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# The Impact of Everyday Stressors on the Immune System and Health

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Lisa M. Christian and Ronald Glaser

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## 4.1 Stress and Inflammation

Much research linking stress and immune function has focused on inflammatory processes. Although inflammation is an essential immune response to infection or injury, exaggerated and/or chronic elevations in inflammatory proteins are detrimental to health. Indeed, inflammation contributes to risk and severity of chronic health conditions including cardiovascular disease, arthritis, diabetes, inflammatory bowel disease, periodontal disease, certain cancers, and age-related functional decline (Hamerman et al. 1999; Ershler and Keller 2000; Bruunsgaard et al. 2001; Black and Garbutt 2002; Ishihara and Hirano 2002). Via neuroendocrine pathways, psychological stress directly promotes elevations in circulating inflammatory proteins and primes the immune system to exhibit exaggerated inflammatory responses when faced with an immune challenge (e.g., exposure to an infectious agent).

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L.M. Christian (✉)

Department of Psychiatry, The Ohio State University Medical Center,  
Columbus, OH, USA

Institute for Behavioral Medicine Research, The Ohio State University,  
Columbus, OH, USA

Department of Psychology, The Ohio State University,  
Columbus, OH, USA

Department of Obstetrics and Gynecology,  
The Ohio State University Medical Center, Columbus, OH, USA  
e-mail: lisa.christian@osumc.edu

R. Glaser

Institute for Behavioral Medicine Research, The Ohio State University,  
Columbus, OH, USA

Molecular Virology, Immunology, and Medical Genetics, The Ohio State University,  
Columbus, OH, USA

Caregiving provides an important model for assessing the effects of chronic stress on health; individuals who provide care for loved ones with chronic medical conditions, such as a spouse with dementia, commonly experience long-term stress characterized by significant life change and social isolation. We found that the chronic stress of caregiving exacerbated typical age-related increases in the proinflammatory cytokine interleukin(IL)-6; caregivers experienced fourfold greater increases in IL-6 in a 6-year longitudinal study compared to controls (Kiecolt-Glaser et al. 2003). Thus, stress accelerated this aspect of the aging process and increased risk for age-related diseases as already mentioned.

Proinflammatory cytokines also rise in response to acute stressors such as being told that one is laid off or having an argument. Indeed, relatively minor and brief laboratory stress tasks, such as public speaking, result in increases in circulating inflammatory markers (Steptoe et al. 2001; Brydon et al. 2004). The magnitude of inflammatory response seen following objective stressors is not necessarily predicted by subjective perceptions of stress (e.g., Brydon et al. 2004).

Importantly, repeated exposure to a stressor may not lead to habituation of inflammatory responses. For example, healthy middle-aged men were exposed to the same laboratory stressor involving public speaking three times with 1-week intervals between sessions. Although cortisol and blood pressure reactivity to the task habituated over time, stress-induced elevations in IL-6 were equivalent across visits (von Kanel et al. 2005). Thus, exposure to relatively minor but recurrent stress in daily life may contribute to morbidity and mortality by promoting inflammation.

In addition to directly promoting elevations in inflammatory markers, chronic stress and depressive symptoms can also "prime" the immune system to show an exaggerated inflammatory response upon exposure to psychological stressors and biological challenges (Anisman et al. 1999; Maes 1995; 1999; Glaser et al. 2003, Johnson et al. 2002; Maes et al. 2001; Stark et al. 2002; Avitsur et al. 2005; Quan et al. 2001; LeMay et al. 1990; Zhou et al. 1993). For example, rats exposed to repeated stressors mount exaggerated inflammatory responses upon exposure to an antigen *in vivo* and by cells stimulated *in vitro* (Johnson et al. 2002; Stark et al. 2002; Avitsur et al. 2005). Similarly, we have shown that, among older adults (Glaser et al. 2003) as well as healthy pregnant women (Christian et al. 2010), greater depressive symptoms predicted greater inflammatory responses to a challenge with an influenza virus vaccine.

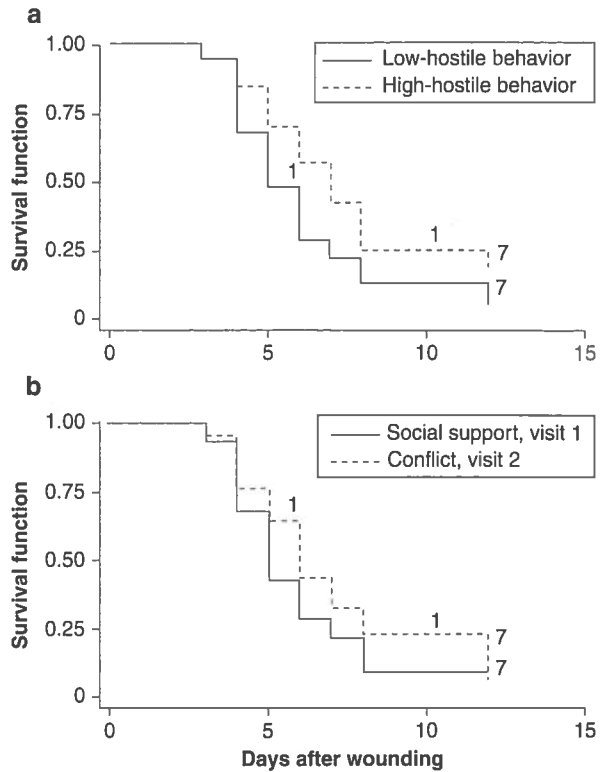
In sum, stress as well as psychological distress (e.g., depressive symptoms) can promote inflammation directly, and prime the immune system to show an exaggerated inflammatory response when challenged. Via these pathways, exposure to chronic psychological stress as well as minor but repeated stressors may ultimately contribute to risk of a variety of health conditions for which inflammatory processes are implicated.

