Chapter 3
The Chronic Stress of Caregiving Accelerates the Natural Aging of the Immune System

Jeanette M. Bennett, Christopher P. Fagundes and Janice K. Kiecolt-Glaser

3.1 Introduction

Caregiving for a spouse with dementia is highly distressing (Taylor Jr et al. 2008). On average, spouses serving as dementia caregivers spend more than 10 h per day providing care for over 5 years (Donelan et al. 2002; Wimo et al. 2002). During this time, they experience a type of "living bereavement" as they watch their partners slowly lose their personality and intellect (Kiecolt-Glaser et al. 1991).

Given this burden, spouses serving as dementia caregivers are at heightened risk for depression with a 46 % prevalence rate (Clyburn et al. 2000; Gallagher et al. 1989), anxiety with a 25 % prevalence rate (Cooper et al. 2007; Mahoney et al. 2005), and poor sleep quality (Brummett et al. 2006). In addition, having lower social support increases the burden perceived by caregivers (Clipp and George 1990; Zarit et al. 1980). These negative effects are particularly detrimental for spousal dementia caregivers because they are typically older adults who are also experiencing a natural decline in immunocompetence (Allen 1994). In turn, they are at increased risk for a number of different illnesses as well as earlier mortality (Schulz and Beach, 1999).

Chronic stressors like caregiving have been linked to many diseases. Stressed individuals are more likely to be depressed and anxious (Cohen and Herbert 1996;

J. M. Bennett (✉)
Division of Oral Biology, College of Dentistry, Institute for Behavioral Medicine Research, College of Medicine, The Ohio State University, OH, USA
e-mail: Jeanette.Bennett@osumc.edu

Department of Psychology, The University of North Carolina at Charlotte, 9201 University City Blvd, Charlotte, NC 28223
e-mail: jeanette.bennett@uncc.edu

C. P. Fagundes
Institute for Behavioral Medicine Research, College of Medicine, The Ohio State University, OH, USA

J. K. Kiecolt-Glaser
Departments of Psychiatry and Psychology, Institute for Behavioral Medicine Research, College of Medicine, The Ohio State University, OH, USA
e-mail: Janice.Kiecolt-Glaser@osumc.edu

J. A. Bosch et al. (eds.), *Immunosenescence*,
DOI 10.1007/978-1-4614-4776-4_3,

Cooper et al. 2007; Gallagher et al. 1989). Stress also has been linked to obesity, cardiovascular disease, cancer, asthma, type 2 diabetes, infectious diseases, and autoimmune diseases (Black and Garbutt 2002; Bloomberg and Chen 2005; Elenkov and Chrousos 2002; Glaser and Kiecolt-Glaser 2005; Godbout and Glaser 2006). The immune system plays a critical role in the relationship between stress and disease (Kiecolt-Glaser 2009; Kiecolt-Glaser and Glaser 1995; Kiecolt-Glaser et al. 1987).

The immune system is a highly complex network of cells and communication mediators that are affected independently by stress and aging (Glaser and Kiecolt-Glaser 2005; Pawelec and Solana 1997). Due to its complexity, investigators commonly study components of the immune system by focusing on a particular facet or process such as cell-mediated immunity or wound healing. Therefore, in this chapter, we review how the chronic stress of caregiving accelerates the natural decline of immune function associated with aging on local immune responses (wound healing), cell-mediated immunity (herpesvirus latency and vaccination responses), systemic inflammation (circulating cytokines), and cellular aging (telomere length).

3.2 Wound Healing

Proper wound healing is critical for maintaining good health by re-establishing the integrity of the skin as a physical barrier and preventing infection. The inflammatory phase, which begins immediately after initial damage, is important for all other phases (Christian et al. 2006). Proinflammatory cytokines protect against infection and prepare injured tissue to be repaired by enhancing phagocytic cell recruitment and activation (Lowry 1993). In addition, proinflammatory cytokines regulate fibroblasts and epithelial cells in order to remodel damaged tissue (Lowry 1993).

Glucocorticoids can suppress production of proinflammatory cytokines such as interleukin (IL)-6, IL-1-beta (1β), and tumor necrosis factor-alpha (TNF-α) (Glaser et al. 1999). Stress facilitates glucocorticoid secretion, which, in turn, delays wound healing. Padgett et al. (1998) demonstrated that mice under stress exhibited slower wound healing compared to non-stressed mice. Yet, when mice under stress were injected with a glucocorticoid receptor antagonist, they healed at the same rate as non-stressed mice. This rodent study confirmed that stress-induced glucocorticoid secretion is one mechanism by which stress retards the wound healing process.

