

REVIEW

Stress effects on immunity and its application to clinical immunology

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Introduction

Various stressors, including both psychological as well as physiological, have been demonstrated to influence the immune response, presumably through activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. Anecdotal evidence, and retrospective and prospective studies, have demonstrated an effect of psychological and physiological stress on immune-based diseases such as asthma, atopy and infections. Alterations in immune function, in particular the type-1/type-2 cytokine balance, secondary to increased psychological stress, are thought to mediate these changes in health. The field of psychoneuroimmunology seeks to establish the link between behaviour, neuroendocrine functions, immune responses and health. The current review will describe the effect of psychological stress on immune function, the impact of psychological stress on immune-based pathology, and the future directions of research to determine the mechanisms and clinical significance of the field of psychoneuroimmunology.

Stress and the stress response

Stress may be best defined as a psychophysiological process, usually experienced as a negative emotional state. It is a product of the appraisal of a situation and the resulting coping ability available to the individual. Stressors, defined as events posing threat, are judged in the context of dispositional and environmental factors. Stressors (Table 1) may be physical (i.e. infection, chemical exposure), cognitive (death of a loved one, perception of imminent danger), or a combination of both physical and cognitive (firefighter on a 24-h shift).

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Stressors are further classified into acute (minutes to hours), subchronic (less than 1 month), and chronic (months to years). Some investigators have used the terms 'eustress' and 'distress' to describe situations in which stressors do not cause harm or alter homeostasis, respectively. Different types of stressors as well as durations of stress may elicit different neuroendocrine responses and immune alterations; however, these relationships have not been conclusively identified.

Psychological stress precipitates a coordinated series of physiological and behavioural responses from the host, known as the stress response, aimed at protecting the host and restoring homeostasis. The stress response results in activation of both the hypothalamic-pituitary-adrenal axis (H-P-A) and the sympathetic nervous system (SNS) (Fig. 1) [1,2]. The paraventricular nucleus (PVN) of the hypothalamus receives excitatory stimuli from the catecholaminergic pathways of the brainstem and limbic forebrain circuits [3]. The central, medial and cortical amygdaloid nuclei connect with the PVN via GABA-containing neurones in the bed of the nucleus of the stria terminalis [3].

The PVN may also be activated by aminergic input from the locus coeruleus. Activation of glutamatergic neurones in the PVN results in the secretion of corticotropin-releasing hormone (CRH) from nerve terminals in the median eminence. CRH reaches the anterior pituitary gland via the hypophysial portal circulation and stimulates corticotrophs to release adrenocorticotropic hormone (ACTH) into the peripheral circulation. ACTH subsequently stimulates the production of glucocorticoids by the cells of the zona fasciculata and the zona reticularis of the adrenal cortex. Activation of the SNS causes an increased secretion of catecholamines in nerve termini as well as the adrenal medulla. Psychological stress also has effects on other neuroendocrine pathways such as the hypothalamic-pituitary-gonadal axis, which may result in alterations in menstrual cycle regulation [4].

Table 1 Types of stressors

Physical	Cognitive	Chemical
Trauma/injury	Anxiety	Environmental toxins
Exercise/exhaustion	Depression	Diet
Pain	Anger	Medications
Infection	Major life events	Recreational drugs
Hyper-/hypothermia	Daily 'hassles'	Occupational exposures

The autonomic nervous system and the H-P-A axis provide an interface between psychological stress and other organ systems [5]. The stress-induced release of hormones mediates, at least in part, the effects of stressors on immune function. Such effects appear to occur in both health and disease. The neuroendocrine mediators reach the cells of the immune system either through the peripheral circulation or through direct innervation of lymphoid organs. Primary and secondary lymphoid organs are innervated by sympathetic nerve fibers [6]. Lymphocytes and monocytes express receptors for several stress hormones, including CRH, ACTH, cortisol, norepinephrine and epinephrine [7]. Therefore it is reasonable to conclude that the neuroendocrine hormones released during a stressful event could alter

immune function and subsequently alter the course of immune-based diseases.

Immune-health link

The balance between cell-mediated immunity (CMI) and humoral immunity is largely regulated by cytokines produced by subpopulations of CD4+ T-helper cells, Th1 and Th2 [8]. Th1 cytokines (interferon-gamma (IFN-γ) and IL-12) support CMI for host defence against intracellular parasites such as viruses. Th2 cytokines (IL-4, IL-5, IL-10, IL-13) support humoral immunity for host defence against extracellular parasites [9]. It is now appreciated that other populations of immune cells in addition to T-helper cells, including cytotoxic T-lymphocytes (CTL) and dendritic cells, secrete these cytokines in similar patterns. Therefore the nomenclature, type-1 (Th1-like) and type-2 (Th2-like), is commonly used to delineate a systemic response to antigen challenge.