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## 4.2 Stress and Wound Healing

The skin provides the body's first line of immune defense by providing a physical barrier against invasion by pathogens as well as antigens and limiting the movement of water in and out of the body (Elias 2005; Marks 2004). Thus, the integrity of the

**Fig. 4.1** Kaplan–Meier survival curves for time to healing of the standard wound across both visits by high- or low-hostile behavior (a) and for time to healing of the standard wound by visit (b). Couples who demonstrated consistently higher levels of hostile behaviors across both their interactions healed at 60% of the rate of low-hostile couples, and healing during the conflict visit was at 72% of the rate observed following the social support visit. Annotations on the curves show the number of censored observations at each point, indicating patients who were unhealed on their last day of observation (Reprinted from Kiecolt-Glaser et al. 2005)



skin and the ability of the skin to heal quickly following injury are important measures of immune competence. When tissue damage occurs in healthy people, healing progresses sequentially through three overlapping phases: inflammation, proliferation, and remodeling (Baum and Arpey 2005; Singer and Clark 1999). Success in later phases is highly dependent on preceding phases. A variety of stressors can delay wound healing in humans and there is evidence that this is mediated, in part, by effects of stress on the inflammatory stage of the healing process.

In one study, we found that women experiencing the chronic stress of caregiving for a spouse with dementia required 24% longer to heal a small standardized punch biopsy wound than controls (Kiecolt-Glaser et al. 1995). Similarly, dental students who received mucosal punch biopsy wounds in the hard palate healed an average of 40% more slowly during an academic examination period than during a vacation period, which was rated as less stressful by participants (Marucha et al. 1998). Stress of an even shorter duration has measurable effects on healing (Fig. 4.1). In a study of married couples, participants healed more slowly when they completed a 30-min conflictive interaction with their spouses in a laboratory setting than when they completed a supportive interaction (Kiecolt-Glaser et al. 2005). Those who demonstrated consistently high levels of hostile behavior during both interactions healed wounds at 60% of the rate of low-hostile individuals.

Each of the studies described above also provides evidence that stress disrupts the inflammatory stage of healing; in this context, a robust local inflammatory response is beneficial. Among married couples, decreased production of three key cytokines – IL-6, IL-1 $\beta$ , and TNF- $\alpha$  – was observed at the wound site following the conflictive compared to supportive interaction. Similarly, compared to controls, circulating peripheral blood leukocytes (PBLs) from caregivers expressed less IL-1 $\beta$ -encoded messenger RNA (mRNA) in response to lipopolysaccharide (LPS) stimulation (Kiecolt-Glaser et al. 1995). Finally, in the study with dental students, production of IL-1 $\beta$  mRNA by LPS-stimulated PBLs was lower in every dental student during exams compared to vacation.

In addition to studies of wound healing, effects of stress on skin function can also be assessed using tape stripping, a minimally invasive procedure. Through repeated applications of cellophane tape, commonly to the forearm, a layer of epithelial skin cells is removed from the outermost layer (stratum corneum) causing mild skin barrier disruption. Tape stripping impairs the skin's ability to regulate moisture, resulting in greater transepidermal water loss (TEWL) (Marks 2004). Skin barrier recovery can be quantified by measuring changes in TEWL over time.

Several studies have demonstrated that stress slows skin barrier recovery following tape stripping. Dental students recovered significantly more slowly when assessed during academic exams as compared to vacation with approximately 30% versus 45% recovery at 3 h following tape stripping (Garg et al. 2000). Brief laboratory stressors such as public speaking also reduce the speed of skin barrier recovery by 10–15% (Altemus et al. 2001; Robles 2007).

The magnitude to which the same stressor exerts an impact on healing may differ across individuals. Dental students reporting the greatest stress during academic exams showed the greatest decrements in skin barrier recovery following tape stripping (Garg et al. 2000). Conversely, certain traits may buffer individuals from negative effects of stress; individuals high in trait positive affect did not show decrements in skin barrier recovery upon exposure to an acute laboratory stressor, although decrements were seen among those low in trait positive affect (Robles et al. 2009).

