

Cole, S.W., Kemeny, M.E., Fahey, J.L., Zack, J.A., Naliboff, B.D., 2003. Psychological risk factors for HIV pathogenesis: mediation by the autonomic nervous system. Biol. Psychiatry 54, 1444–1456.

Dekkers, J.C., Geenen, R., Godaert, G.L., Glaudemans, K.A., Lafeber, F.P., van Doornen, L.J., Bijlsma, J.W., 2001. Experimentally challenged reactivity of the hypothalamic pituitary adrenal axis in patients with recently diagnosed rheumatoid arthritis. J. Rheumatol. 28, 1496–1504.

Edwards, K.M., Burns, V.E., Reynolds, T., Carroll, D., Drayson, M., Ring, C., 2006. Acute stress exposure prior to influenza vaccination enhances antibody response in women. Brain Behav. Immun. 20, 159–168.

Fawzy, F.I., Fawzy, N.W., Hyun, C.S., Elashoff, R., Guthrie, D., Fahey, J.L., Morton, D.L., 1993. Malignant melanoma: effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. Arch. Gen. Psychiatry 50, 681–689.

Gaston, L., Lassonde, M., Bernier-Buzzanga, J., Hodgins, S., Crombez, J.C., 1987. Psoriasis and stress: a prospective study. J. Am. Acad. Dermatol. 17, 82–86.

Glaser, R., Rice, J., Sheridan, J., Fertel, R., Stout, J., Speicher, C., Pinsky, D., Kotur, M., Post, A., Beck, M., et al., 1987. Stress-related immune suppression: health implications. Brain Behav. Immun. 1, 7–20.

Glaser, R., Friedman, S.B., Smyth, J., Ader, R., Bijur, P., Brunell, P., Cohen, N., Krilov, L.R., Lifrak, S.T., Stone, A., Toffler, P., 1999. The differential impact of training stress and final examination stress on herpesvirus latency at the United States Military Academy at West Point. Brain Behav. Immun. 13, 240–251.

Glaser, R., 2005. Stress-associated immune dysregulation and its importance for human health: a personal history of psychoneuroimmunology. Brain Behav. Immun. 17, 321–328.

Glaser, R., Kiecolt-Glaser, J.K., 2005. Stress-induced immune dysfunction: implications for health. Nat. Rev. Immunol. 5, 243–251.

Gold, S.M., Mohr, D.C., Huitinga, I., Flachenecker, P., Sternberg, E.M., Heesen, C., 2005. The role of stress-response systems for the pathogenesis and progression of MS. Trends Immunol. 26, 644–652.

Grant, I., Brown, G.W., Harris, T., McDonald, W.I., Patterson, T., Trimble, M.R., 1989. Severely threatening events and marked life difficulties preceding onset or exacerbation of multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 52, 8–13.

Griffin, A.C., Lo, W.D., Wolny, A.C., Whitacre, C.C., 1993. Suppression of experimental autoimmune encephalomyelitis by restraint stress: sex differences. J. Neuroimmunol. 44, 103–116.

Kelley, K.W., Weigent, D.A., Kooijman, R., 2007. Protein hormones and immunity. Brain Behav. Immun. 21, 384–392.

Kuis, W., de Jong-de Vos van Steenwijk, C., Sinnema, G., Kavelaars, A., Prakken, B., Helders, P.J., Heijnen, C.J., 1996. The autonomic nervous system and the immune system in juvenile rheumatoid arthritis. Brain Behav. Immun. 10, 387–398.

Leserman, J., Petitto, J.M., Golden, R.N., Gaynes, B.N., Gu, H., Perkins, D.O., Silva, S.G., Folds, J.D., Evans, D.L., 2000. Impact of stressful life events, depression, social support, coping, and cortisol on progression to AIDS. Am. J. Psychiatry 157, 1221–1228.

Lombardi, M.S., Kavelaars, A., Cobelens, P.M., Schmidt, R.E., Schedlowski, M., Heijnen, C.J., 2001. Adjuvant arthritis induces down-regulation of G protein-coupled receptor kinases in the immune system. J. Immunol. 166, 1635–1640.

Lombardi, M.S., Kavelaars, A., Schedlowski, M., Bijlsma, J.W., Okihara, K.L., Van de Pol, M., Ochsmann, S., Pawlak, C., Schmidt, R.E., Heijnen, C.J., 1999. Decreased expression and activity of G-protein-coupled receptor kinases in peripheral blood mononuclear cells of patients with rheumatoid arthritis. FASEB J. 13, 715–725.