Dysregulation of the type-1/type-2 cytokine production is thought to be involved in the pathogenesis of several infectious, atopic and asthmatic diseases [10–12]. As will be discussed later, the involvement of the type-1/type-2 cytokine balance in the pathogenesis of these diseases may render them vulnerable to the adverse effects of psychological stress. The type-1/type-2 cytokine balance is important in the maintenance of an adequate CMI against HIV and is believed to be altered during the progression of HIV infection. As HIV infection progresses, the type-1/type-2 cytokine balance shifts from a predominant type-1 cytokine profile towards a type-2 cytokine profile [10,13]. Plasma from HIV+ patients with more advanced disease has increased total IgE levels [10,14] and increased type-2 cytokines with concurrent decreased type-1 cytokines [10]. These studies suggest that HIV progression is associated with a type-2 cytokine shift.

Dysregulation of the type-1/type-2 cytokine balance also plays a significant role in the pathogenesis of asthma and atopic diseases. Bronchial biopsies, bronchoalveolar lavage cells, and peripheral blood mononuclear cells (PBMC) obtained from asthmatics, contain increased IL-4, IL-5 and IL-13 mRNA and protein [12,15]. Furthermore, antigen-specific T-cell clones from atopic and allergic subjects are more polarized towards the Th2 type compared to T-cell clones from healthy subjects [16]. IL-4 is necessary for the isotype switch from IgM to IgE, functions as a mast cell growth factor, and upregulates the expression of eosinophil-related adhesion molecules on lung fibroblasts [17,18]. Eosinophil chemotaxis, differentiation and survival are all supported by IL-5 [19,20]. IL-13, in conjunction with IL-4, contributes to the IgE isotype switch and elicits some of the pathological findings of asthma independent of IL-4 [21–24]. Therefore, conditions that increase type-2 cytokine

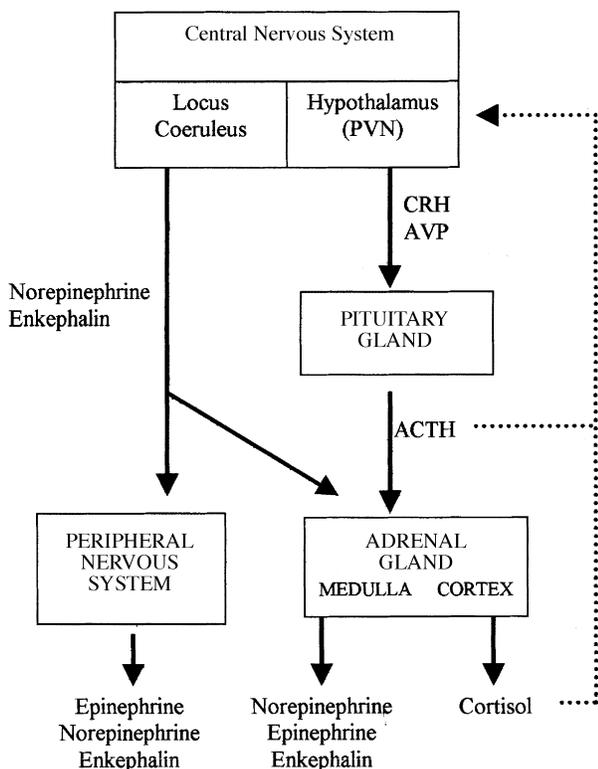


Fig. 1. The stress response. → = activation; = inhibition.

production may lead to a worsening of asthmatic and atopic symptoms.

Stress-immune link

The impact of psychological stress on immune function has been the subject of extensive research efforts. Many models, such as bereavement, marital discord, caregiving for a relative with a chronic disease, living with a cancer diagnosis, and academic exam stress, have been utilized to investigate the affect of chronic stress on immune function [25–30]. Using these models, it has been reported that stress is associated with a suppression of NK cell cytotoxicity, lymphocyte proliferation, and PBMC production of IL-2 and IFN- γ [25,30–34]. Psychological stress is also associated with a higher rate of hypoergy to the common recall delayed type hypersensitivity antigens [35]. These studies suggest that psychological stress suppresses various components of CMI responses.