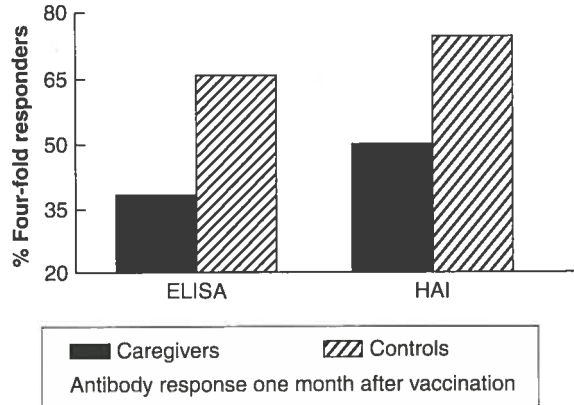
Together, data from these studies show that objective stressors ranging from chronic (e.g., caregiving) to acute (e.g., brief laboratory task) significantly impact healing and skin barrier recovery. Further, subjective ratings of stress as well as individual characteristics (e.g., hostility, trait positive affect) can affect the magnitude of such effects. Thus, although the experience of objective stressors affects healing, coping abilities, and personality characteristics that promote resilience may buffer such effects, making some individuals less susceptible to stress-induced decrements in healing.

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### 4.3 Stress and Infectious Agents

Central to immune function is the ability to respond quickly and adequately in response to infectious agents. As described below, it is well established that stress not only makes individuals more susceptible to illness after exposure to infectious

**Fig. 4.2** Percentage of caregivers and controls showing a clinically significant fourfold increase in antibody 1 month after seasonal influenza virus vaccination using antibody data from two different assays (Reprinted from Kiecolt-Glaser et al. 1996). *HAI* hemagglutination-inhibition assay



agents, but can also inhibit the antibody and virus-specific T-cell response to vaccines and can induce the reactivation of latent herpes viruses.

#### 4.3.1 Vaccination Studies

Psychological stress predicted poorer immune responses to vaccines including influenza, pneumococcal pneumonia, hepatitis B (Hep B), and meningococcal C (Glaser et al. 1998, 2000; Kiecolt-Glaser et al. 1996; Vedhara et al. 1999; Phillips et al. 2005; Burns et al. 2002, 2003; Glaser et al. 1992; Miller et al. 2004; Christian et al. 2009; Cohen et al. 2001; Pedersen et al. 2009). This can result in inadequate protection upon exposure to the infectious agent of interest (Couch and Kasel 1983). Poor antibody responses to a bacterial vaccine (pneumococcus) and poor antibody and virus-specific T-cell responses to viral vaccines (influenza and Hepatitis B) also serve as a marker of diminished immune function in general, which may have implications beyond vulnerability to a specific infectious illness (Kiecolt-Glaser et al. 1996).

Effects of caregiving stress on antibody responses to influenza virus vaccination have been demonstrated by our group and others in elderly and nonelderly caregivers (Fig. 4.2) (Vedhara et al. 1999, 2002; Glaser et al. 1998; Kiecolt-Glaser et al. 1996; Segerstrom et al. 2008). In addition, greater perceived stress and more frequent stressful life events have been associated with lower antibody responses and poorer maintenance of antibody levels following influenza vaccination among young adults (Phillips et al. 2005; Burns et al. 2003; Miller et al. 2004). A recent meta-analysis of 13 studies concluded that the effect of stress on antibody responses to influenza virus vaccination corresponded to adequate antibody responses among 41% of stressed individuals versus 59% of less stressed individuals with similar effects among older and younger adults (Pedersen et al. 2009).

Life stress has also been associated with poorer maintenance of antibody levels against a pneumococcus vaccine (Glaser et al. 2000), poorer seroconversion and maintenance of antibody against Hep B (Burns et al. 2002; Glaser et al. 1992), and slower antibody responses to meningococcal C vaccination (Phillips et al. 2005). Although detailed coverage of neuroendocrine mechanisms underlying these associations is beyond the scope of the current chapter, animal models demonstrate multiple effects of glucocorticoid hormones on cell-trafficking, and production of proinflammatory cytokines and chemokines which contribute to these effects (for review see Godbout and Glaser 2006; Padgett and Glaser 2003).

### 4.3.2 Infectious Illness

Stress affects susceptibility, severity, and duration of infectious illnesses including influenza and the common cold virus. A number of naturalistic studies have reported associations between stress and frequency of infectious illness (e.g., Turner-Cobb and Steptoe 1996; Graham et al. 1986). However, the strongest evidence of effects of stress on infectious illness comes from controlled laboratory studies in which participants have been exposed to infectious agents. In a key study, Cohen and colleagues demonstrated that self-reported stress predicted susceptibility to respiratory viruses in a dose-response manner. Healthy subjects were exposed to one of five respiratory viruses, quarantined, and assessed for respiratory symptoms and virus-specific antibody titers. Those reporting greater stress (a composite measure of major life events, perceptions of stress, and negative affect) showed greater likelihood of developing respiratory infections as well as clinically defined colds (Cohen et al. 1991). This effect was found across each of the five types of virus strains, and the effect remained after controlling for numerous potential confounding factors. Subsequent research from the same laboratory demonstrated that chronic life stress lasting 1 month or longer is key to such effects (Cohen et al. 1998).