The first human demonstration of stress and wound healing compared female dementia caregivers ($N = 13$; age: 62.3 ± 2.3 years [$\pm$ SEM]) and matched controls ($N = 13$; age: 60.4 ± 2.8 years [$\pm$ SEM]) (Kiecolt-Glaser et al. 1995). Wounds, created via a punch biopsy, took 9 days (24 %) longer to close in the caregiver group than wounds in the control group. Furthermore, caregivers' peripheral blood lymphocytes produced less IL-1β mRNA in response to lipopolysaccharide stimulation than matched controls, suggesting that caregivers' lymphocytes at the wound site also produced less IL-1β, which is responsible for stimulating the wound healing process (Kiecolt-Glaser et al. 1995). These findings have important health implications, because delayed wound healing increases the likelihood of infection and other complications, particularly after surgery.

3.3 Control of Latent Herpesviruses

Infection with herpesviruses such as Epstein–Barr virus (EBV), herpes simplex virus type (HSV)-1, and varicella-zoster virus are very common. For example, 90 % of adults have antibody to EBV (Glaser and Kiecolt-Glaser 1994), and more than 90 % of individuals are HSV-1 seropositive (previously infected) by their 40s (Nahmias and Roizman 1973). Herpesviruses incorporate their genetic material into the host's DNA and establish a latent infection in the host. Latency, or a dormant period, occurs when the cellular immune response controls viral replication. However, when the cellular immune response is compromised, the virus is reactivated (Croen 1991). Viral reactivation stimulates the humoral immune response, increasing antibody production to the latent virus. Therefore, herpesvirus antibody titers serve as a functional marker of cell-mediated immunity, whereby higher herpesvirus titers represent poorer cellular immune system control of latent viruses. For example, older adults have higher herpesvirus antibody titers compared to younger adults; suggesting that as one ages, immunosenescence results in more frequent herpesvirus reactivation (Pawelec et al. 2009).

Caregiver stress can promote reactivation of latent herpesviruses. In one study, investigators examined spousal dementia caregivers ($N = 69$; age: 67.26 ± 0.98 years [$\pm$ SEM]) and matched controls ($N = 69$; age: 67.75 ± 0.93 years $\pm$ SEM]) over a 1-year period to understand how chronic stress affects EBV latency. Dementia caregivers had higher EBV antibody titers compared to matched controls (Kiecolt-Glaser et al. 1991). In addition, caregivers' peripheral blood lymphocytes proliferated less in response to mitogenic stimulation than those from controls (Kiecolt-Glaser et al. 1991). The fact that caregivers had higher antibody titers to latent EBV as well as lower lymphocyte proliferation than controls suggests that caregivers have a poorer cell-mediated immune response than what might be expected simply as a result of aging.

Another study addressed the effects of chronic stress on HSV-1 latency in family dementia caregivers ($N = 71$; age: 60.55 ± 1.52 years [$\pm$ SEM]) and controls ($N = 58$; age: 62.41 ± 1.98 years [$\pm$ SEM]) (Glaser and Kiecolt-Glaser 1997). Caregivers had higher HSV-1 antibody titers than controls. However, caregivers' and controls' antibody titers showed the same ability to neutralize the latent virus, suggesting that chronic stress decreases control over viral reactivation, but does not modulate the antibody's ability to function. Furthermore, caregivers had poorer *in vitro* memory T cell proliferation to HSV-1 infected cells compared to controls (Glaser and Kiecolt-Glaser 1997). Again, these findings suggest that chronic stress makes individuals less able to control reactivation of a latent herpesvirus in addition to the natural age-related declines in cell-mediated immunity.

3.4 Vaccine Responses

Among adults aged 65 years or older, influenza and pneumonia infections are the fourth leading cause of death (Thompson et al. 2003). Accordingly, the Center for Disease Control and Prevention (CDC) recommends that individuals 50 or

older receive a protective pneumococcal pneumonia vaccination, and yearly influenza vaccinations (Smith et al. 2006). These vaccinations not only reduce infection-related mortality, but also decrease the number of hospitalizations as well as the duration of hospital stays (Smith et al. 2006). Given the importance of vaccine responses, they have been the subject of many studies. In vaccine response studies, seroconversion, a four-fold or greater increase in vaccine specific antibody titers relative to pre-vaccination levels, is considered a protective vaccine response (Levine et al. 1987).

Chronic stress of caregiving can impair vaccine responses. For example, caregivers had a poorer influenza vaccine response than matched controls (Kiecolt-Glaser et al. 1996). Specifically, when analyzing only those who had a four-fold antibody titer increase to at least one of three vaccine specific viral strains, caregivers had lower antibody titers than controls. Furthermore, age intensified the effect of chronic stress on the vaccine response. In individuals over 70-years old, only 26 % of caregivers had a four-fold response compared to 60 % of controls. In addition, caregivers' lymphocytes produced less IL-2 and IL-1β after exposure to vaccine-specific pathogen compared to controls (Kiecolt-Glaser et al. 1996). These immunological differences were not explained by depression, although caregivers were more depressed than controls (Kiecolt-Glaser et al. 1996).