The effects of psychological stress on latent herpes virus reactivation have also been investigated in both animal and human models [36,37]. Plasma obtained from volunteers during medical student exams contained elevated levels of immunoglobulins specific for the EBV viral capsid antigen, indicating reactivation of EBV [32,34,38]. In addition, stress inhibited EBV-stimulated PBMC proliferation and EBV-specific CTL activity [32,36]. In another study, Glaser and colleagues demonstrated that caregivers of patients with Alzheimer's disease had significantly higher antibody titres to herpes simplex virus type-1 (HSV-1) and lower HSV-1 specific PBMC proliferation than matched controls [39]. These changes in latent virus expression are thought to be secondary to the stress-associated inhibition of CMI.

Psychological stress has also been reported to alter the immune response to vaccines [39–41]. A lower rate of seroconversion after the first hepatitis B vaccine injection has been associated with higher levels of psychological stress [39]. In addition, students with greater social support had higher serum antibody titres to hepatitis B surface antigen (HBsAg) and PBMC proliferation to a HBsAg than those with lower levels of social support [39]. In another study, caregivers of Alzheimer's patients had lower influenza-specific antibody titres and influenza-stimulated IL-2 production by PBMC following influenza virus vaccination compared to the control subjects. Therefore, chronic psychological stress can have a significant adverse impact on the immune response against vaccines.

Based on the stress-associated alterations in *in vitro* immune responses, latent virus reactivation, and vaccine responses discussed above, the postulated mechanism most often advanced to explain these results involves immunosuppression as a fundamental effect of stress [34].

However, recent data have suggested that a dysregulation of the type-1/type-2 cytokine balance may play a more significant role in stress-associated immune alterations [42]. Using the academic stress model, we recently demonstrated that PBMC production of IFN- γ , a type-1 cytokine, was decreased with a concurrent increase in IL-10, a type-2 cytokine, production during an examination period compared with a period of lower stress. Furthermore, the increase in IL-10 production and the decrease in the IFN γ :IL-10 ratio correlated with the level of psychological distress as measured by the Hassles Scale. These data suggest that chronic stress does not simply suppress the immune system, but induces a shift in the type-1/type-2 cytokine balance towards a type-2 cytokine response. A stress-associated alteration in the type-1/type-2 cytokine balance may better explain the fluctuations in the clinical course of several immune-based diseases (discussed below).

In vitro models are currently being utilized to investigate the mechanisms of the *in vivo* stress-associated immune dysregulation. Glucocorticoids and catecholamines, at concentrations observed during periods of stress, decrease IFN- γ production and increase IL-4 and IL-10 production by human PBMC, indicating a shift in the type-1/type-2 cytokine balance towards a type-2 response [43,44]. In addition, *in vitro* exposure to cortisol analogs, ACTH, somatostatin and CRH causes a viral production in cell lines latently infected with EBV [45] and HIV [46]. These data demonstrate the ability of the neuroendocrine hormones to directly modulate immune function and may in part explain the type-1/type-2 cytokine alterations and latent virus reactivation observed in subjects during periods of increased psychological stress.

Stress-health link

A common clinical observation is the adverse relationship between stress and human disease [47]. Although the effects of stress on health have been difficult to demonstrate due to the difficulty in assessing stress levels, the number of potential confounding variables, and the low incidence of an illness in study populations, several investigators have demonstrated a significant interaction between psychological stress and health. This association appears to be particularly true with regards to immune-based diseases such as increased susceptibility to infections [48,49], atopic diseases [50–52] and asthma [53,54]. Stress is also suspected of playing a role in morbidity and mortality in other immune-based diseases such as cancer [55], HIV disease [56], and the immune senescence associated with ageing [57,58]. The adverse effects of stress on health are potentially mediated by the stress-associated type-1/type-2 cytokine alterations [42].

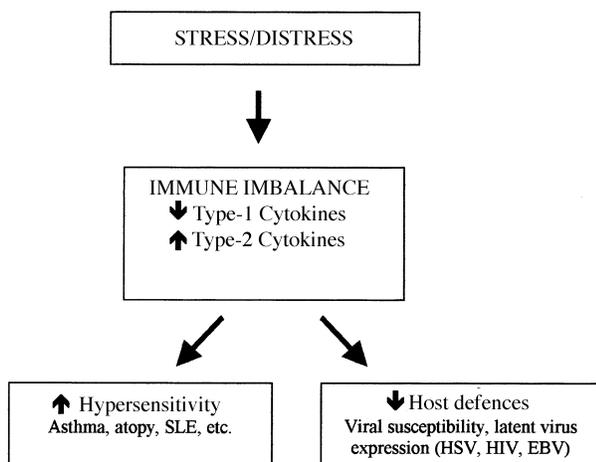


Fig. 2. The stress-distress-immune-health paradigm.