Individuals who experience greater physiological reactivity when facing stressful situations may be more vulnerable to infectious illness. Among 115 healthy individuals, those who showed larger cortisol responses to a laboratory stressor experienced greater risk of developing clinically verified colds under conditions of higher stress (Cohen et al. 2002). Stress level was unrelated to risk of colds among those showing smaller cortisol responses to acute stress.

In addition to affecting risk of illness, stress can affect symptom severity in part by causing dysregulation of inflammatory responses. In a study of people experimentally exposed to an influenza virus, those reporting higher stress experienced greater symptoms of illness, greater mucus weight, as well as greater inflammatory responses to the infection, as indicated by higher IL-6 levels in nasal secretions (Cohen et al. 1999).

### 4.3.3 Latent Viruses

After exposure to most infectious agents, the immune system clears the body of the pathogen. However, some viruses become cell associated after primary infection,

where they remain for life. This is known as latency. These include herpes viruses, such as herpes simplex virus (HSV) I and II, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). One of the most prevalent latent viruses, EBV, is carried by more than 95% of the adult North American population (Wolf and Morag 1998). Reactivation of latent EBV typically causes little or no symptoms in healthy individuals (Hess 2004). For example, reactivation of HSV I or II can cause cold sores (Bystricka and Russ 2005). However, in some instances, severe symptoms can result as is the case of VZV reactivation which can cause shingles (Quinlivan and Breuer 2006). Even in the absence of clinical disease, reactivation of a latent virus provides a sensitive marker for impairment/deficiencies in cell-mediated immunity. Thus, studies of viral latency and viral-specific markers can provide clinically relevant information even among asymptomatic individuals.

As seen with other markers of immune dysfunction such as virus-specific antibody titers, caregivers show more evidence of reactivation of latent viruses including EBV and HSV-1 compared to well-matched controls (Kiecolt-Glaser et al. 1991; Glaser and Kiecolt-Glaser 1997). The stress associated with disruption of significant relationships also affects viral latency. Women who were recently divorced or separated showed poorer control of latent EBV than demographically matched married women (Kiecolt-Glaser et al. 1987). Similarly, men who were unsatisfied in their marriage had higher levels of EBV antibody titers than their happily married counterparts (Kiecolt-Glaser et al. 1988).

Stressors of a more transient nature also affect viral latency. In prospective studies, medical students exhibited higher EBV, HSV-1, and CMV antibody titers on the day of an academic examination, as compared to several weeks before or after the exam (Glaser et al. 1985, 1999; Sarid et al. 2001).

In addition to effects of objective stressors, psychological factors have been associated with immune control of latent virus. Higher levels of EBV-specific antibodies are reported among those with a greater tendency to repress their emotions (Esterling et al. 1990), higher levels of anxiety (Esterling et al. 1993), and greater loneliness (Glaser et al. 1985). Similarly, individuals with syndromal or subsyndromal symptoms of depression have shown higher levels of HSV-1 antibody and poorer VZV-specific T-cell immunity than those without depressive symptoms (Delisi et al. 1986; Robertson et al. 1993; Irwin et al. 1998). Conversely, among older women undergoing the stressor of housing relocation, higher self-reported vigor was associated with better immune control of latent EBV (Lutgendorf et al. 2001). Thus, in addition to objective stressors, certain psychological characteristics (e.g., mood, ways of coping) may affect immune control of latent viruses. Physiological mechanisms by which stress may impair control of latent viruses include impairment of cytotoxic and proliferative T-cells responses (Glaser et al. 1987, 1993).

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## 4.4 Interventions

Given the clear negative impact of stress on immune parameters, interventions addressing stress from a psychosocial, physical, nutritional/dietary, and pharmacological perspective are receiving attention (see also chapters in Part V of this volume).

Stress management groups which involve elements of social support, emotional disclosure, and a focus on problem solving have improved antibody responses to influenza vaccination among caregivers (Vedhara et al. 2003) and immune control of latent viruses among HIV-infected (Lutgendorf et al. 1997; Esterling et al. 1992; Carrico et al. 2005; Cruess et al. 2000). In addition, stress reduction through relaxation training improved immune control of latent HSV-1 among older adults (Kiecolt-Glaser et al. 1985). Among healthy adults, an 8-week meditation intervention prior to influenza vaccination resulted in better antibody responses as compared to a waiting-list control group (Davidson et al. 2003). A 16-week Tai Chi intervention, which involves physical activity as well as meditation, improved mental health and antibody responses to VZV vaccine among older adults (Irwin et al. 2007). We found that regular practice of yoga, which also involves elements of meditation and physical activity, is associated with reduced proinflammatory cytokine activity; compared to women with a regular yoga practice, women with limited yoga experience had 41% higher IL-6 levels, 4.75 times greater likelihood of detectable CRP levels, and greater stress-induced in vitro cytokine production (Kiecolt-Glaser et al. 2010). Similarly, a study of mindfulness-based stress reduction for breast cancer patients, which included elements of meditation and gentle yoga, demonstrated improvements in mood, reductions in perceived stress, and beneficial immunological changes including decreased production of inflammatory cytokines and increased production of anti-inflammatory cytokines by stimulated T-cells (Carlson et al. 2003).