Lutgendorf, S.K., Costanzo, E.S., Siegel, S.D., 2007. Psychosocial influences on oncology: an expanded model of biobehavioral mechanisms. In: Ader, R. (Ed.), Psychoneuroimmunology. Academic Press, San Diego, pp. 869–895.

Lutgendorf, S.K., Sood, A.K., Anderson, B., McGinn, S., Maiseri, H., Dao, M., Sorosky, J.I., De Geest, K., Ritchie, J., Lubaroff, D.M.,

2005. Social support, psychological distress, and natural killer cell activity in ovarian cancer. J. Clin. Oncol. 23, 7105–7113.

Malarkey, W.B., Mills, P.J., 2007. Endocrinology: the active partner in PNI research. Brain Behav. Immun. 21, 161–168.

Marucha, P.T., Crespin, T.R., Shelby, R.A., Andersen, B.I., 2005. TNF-Alpha levels in cancer patients relate to social variables. Brain Behav. Immun. 19, 521–525.

Marucha, P.T., Engeland, C.G., 2007. Stress, neuroendocrine hormones, and wound healing: human models. In: Ader, R. (Ed.), Psychoneuroimmunology. Academic Press, San Diego, pp. 825–835.

Miller, G.E., Cohen, S., Pressman, S., Barkin, A., Rabin, B.S., Treanor, J.J., 2004. Psychological stress and antibody response to influenza vaccination: when is the critical period for stress, and how does it get inside the body? Psychosomatic Med. 66, 215–223.

Mohr, D.C., Pelletier, D., 2006. A temporal framework for understanding the effects of stressful life events on inflammation in patients with multiple sclerosis. Brain Behav. Immun. 20, 27–36.

Pacheco-Lopez, G., Engler, H., Niemi, M.B., Schedlowski, M., 2006. Expectations and associations that heal: immunomodulatory placebo effects and its neurobiology. Brain Behav. Immun. 20, 430–446.

Padgett, D.A., Marucha, P.T., Sheridan, J.F., 1998. Restraint stress slows cutaneous wound healing in mice. Brain Behav. Immun. 12, 64–73.

Paus, R., Theoharides, T.C., Arck, P.C., 2006. Neuroimmunoendocrine circuitry of the 'brain–skin connection'. Trends Immunol. 27, 32–39.

Pawlak, C.R., Jacobs, R., Mikeska, E., Ochsmann, S., Lombardi, M.S., Kavelaars, A., Heijnen, C.J., Schmidt, R.E., Schedlowski, M., 1999. Patients with systemic lupus erythematosus differ from healthy controls in their immunological response to acute psychological stress. Brain Behav. Immun. 13, 287–302.

Reed, G.M., Kemeny, M.E., Taylor, S.E., Wang, H.Y., Visscher, B.R., 1994. Realistic acceptance as a predictor of decreased survival time in gay men with AIDS. Health Psychol. 13, 299–307.

Reiche, E.M.V., Nunes, S.O.V., Morimoto, H.K., 2004. Stress, depression, the immune system, and cancer. Lancet Oncol. 5, 617–625.

Rosenkranz, M.A., in press. Dysregulation of Substance P in chronic inflammatory disease and affective disorders. Psychol. Bull.

Sanders, V.M., Kavelaars, A., 2007. Adrenergic regulation of immunity. In: Ader, R., Felten, D.L., Cohen, N. (Eds.), Psychoneuroimmunology. Academic Press, New York.

Segerstrom, S.C., Miller, G.E., 2004. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psych. Bull. 130, 601–630.

Sephton, S., Spiegel, D., 2003. Circadian disruption in cancer: a neuroendocrine–immune pathway from stress to disease? Brain Behav. Immun. 17, 321–328.

Sloan, E., Collado-Hidalgo, A., Cole, S., 2007. Psychobiology of HIV infection. In: Ader, R. (Ed.), Psychoneuroimmunology. Academic Press, San Diego, pp. 869–895.

Spiegel, D., 2002. Effects of psychotherapy on cancer survival. Nat. Rev. Cancer 2, 383–389.

Spiegel, D., Bloom, J.R., Kraemer, H.C., Gottheil, E., 1989. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. Lancet 2, 888–891.

Straub, R.H., Dhabhar, F.S., Bijlsma, J.W., Cutolo, M., 2005. How psychological stress via hormones and nerve fibers may exacerbate rheumatoid arthritis. Arthritis Rheum. 52, 16–26.

Wilder, R.L., 1995. Neuroendocrine–immune system interactions and autoimmunity. Annu. Rev. Immunol. 13, 307–338.