Stress and viral infections

Psychological stress has been associated with increased susceptibility and/or risk of infectious diseases, including upper respiratory infections (URI), herpes reactivation and HIV. A recent report demonstrated that persistent stressors and anxiety predict recurrence of genital herpes in women [59]. Graham and colleagues prospectively followed 235 adults, and found that higher levels of self-reported stress were associated with increased coryzal symptoms and confirmed URIs [60]. A subsequent study found that children with a history of recurrent URI had increased levels of distress and lower salivary IgA levels, suggesting a suppression of local mucosal immunity [61]. In a recent report, life stress was associated with an increase in URI incidence in children that was moderated by social support [62].

The studies discussed above suggest an association between stress and URI susceptibility, but do not differentiate between the stress-associated changes in host resistance or increased exposure to viruses due to changes in social behaviour. To address this issue, Cohen *et al.* administered an experimental intranasal viral challenge to volunteers who were kept in isolation, to minimize the effect of prior viral exposure and person-to-person spread. The rates of viral infection as well as coryzal symptoms correlated with increased psychological stress levels [63]. In a subsequent study, only stressors of at least 1 month in duration were sufficient to increase an individual's risk for URIs [64]. These studies suggest that psychological stress is associated with increased URI susceptibility due to intrinsic changes in host resistance.

The relationship between stress, immune function and health has sparked an interest in the potential adverse impact of stress on the progression of HIV infection. Psychological stress is associated with decreased PBMC

proliferation, decreased numbers of NK cells and CTL, and increased latent viral expression in HIV+ subjects [65,66]. In addition, asymptomatic HIV+ subjects reporting increased psychological stress levels had lower CD4+ T-lymphocyte numbers that were moderated by an active coping style [67,68]. Finally, several reports have demonstrated beneficial effects of interventions that decrease stress levels, on immune function and CD4+ T-lymphocyte numbers of HIV+ subjects [69–71]. These studies suggest that stress-associated immune alterations, particularly during the early stages of HIV infection, may place patients at increased risk for rapid progression. Additional studies utilizing more sensitive surrogate markers (e.g. viral load) are necessary to better define the relationship between stress and HIV.

Stress and asthma

Anecdotal evidence supports a relationship between increased emotional states and asthma exacerbations. Indeed, compared to healthy controls, asthmatics have higher levels of life stress and negative emotions, such as panic, fear and irritability [72–76]. Furthermore, some asthmatics have been found to have higher levels of psychological symptoms [77] and depression [78]. While these studies show a relationship between emotion, stress and asthma they do not adequately define the cause and effect relationship. Some studies have shown that the increased psychological symptoms are a result of asthma exacerbations [79]. On the other hand, other studies suggest that extreme emotional manifestations can worsen asthma symptoms [72].

Recently there have been several studies using the academic stress model in teenage asthmatics [80–82]. These studies demonstrated that mild to moderate asthmatic subjects have immunological changes (decreased NK cell cytotoxicity and cytokine alterations) in response to exam stress. These immune alterations are consistent with a cytokine milieu that could potentially worsen asthma; however, there were no changes in peak flow rates, self-report asthma symptoms or medication utilization. The lack of correlation between stress and asthma symptoms may be related to the timing of the visits in relation to the stressor, the duration of the stressor, disease severity, or a lack of accurate self-report data. Alternatively, stress-mediated exacerbations of asthma may require multiple alterations by stress, including cytokine dysregulation and/or vagal-mediated airway hyperresponsiveness.

A recent intervention study suggests that psychological stress may play an important role in asthma [83]. Asthmatics who wrote about past stressful experiences had an improvement in the predicted FEV₁ compared to control groups, which was associated with decreases in

self-reported distress levels. These results are provocative in that they demonstrate a relationship between psychological stress and asthma and suggest a role for stress management in the treatment of complicated asthmatics.

Future directions in psychoneuroimmunology

As discussed above, extensive research has demonstrated a marked effect of psychological stress on immunity in humans. Currently, it is hypothesized that through activation of the H-P-A axis and the SNS, stress induces a dysregulation of the type-1/type-2 cytokine. We believe that these type-1/type-2 cytokine alterations are a major mechanism of the stress-associated increased susceptibility and/or severity of immune-based diseases (Fig. 2). It remains to be determined whether the effects of psychological stress on immune balance are mediated through alterations in type-1/type-2 cellular differentiation, cellular trafficking, chemokine production, and/or adhesion molecule expression.