Other research has examined the ability of physical/aerobic exercise to foster immune responses: Older adults who completed a 3-month aerobic exercise intervention healed standard punch biopsy wounds 25% more quickly than did their less active counterparts (Emery et al. 2005).

Another important avenue for counteracting or preventing the negative effects of psychological stress is diet. Among others, omega-3 (*n*-3) polyunsaturated fatty acids (PUFAs) are an important dietary factor for mood and immune function. Due to their inhibitory effects on proinflammatory cytokine production (Logan 2003), higher *n*-3 PUFA levels are related to lower levels of circulating proinflammatory cytokines (Ferrucci et al. 2006; Kiecolt-Glaser et al. 2007). Via effects of inflammatory processes, *n*-3 supplementation may help to prevent stress-induced depressive symptoms (for review, see Parker et al. 2006). Nutritional and further pharmacological interventions warrant further investigation to reduce and modulate stress-dependent negative effects on distinct immune functions (see also Chaps. 29 and 30).

In sum, a variety of interventions show promise for counteracting the negative effects of psychological stress. The particular intervention (i.e., stress management, physical activity, meditation) which is most beneficial likely depends on the outcome of interest, type of stressors experienced, as well as personality characteristics and preexisting behaviors of the person in question. An emphasis of future research should be on targeted, individualized risk assessments and interventions.



## 4.5 From Daily Life to Space Travel

Clearly, daily life stressors ranging in magnitude and duration affect clinically meaningful health outcomes including inflammatory processes, wound healing, and responses to infectious agents and other immune challenges (e.g., vaccination). Individuals vary in their ability to cope with stress, and differences in perceptions of stress, mood (e.g., depressive symptoms), and personality (e.g., hostility) can modify the magnitude to which stressors exert a negative influence on immune function. Research provides support for several promising avenues for interventions to prevent stress-induced immune dysregulation. However, more information is needed to provide individualized intervention strategies.

Space travel presents an exceptional and intense combination of physical and psychological challenges. It provides a unique opportunity to examine the susceptibility of the human body to stress and to explore interventions promoting psychological and physiological resilience. Thus, studies of daily life stress inform our understanding of potential impacts of the stressors of space travel. In turn, studies of stressors encountered in space travel can also benefit our understanding of stress in our daily lives.

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## References

- Altemus M, Rao B, Dhabhar FS, Ding W, Granstein RD (2001) Stress-induced changes in skin barrier function in healthy women. *J Invest Dermatol* 117:309–317
- Anisman H, Ravindran AV, Griffiths J, Merali Z (1999) Endocrine and cytokine correlates of major depression and dysthymia with typical or atypical features. *Mol Psychiatry* 4:182–188
- Avitsur R, Kavelaars A, Heijnen C, Sheridan JF (2005) Social stress and the regulation of tumor necrosis factor- $\alpha$  secretion. *Brain Behav Immun* 19(4):311–317
- Baum CL, Arpey CJ (2005) Normal cutaneous wound healing: clinical correlation with cellular and molecular events. *Dermatol Surg* 31(6):674–686
- Black PH, Garbutt LD (2002) Stress, inflammation and cardiovascular disease. *J Psychosom Res* 52:1–23
- Bruunsgaard H, Pedersen M, Pedersen BK (2001) Aging and proinflammatory cytokines. *Curr Opin Hematol* 8:131–136
- Brydon L, Edwards S, Mohamed-Ali V, Steptoe A (2004) Socioeconomic status and stress-induced increases in interleukin-6. *Brain Behav Immun* 18:281–290
- Burns VE, Carroll D, Ring C, Harrison LK, Drayson M (2002) Stress, coping, and hepatitis B antibody status. *Psychosom Med* 64(2):287–293
- Burns VE, Carroll D, Drayson M, Whitham M, Ring C (2003) Life events, perceived stress and antibody response to influenza vaccination in young, healthy adults. *J Psychosom Res* 55(6):569–572