Additional prospective studies using clinically relevant outcome measures are necessary to further define the impact of psychological stress on immune-based diseases. Better definition of the mechanisms of the stress-associated immune alterations, the specific nature of the stressors that adversely impact health, and the clinical course of stress-mediated alterations in disease, will provide valuable insight for the development of pharmacological and/or behavioural interventions to prevent and/or treat the clinical sequelae of stress-associated immune dysregulation.

References

- Meyerhoff JL, Oleshansky MA, Mougey EH. Psychologic stress increases plasma levels of prolactin, cortisol, and POMC-derived peptides in man. *Psychosom Med* 1988; 50:295–303.
- Richter SD, Schurmeyer TH, Schedlowski M, Hadicke A, Tewes U, Schmidt RE, Wagner TO. Time kinetics of the endocrine response to acute psychological stress. *J Clin Endocrinol Metab* 1996; 81:1956–60.
- Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci* 1997; 20:78–84.
- Chrousos GP, Torpy DJ, Gold PW. Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: clinical implications. *Ann Intern Med* 1998; 129:229–40.
- Wilder RL. Neuroendocrine-immune system interactions and autoimmunity. *Annu Rev Immunol* 1995; 13:307–38.
- Felten DL. Direct innervation of lymphoid organs: substrate for neurotransmitter signaling of cells of the immune system. *Neuropsychobiology* 1993; 28:110–12.
- Blalock JE, Bost KL, Smith EM. Neuroendocrine peptide hormones and their receptors in the immune system. Production, processing and action. *J Neuroimmunol* 1985; 10:31–40.
- Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol* 1986; 136:2348–57.
- Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunol Today* 1996; 17:138–46.
- Agarwal SK, Marshall GD. In vivo alteration in type-1 and type-2 cytokine balance: a possible mechanism for elevated total IgE in HIV-infected patients. *Hum Immunol* 1998; 59:99–105.
- Kuchroo VK, Das MP, Brown JA, Ranger AM, Zamvil SS, Sobel RA et al. B7-1 and B7-2 costimulatory molecules activate differentially the Th1/Th2 developmental pathways: application to autoimmune disease therapy. *Cell* 1995; 80:707–18.
- Robinson D, Hamid Q, Bentley A, Ying S, Kay AB, Durham SR. Activation of CD4+ T cells, increased TH2-type cytokine mRNA expression, and eosinophil recruitment in bronchoalveolar lavage after allergen inhalation challenge in patients with atopic asthma. *J Allergy Clin Immunol* 1993; 92:313–24.
- Clerici M, Shearer GM. The Th1-Th2 hypothesis of HIV infection: new insights. *Immunol Today* 1994; 15:575–81.
- Israel-Biet D, Labrousse F, Tourani JM, Sors H, Andrieu JM, Even P. Elevation of IgE in HIV-infected subjects: a marker of poor prognosis. *J Allergy Clin Immunol* 1992; 89:68–75.
- Del Prete GF, De Carli M, D'Elios MM, Maestrelli P, Ricci M, Fabbri L, Romagnani S. Allergen exposure induces the activation of allergen-specific Th2 cells in the airway mucosa of patients with allergic respiratory disorders. *Eur J Immunol* 1993; 23:1445–49.
- Essayan DM, Han WF, Li XM, Xiao HQ, Kleine-Tebbe J, Huang SK. Clonal diversity of IL-4 and IL-13 expression in human allergen-specific T lymphocytes. *J Allergy Clin Immunol* 1996; 98:1035–44.
- Romagnani S, Del Prete G, Maggi E, Parronchi P, Tiri A, Macchia D et al. Role of interleukins in induction and regulation of human IgE synthesis. *Clin Immunol Immunopathol* 1989; 50:S13–S23.
- Doucet C, Brouty-Boye D, Pottin-Clemenceau C, Canonica GW, Jasmin C, Azzarone B. Interleukin (IL) 4 and IL-13 act on human lung fibroblasts. Implication in asthma. *J Clin Invest* 1998; 101:2129–39.
- Dent LA, Strath M, Mellor AL, Sanderson CJ. Eosinophilia in transgenic mice expressing interleukin 5. *J Exp Med* 1990; 172:1425–31.
- Sanderson CJ, Warren DJ, Strath M. Identification of a lymphokine that stimulates eosinophil differentiation in vitro. Its relationship to interleukin 3, and functional properties of eosinophils produced in cultures. *J Exp Med* 1985; 162:60–74.
- Punnonen J, Yssel H, de Vries JE. The relative contribution of IL-4 and IL-13 to human IgE synthesis induced by activated CD4+ or CD8+ T cells. *J Allergy Clin Immunol* 1997; 100:792–801.
- Grunig G, Warnock M, Wakil AE, Venkayya R, Brombacher

- F, Rennick DM et al. Requirement for IL-13 independently of IL-4 in experimental asthma. *Science* 1998; 282:2261–63.
- 23 Wills-Karp M, Luyimbazi J, Xu X, Schofield B, Nelsen TY, Karp CL, Donaldson DD. Interleukin-13: central mediator of allergic asthma. *Science* 1998; 282:2258–61.
- 24 Parronchi P, De Carli M, Manetti R et al. Aberrant interleukin (IL)-4 and IL-5 production *in vitro* by CD4+ helper T cells from atopic subjects. *Eur J Immunol* 1992; 22:1615–20.
- 25 Schleifer SJ, Keller SE, Camerino M, Thornton JC, Stein M. Suppression of lymphocyte stimulation following bereavement. *JAMA* 1983; 250:374–7.
- 26 Kiecolt-Glaser JK, Fisher LD, Ogrocki P, Stout JC, Speicher CE, Glaser R. Marital quality, marital disruption, and immune function. *Psychosom Med* 1987; 49:13–34.
- 27 Esterling BA, Kiecolt-Glaser JK, Bodnar JC, Glaser R. Chronic stress, social support, and persistent alterations in the natural killer cell response to cytokines in older adults. *Health Psychol* 1994; 13:291–8.
- 28 Kiecolt-Glaser JK, Dura JR, Speicher CE, Trask OJ, Glaser R. Spousal caregivers of dementia victims: longitudinal changes in immunity and health. *Psychosom Med* 1991; 53:345–62.
- 29 Andersen BL, Farrar WB, Golden-Kreutz D, Kutz LA, MacCallum R, Courtney ME, Glaser R. Stress and immune responses after surgical treatment for regional breast cancer. *J Natl Cancer Inst* 1998; 90:30–36.
- 30 Kiecolt-Glaser JK, Garner W, Speicher C, Penn GM, Holliday J, Glaser R. Psychosocial modifiers of immunocompetence in medical students. *Psychosom Med* 1984; 46:7–14.
- 31 Kiecolt-Glaser JK, Glaser R, Strain EC, Stout JC, Tarr KL, Holliday JE, Speicher CE. Modulation of cellular immunity in medical students. *J Behav Med* 1986; 9:5–21.
- 32 Glaser R, Pearson GR, Bonneau RH, Esterling BA, Atkinson C, Kiecolt-Glaser JK. Stress and the memory T-cell response to the Epstein-Barr virus in healthy medical students. *Health Psychol* 1993; 12:435–42.
- 33 Dobbins JP, Harth M, McCain GA, Martin RA, Cousin K. Cytokine production and lymphocyte transformation during stress. *Brain Behav Immun* 1991; 5:339–48.
- 34 Glaser R, Rice J, Sheridan J, Fertel R, Stout J, Speicher C et al. Stress-related immune suppression: health implications. *Brain Behav Immun* 1987; 1:7–20.
- 35 Muller HK, Lugg DJ, Quinn D. Cell mediated immunity in Antarctic wintering personnel; 1984–92. *Immunol Cell Biol* 1995; 73:316–20.
- 36 Glaser R, Pearson GR, Jones JF, Millhouse J, Kennedy S, Mao HY, Kiecolt-Glaser JK. Stress-related activation of Epstein-Barr virus. *Brain Behav Immun* 1991; 5:219–32.
- 37 Padgett DA, Sheridan JF, Dorne J, Berntson GG, Candelora J, Glaser R. Social stress and the reactivation of latent herpes simplex virus type 1 [published erratum appears in *Proc Natl Acad Sci USA* 1998; 95(20):12070]. *Proc Natl Acad Sci USA* 1998; 95:7231–35.
- 38 Glaser R, Pearl DK, Kiecolt-Glaser JK, Malarkey WB. Plasma cortisol levels and reactivation of latent Epstein-Barr virus in response to examination stress. *Psychoneuroendocrinology* 1994; 19:765–72.