- Bystricka M, Russ G (2005) Immunity in latent Herpes simplex virus infection. *Acta Virol* 49: 59–67
- Carlson LE, Specia M, Patel KD, Goodey E (2003) Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients. *Psychosom Med* 65(4):571–581
- Carrico AW, Antoni MH, Pereira DB, Fletcher MA, Klimas N, Lechner SC, Schneiderman N (2005) Cognitive behavioral stress management effects on mood, social support, and a marker of antiviral immunity are maintained up to 1 year in HIV-infected gay men. *Int J Behav Med* 12(4):218–226
- Christian LM, Deichert N, Gouin JP, Graham JE, Kiecolt-Glaser JK (2009) Psychological influences on neuroendocrine and immune outcomes. In: Cacioppo JT, Berntson G (eds) *Handbook of neuroscience for the behavioral sciences*. John Wiley & Sons, Inc, New Jersey, pp 1260–1279
- Christian LM, Franco A, Iams J, Sheridan J, Glaser R (2010) Depressive symptoms predict exaggerated inflammatory response to in vivo immune challenge during human pregnancy. *Brain Behav Immun* 24(1):49–53
- Cohen S, Tyrrell DA, Smith AP (1991) Psychological stress and susceptibility to the common cold. *N Engl J Med* 325:606–612
- Cohen S, Frank E, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM (1998) Types of stressors that increase susceptibility to the common cold in healthy adults. *Health Psychol* 17:214–223
- Cohen S, Doyle WJ, Skoner DP (1999) Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosom Med* 61:175–180
- Cohen S, Miller GE, Rabin BS (2001) Psychological stress and antibody response to immunization: a critical review of the human literature. *Psychosom Med* 63:7–18
- Cohen S, Harmrick N, Rodriguez MS, Fedman PJ, Rabin BS, Manuck SB (2002) Reactivity and vulnerability to stress-associated risk for upper respiratory illness. *Psychosom Med* 64(2):302–312
- Couch RB, Kasel JA (1983) Immunity to influenza in man. *Annu Rev Microbiol* 37:529–549
- Cruess S, Antoni M, Cruess D, Fletcher MA, Ironson G, Kumar M, Lutgendorf S, Hayes A, Klimas N, Schneiderman N (2000) Reductions in herpes simplex virus type 2 antibody titers after cognitive behavioral stress management and relationships with neuroendocrine function, relaxation skills, and social support in HIV-positive men. *Psychosom Med* 62(6):828–837
- Davidson RJ, Kabat-Zinn J, Schumacher J, Rosenkranz M, Muller D, Santorelli SF, Urbanowski F, Harrington A, Bonus K, Sheridan JF (2003) Alterations in brain and immune function produced by mindfulness meditation. *Psychosom Med* 65(4):564–570
- Delisi LE, Smith SB, Hamovit JR, Maxwell ME, Glodwin LR, Dingman CW, Gerson ES (1986) Herpes simplex virus, cytomegalovirus and Epstein-Barr virus antibody titres in sera from schizophrenic patients. *Psychol Med* 16:757–763
- Elias PM (2005) Stratum corneum defensive functions: an integrated view. *J Invest Dermatol* 125(2):183–200
- Emery CF, Kiecolt-Glaser JK, Glaser R, Malarkey WB, Frid DJ (2005) Exercise accelerates wound healing among healthy older adults: a preliminary investigation. *J Gerontol A Biol Sci Med Sci* 60(11):1432–1436
- Ershler W, Keller E (2000) Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annu Rev Med* 51:245–270
- Esterling BA, Antoni M, Kumar M, Schneiderman N (1990) Emotional repression, stress disclosure responses, and Epstein-Barr viral capsid antigen titers. *Psychosom Med* 52:397–410
- Esterling BA, Antoni MH, Schneiderman N, Carver CS, LaPerriere A, Ironson G, Klimas NG, Fletcher MA (1992) 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* 54:354–371
- Esterling BA, Antoni MH, Kumar M, Schneiderman N (1993) Defensiveness, trait anxiety, and Epstein-Barr viral capsid antigen antibody titers in healthy college students. *Health Psychol* 12(2):132–139

- Ferrucci L, Cherubini A, Bandinelli S, Bartali B, Corsi A, Lauretani F, Martin A, Andres-Lacueva C, Senin U, Guralnik JM (2006) Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. *J Clin Endocrinol Metab* 91:439–446
- Garg A, Chren MM, Sands LP, Matsui MS, Marenus KD, Feingold KR, Elias PM (2000) Psychological stress perturbs epidermal permeability barrier homeostasis: implications for the pathogenesis of stress-associated skin disorders. *Arch Dermatol* 137:53–59
- Glaser R, Kiecolt-Glaser JK (1997) Chronic stress modulates the virus-specific immune response to latent herpes simplex virus Type 1. *Ann Behav Med* 19:78–82
- Glaser R, Kiecolt-Glaser JK, Speicher CE, Holliday JE (1985) Stress, loneliness, and changes in herpesvirus latency. *J Behav Med* 8:249–260
- Glaser R, Rice J, Sheridan J, Fertel R, Stout J, Speicher CE, Pinsky D, Kotur M, Post A, Beck M, Kiecolt-Glaser JK (1987) Stress-related immune suppression: health implications. *Brain Behav Immun* 1:7–20
- Glaser R, Kiecolt-Glaser JK, Bonneau RH, Malarkey W, Kennedy S, Hughes J (1992) Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. *Psychosom Med* 54:22–29
- Glaser R, Pearson GR, Bonneau RH, Esterling BA, Atkinson C, Kiecolt-Glaser JK (1993) Stress and the memory T-cell response to Epstein-Barr virus in healthy medical students. *Health Psychol* 12:435–442
- Glaser R, Kiecolt-Glaser JK, Malarkey WB, Sheridan JF (1998) The influence of psychological stress on the immune response to vaccines. *Ann N Y Acad Sci* 840:656–663
- Glaser R, Friedman SB, Smyth J, Ader R, Bijur P, Brunell P, Cohen N, Krilov LR, Lifrak ST, 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, Sheridan JF, Malarkey WB, MacCallum RC, Kiecolt-Glaser JK (2000) Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. *Psychosom Med* 62:804–807
- Glaser R, Robles TF, Sheridan J, Malarkey WB, Kiecolt-Glaser JK (2003) Mild depressive symptoms are associated with amplified and prolonged inflammatory responses after influenza virus vaccination in older adults. *Arch Gen Psychiatry* 60(10):1009–1014
- Godbout JP, Glaser R (2006) Stress-induced immune dysregulation: implications for Wound Healing, Infectious Disease, and Cancer. *J Neuroimmune Pharmacol* 1:421–427
- Graham NMH, Douglas RM, Ryan P (1986) Stress and acute respiratory infection. *Am J Epidemiol* 124:389–401
- Hamerman D, Berman JW, Albers GW, Brown DL, Silver D (1999) Emerging evidence for inflammation in conditions frequently affecting older adults: report of a symposium. *J Am Geriatr Soc* 47:1016–1025
- Hess RD (2004) Routine Epstein-Barr virus diagnostics from the laboratory perspective: still challenging after 35 years. *J Clin Microbiol* 42(8):3381–3387
- Irwin M, Costlow C, Williams H, Artin KH, Chan CY, Stinson DL, Levin MJ, Hayward AR, Oxman MN (1998) Cellular immunity to varicella-zoster virus in patients with major depression. *J Infect Dis* 178(Suppl 1):S104–S108
- Irwin MR, Olmstead R, Oxman MN (2007) Augmenting immune responses to varicella zoster virus in older adults: a randomized, controlled trial of Tai Chi. *J Am Geriatr Soc* 55(4):511–517
- Ishihara K, Hirano T (2002) IL-6 in autoimmune disease and chronic inflammatory proliferative disease. *Cytokine Growth Factor Rev* 13:357–368
- Johnson JD, O'Connor KA, Deak T, Stark M, Watkins LR, Maier SF (2002) Prior stressor exposure sensitizes LPS-induced cytokine production. *Brain Behav Immun* 16:461–476
- Kiecolt-Glaser JK, Glaser R, Williger D, Stout J, Messick G, Sheppard S, Ricker D, Romisher SC, Briner W, Bonnell G, Donnerberg R (1985) Psychosocial enhancement of immunocompetence in a geriatric population. *Health Psychol* 4:25–41