- 39 Glaser R, Kiecolt-Glaser JK, Bonneau RH, Malarkey W, Kennedy S, Hughes J. Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. *Psychosom Med* 1992; 54:22–9.
- 40 Glaser R, Kiecolt-Glaser JK, Malarkey WB, Sheridan JF. The influence of psychological stress on the immune response to vaccines. *Ann NY Acad Sci* 1998; 840:649–55.
- 41 Jabaaaj L, Grosheide PM, Heijtkink RA, Duivenvoorden HJ, Ballieux RE, Vingerhoets AJ. Influence of perceived psychological stress and distress on antibody response to low dose rDNA hepatitis B vaccine. *J Psychosom Res* 1993; 37:361–9.
- 42 Marshall GD, Agarwal SK, Lloyd C, Cohen L, Henninger EM, Morris GJ. Cytokine dysregulation in healthy medical students associated with exam stress. *Brain Behav Immun* 1998; 12:297–307.
- 43 Agarwal SK, Marshall GD. Glucocorticoid-induced type 1/type 2 cytokine alterations in humans: a model for stress-related immune dysfunction. *J Interferon Cytokine Res* 1998; 18:1059–68.
- 44 Agarwal SK, Marshall GD. beta-Adrenergic modulation of human type-1/type-2 cytokine balance. *J Allergy Clin Immunol* 2000; 105:91–8.
- 45 Glaser R, Kutz LA, MacCallum RC, Malarkey WB. Hormonal modulation of Epstein-Barr virus replication. *Neuroendocrinology* 1995; 62:356–61.
- 46 Marshall GD, Agarwal SK, Glaser R. Enhancement of chronic HIV infection *in vitro* by stress hormones. *Neuroimmunomodulation* 1999; 6:235 (Abstract).
- 47 McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. *Arch Intern Med* 1993; 153:2093–101.
- 48 Sheridan JF, Dobbs C, Brown D, Zwillig B. Psychoneuroimmunology: stress effects on pathogenesis and immunity during infection. *Clin Microbiol Rev* 1994; 7:200–12.
- 49 Shephard RJ, Shek PN. Infectious diseases in athletes: new interest for an old problem. *J Sports Med Phys Fitness* 1994; 34:11–22.
- 50 Michel FB. Psychology of the allergic patient. *Allergy* 1994; 49:28–30.
- 51 Parker CW. Environmental stress and immunity: possible implications for IgE-mediated allergy. *Perspect Biol Med* 1991; 34:197–212.
- 52 Kodama A, Horikawa T, Suzuki T, Ajiki W, Takashima T, Haroda S, Ichihashi M. Effect of stress on atopic dermatitis: investigation in patients after the Great Hanshin earthquake. *J Allergy Clin Immunol* 1999; 104:173–6.
- 53 Koh KB, Hong CS. The relationship of stress with serum IgE level in patients with bronchial asthma. *Yonsei Med J* 1993; 34:166–74.
- 54 Busse WW, Kiecolt-Glaser JK, Coe C, Martin RJ, Weiss ST, Parker SR. NHLBI Workshop summary. Stress and asthma. *Am J Respir Crit Care Med* 1995; 151:249–52.
- 55 Chorot P, Sandin B. Life events and stress reactivity as predictors of cancer, coronary heart disease and anxiety disorders. *Int J Psychosom* 1994; 41:34–40.
- 56 Evans DL, Leserman J, Perkins DO et al. Stress-associated reductions of cytotoxic T lymphocytes and natural killer cells in asymptomatic HIV infection. *Am J Psychiatry* 1995; 152:543–50.