- Kiecolt-Glaser JK, Fisher LD, Ogrocki P, Stout JC, Speicher CE, Glaser R (1987) Marital quality, marital disruption, and immune function. *Psychosom Med* 49:31–34
- Kiecolt-Glaser JK, Kennedy S, Malkoff S, Fisher L, Speicher CE, Glaser R (1988) Marital discord and immunity in males. *Psychosom Med* 50:213–229
- Kiecolt-Glaser JK, Dura JR, Speicher CE, Trask OJ, Glaser R (1991) Spousal caregivers of dementia victims: longitudinal changes in immunity and health. *Psychosom Med* 53:345–362
- Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R (1995) Slowing of wound healing by psychological stress. *Lancet* 346:1194–1196
- Kiecolt-Glaser JK, Glaser R, Gravenstein S, Malarkey WB, Sheridan J (1996) Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proc Natl Acad Sci USA* 93:3043–3047
- Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R (2003) Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci USA* 100:9090–9095
- Kiecolt-Glaser JK, Loving TJ, Stowell JR, Malarkey WB, Lemeshow S, Dickinson SL, Glaser R (2005) Hostile marital interactions, proinflammatory cytokine production, and wound healing. *Arch Gen Psychiatry* 62:1377–1384
- Kiecolt-Glaser JK, Belury MA, Porter K, Beversdorf D, Lemeshow S, Glaser R (2007) Depressive symptoms, omega-6:omega-3 fatty acids, and inflammation in older adults. *Psychosom Med* 69(3):217–224
- Kiecolt-Glaser JK, Christian LM, Preston H, Houts CR, Malarkey WB, Emery CF, Glaser R (2010) Stress, inflammation, and yoga practice. *Psychosom Med* 72(2):113–121
- LeMay LG, Vander AJ, Kluger MJ (1990) The effects of psychological stress on plasma interleukin-6 activity in rats. *Physiol Behav* 47:957
- Logan AC (2003) Neurobehavioral aspects of omega-3 fatty acids: possible mechanisms and therapeutic value in major depression. *Altern Med Rev* 8(4):410–425
- Lutgendorf SK, Antoni MH, Ironson G, Klimas N, McCabe P, Cleven K, Fletcher MA, Schneiderman N (1997) 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* 65:31–43
- Lutgendorf SK, Reimer TT, Harvey JH, Marks G, Hong SY, Hillis SL, Lubaroff DM (2001) Effects of housing relocation on immunocompetence and psychosocial functioning in older adults. *J Gerontol A Biol Sci Med Sci* 56(2):M97–M105
- Maes M (1995) Evidence for an immune response in major depression: a review and hypothesis. *Prog Neuropsychopharmacol Biol Psychiatry* 19:11–38
- Maes M (1999) Major depression and activation of the inflammatory response system. *Adv Exp Med Biol* 461:25–46
- Maes M, Ombelet W, De Jongh R, Kenis G, Bosmans E (2001) The inflammatory response following delivery is amplified in women who previously suffered from major depression, suggesting that major depression is accompanied by a sensitization of the inflammatory response system. *J Affect Disord* 63:85–92
- Marks R (2004) The stratum corneum barrier: the final frontier. *J Nutr* 134:2017S–2021S
- Marucha PT, Kiecolt-Glaser JK, Favagehi M (1998) Mucosal wound healing is impaired by examination stress. *Psychosom Med* 60:362–365
- Miller GE, Cohen S, Pressman S, Barkin A, Rabin BS, Treanor JJ (2004) Psychological stress and antibody response to influenza vaccination: when is the critical period for stress, and how does it get inside the body? *Psychosom Med* 66(2):215–223
- Padgett DA, Glaser R (2003) How stress influences the immune response. *Trends Immunol* 24(8):444–448
- Parker G, Gibson NA, Brotchie H, Heruc G, Rees AM, Hadzi-Pavlovic D (2006) Omega-3 fatty acids and mood disorders. *Am J Psychiatry* 163(6):969–978
- Pedersen AF, Zachariae R, Bovbjerg DH (2009) Psychological stress and antibody response to influenza vaccination: a meta-analysis. *Brain Behav Immun* 23(4):427–433

- Phillips AC, Burns VE, Carroll D, Ring C, Drayson M (2005) The association between life events, social support, and antibody status following thymus-dependent and thymus-independent vaccinations in healthy young adults. *Brain Behav Immun* 19(4):325–333
- Quan N, Avitsur R, Stark JL, He LL, Shah M, Caligiuri M, Padgett DA, Marucha PT, Sheridan JF (2001) Social stress increases the susceptibility to endotoxic shock. *J Neuroimmunol* 115(1–2): 36–45
- Quinlivan M, Breuer J (2006) Molecular studies of Varicella zoster virus. *Rev Med Virol* 16: 225–250
- Robertson KR, Wilkins JW, Handy J, Van Der Horst C, Robertson WT, Fryer JG, Evans D, Hall CD (1993) Psychoimmunology and AIDS: psychological distress and herpes simplex virus in human immunodeficiency virus infected individuals. *Psychol Health* 8:317–327
- Robles TF (2007) Stress, social support, and delayed skin barrier recovery. *Psychosom Med* 69(8): 807–815
- Robles TF, Brooks KP, Pressman SD (2009) Trait positive affect buffers the effects of acute stress on skin barrier recovery. *Health Psychol* 28(3):373–378
- Sarid O, Anson O, Yaari A, Margalith M (2001) Epstein-Barr Virus specific salivary antibodies as related to stress caused by examinations. *J Med Virol* 64:149–156
- Segerstrom SC, Schipper LJ, Greenberg RN (2008) Caregiving, repetitive thought, and immune response to vaccination in older adults. *Brain Behav Immun* 22(5):744–752
- Singer AJ, Clark RA (1999) Cutaneous wound healing. *N Engl J Med* 341:738–746
- Stark JL, Avitsur R, Hunzeker J, Padgett DA, Sheridan JF (2002) Interleukin-6 and the development of social disruption-induced glucocorticoid resistance. *J Neuroimmunol* 124(1–2):9–15
- Stephoe A, Willemsen G, Owen N, Flower L, Mohamed-Ali V (2001) Acute mental stress elicits delayed increases in circulating inflammatory cytokine levels. *Clin Sci* 101:185–192
- Turner-Cobb JM, Steptoe A (1996) Psychosocial stress and susceptibility to upper respiratory tract illness in an adult population sample. *Psychosom Med* 58(5):404–412
- Vedhara K, Cox NKM, Wilcock GK, Perks P, Hunt M, Anderson S, Lightman SL, Shanks NM (1999) Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. *Lancet* 353:627–631
- Vedhara K, McDermott MP, Evans TG, Treanor JJ, Plummer S, Tallon D, Cruttenden KA, Schifitto G (2002) Chronic stress in nonelderly caregivers – psychological, endocrine and immune implications. *J Psychosom Res* 53(6):1153–1161
- Vedhara K, Bennett PD, Clark S, Lightman SL, Shaw S, Perks P, Hunt MA, Philip JM, Tallon D, Murphy PJ, Jones RW, Wilcock GK, Shanks NM (2003) Enhancement of antibody responses to influenza vaccination in the elderly following a cognitive-behavioural stress management intervention. *Psychother Psychosom* 72(5):245–252
- von Kanel R, Kudielka BM, Preckel D, Hanebuth D, Fischer JE (2005) Delayed response and lack of habituation in plasma interleukin-6 to acute mental stress in men. *Brain Behav Immun* 20: 40–48
- Wolf HJ, Morag AJ (1998) Epstein-Barr virus vaccines. In: Medveczky PG, Bendinelli M, Friedman H (eds) *Herpesviruses and immunity*. Plenum Press, New York, pp 231–246
- Zhou D, Kusnecov AW, Shurin MR, DePaoli M, Rabin BS (1993) Exposure to physical and psychological stressors elevates plasma interleukin 6: relationship to the activation of hypothalamic-pituitary-adrenal axis. *Endocrinology* 133:2523–2530