- 57 Kiecolt-Glaser JK, Glaser R, Williger D et al. Psychosocial enhancement of immunocompetence in a geriatric population. *Health Psychol* 1985; 4:25–41.
- 58 Finkelstein MS. Aging immunocytes and immunity. Characteristics and significance. *Clin Geriatr Med* 1985; 1:899–911.
- 59 Cohen F, Kemeny ME, Kearney KA, Zegans LS, Neuhaus JM, Conant MA. Persistent stress as a predictor of genital herpes recurrence. *Arch Intern Med* 1999; 159:2430–36.
- 60 Graham MB, Braciale VL, Braciale TJ. Influenza virus-specific CD4+ T helper type 2 T lymphocytes do not promote recovery from experimental virus infection. *J Exp Med* 1994; 180:1273–82.
- 61 Drummond PD, Hewson-Bower B. Increased psychosocial stress and decreased mucosal immunity in children with recurrent upper respiratory tract infections. *J Psychosom Res* 1997; 43:271–8.
- 62 Turner CJ, Steptoe A. Psychosocial influences on upper respiratory infectious illness in children. *J Psychosom Res* 1998; 45:319–30.
- 63 Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. *N Engl J Med* 1991; 325:606–12.
- 64 Cohen S, Frank E, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM. Types of stressors that increase susceptibility to the common cold in healthy adults. *Health Psychol* 1998; 17:214–23.
- 65 Ironson G, LaPerriere A, Antoni M, O'Hearn P, Schneiderman N, Klimas N, Fletcher MA. Changes in immune and psychological measures as a function of anticipation and reaction to news of HIV-1 antibody status. *Psychosom Med* 1990; 52:247–70.
- 66 Esterling BA, Antoni MH, Schneiderman N, Carver CS, La Perriere A, Ironson G et al. Psychosocial modulation of antibody to Epstein-Barr viral capsid antigen and human herpesvirus type-6 in HIV-1-infected and at-risk gay men. *Psychosom Med* 1992; 54:354–71.
- 67 Goodkin K, Fuchs I, Feaster D, Leeka J, Rishel DD. Life stressors and coping style are associated with immune measures in HIV-1 infection – a preliminary report. *Int J Psychiatry Med* 1992; 22:155–72.
- 68 Goodkin K, Blaney NT, Feaster D, Fletcher MA, Baum MK, Mantero-Atienza E et al. Active coping style is associated with natural killer cell cytotoxicity in asymptomatic HIV-1 seropositive homosexual men. *J Psychosom Res* 1992; 36:635–50.
- 69 Ironson G, Field T, Scafidi F, Hashimoto M, Kumar M, Price A et al. Massage therapy is associated with enhancement of the immune system's cytotoxic capacity. *Int J Neurosci* 1996; 84:205–17.
- 70 LaPerriere A, Klimas N, Fletcher MA, Perry A, Ironson G, Perna F, Schneiderman N. Change in CD4+ cell enumeration following aerobic exercise training in HIV-1 disease: possible mechanisms and practical applications. *Int J Sports Med* 1997; 18(Suppl. 1):S56–S61.
- 71 Lutgendorf SK, Antoni MH, Ironson G et al. Cognitive-behavioral stress management decreases dysphoric mood and herpes simplex virus-type 2 antibody titers in symptomatic HIV-seropositive gay men. *J Consult Clin Psychol* 1997; 65:31–43.
- 72 Lehrer PM, Isenberg S, Hochron SM. Asthma and emotion: a review. *J Asthma* 1993; 30:5–21.
- 73 Dirks JF, Kinsman RA, Staudenmayer H, Kleiger JH. Panic-fear in asthma. Symptomatology as an index of signal anxiety and personality as an index of ego resources. *J Nerv Ment Dis* 1979; 167:615–9.
- 74 Carr RE, Lehrer PM, Hochron SM. Panic symptoms in asthma and panic disorder: a preliminary test of the dyspnea-fear theory. *Behav Res Ther* 1992; 30:251–61.
- 75 Wade S, Weil C, Holden G, Mitchell H, Evans R 3rd, Kruszon-Moran D et al. Psychosocial characteristics of inner-city children with asthma: a description of the NCICAS psychosocial protocol. National Cooperative Inner-City Asthma Study. *Pediatr Pulmonol* 1997; 24:263–76.
- 76 Sarafino EP, Dillon JM. Relationships among respiratory infections, triggers of attacks, and asthma severity in children. *J Asthma* 1998; 35:497–504.
- 77 Badoux A, Levy DA. Psychologic symptoms in asthma and chronic urticaria. *Ann Allergy* 1994; 72:229–34.
- 78 Miller BD. Depression and asthma: a potentially lethal mixture. *J Allergy Clin Immunol* 1987; 80:481–6.
- 79 Apter AJ, Affleck G, Reisine ST, Tennen HA, Basrows E, Wells M et al. Perception of airway obstruction in asthma: sequential daily analyses of symptoms, peak expiratory flow rate, and mood. *J Allergy Clin Immunol* 1997; 99:605–12.
- 80 Kang DH, Coe CL, Karaszewski J, McCarthy DO. Relationship of social support to stress responses and immune function in healthy and asthmatic adolescents. *Res Nurs Health* 1998; 21:117–28.
- 81 Kang DH, Coe CL, McCarthy DO. Academic examinations significantly impact immune responses, but not lung function, in healthy and well-managed asthmatic adolescents. *Brain Behav Immun* 1996; 10:164–81.
- 82 Kang DH, Coe CL, McCarthy DO et al. Cytokine profiles of stimulated blood lymphocytes in asthmatic and healthy adolescents across the school year. *J Interferon Cytokine Res* 1997; 17:481–7.
- 83 Smyth JM, Stone AA, Hurewitz A, Kaell A. Effects of writing about stressful experiences on symptom reduction in patients with asthma or rheumatoid arthritis: a randomized trial. *JAMA* 1999; 281:1304–09.