Similar to the findings described above, another study also showed that chronic stress left older caregivers more vulnerable due to the non-protective influenza vaccine responses; 16 % of caregivers and 39 % of controls showed a four-fold rise in antibody to the vaccine (Vedhara et al. 1999). In addition, caregivers' daily salivary cortisol output was greater than controls (Vedhara et al. 1999). As described earlier, cortisol has immunoregulatory properties and can modulate cell-mediated immunity. Therefore, caregivers' higher salivary cortisol is consistent with their poorer vaccine responses.

Further work addressed relationship between caregiving and pneumococcal pneumonia vaccine response (Glaser et al. 2000). Pneumococcal pneumonia is caused by bacteria, and bacterial vaccine responses occur independently of T-cell activation. Therefore, this bacterial vaccine addresses an additional dimension of the immune response because immune responses to viral vaccinations, like influenza, are T-cell dependent.

Current and former caregivers and controls had similar pneumococcal pneumonia antibody titers before, and 2 and 4 weeks following the vaccination (Glaser et al. 2000). However, at 3- and 6-month follow-up visits, current caregivers' overall vaccine specific antibody titers were lower than those of former caregivers and controls. This finding suggests that caregiving reduces the stability of the IgG antibody response to the pneumococcal pneumonia vaccine, which limits the expected long-term protection (Glaser et al. 2000).

In a younger, caregiving sample, similar results were found for both influenza and pneumococcal pneumonia vaccinations. Caregivers for children who were disabled had a reduced antibody response to B/Malaysia strain of the influenza vaccine and the pneumococcal pneumonia vaccine at 1- and 6-months post-vaccination compared to parents of healthy children (Gallagher et al. 2009a, b).

Although caregivers are more likely to follow the CDC vaccination guidelines for older adults (Brown et al. 2009), chronic stress dysregulates cell-mediated immune responses. In addition, cell-mediated immunity declines with age. Thus, caregivers respond more poorly to both viral and bacterial vaccines compared to age-matched controls, suggesting that caregiver stress diminishes cell-mediated immunity above age-related decline in both younger and older adult populations.

3.5 Systemic Inflammation

Cytokines are soluble proteins that act as messenger substances, similar to hormones and neurotransmitters, between cells of the immune system as well as with non-immune cells. Acute local inflammation, cytokine production by lymphocytes at the site of injury, can be beneficial because it clears viral and bacterial pathogens and enhances wound healing (Kiecolt-Glaser 1995). However, chronic low-grade systemic inflammation, defined as a two- to three-fold elevation in cytokine levels compared to healthy subjects, is associated with poorer physical functioning and disease (Pedersen and Febbraio 2008). Low-grade systemic inflammation occurs due to cytokine production from several sources, including chronically activated immune cells in adipose tissue (Mohamed-Ali et al. 1998).

Elevated proinflammatory cytokines in serum or plasma are reliable predictors of morbidity and all-cause mortality in older adults (Bruunsgaard and Pedersen 2003; De Martinis et al. 2006). For example, inflammation is a risk factor for most cancers because proinflammatory cytokines facilitate tumor promotion, survival, proliferation, invasion, angiogenesis, and metastases (Aggarwal et al. 2006). In addition, higher levels of inflammation are associated with many diseases including: type 2 diabetes, arthritis, osteoporosis, Alzheimer's disease, and periodontal disease (Ershler and Keller 2000). Furthermore, inflammation is involved in every stage of atherosclerosis (Libby 2002).

Inflammation increases with age, and chronic stress magnifies age-related changes in proinflammatory cytokines. Indeed, data from several laboratories have shown that caregivers have higher IL-6 than controls. For example, in a 6-year longitudinal community study (age range: 55–89 years old at entry), caregivers' ($N = 116$) rate of IL-6 increase was four-fold greater than matched controls ($N = 109$) (Kiecolt-Glaser et al. 2003). The differences in caregivers' and controls' IL-6 could not be explained by depression, loneliness, or health behaviors (e.g., chronic health conditions, medication use, sleep, obesity, or smoking).

The fact that caregivers had greater IL-6 production than controls is particularly noteworthy in another context. Epidemiological data suggested that serum IL-6 values greater than or equal to 3.19 pg/mL put individuals at two-fold greater risk of death compared to those whose IL-6 levels were less than 1.9 pg/mL (Harris et al. 1999). Following these guidelines, caregivers would cross on average into this greater risk category at age 75, while controls would not cross, on average, into this category until after age 90. Thus, caregiving accelerates age-related IL-6 increases and elevates risk of mortality.

Among former caregivers whose spouses had died, IL-6 production remained elevated much like that of current caregivers (Kiecolt-Glaser et al. 2003). Hence, the chronic stress of caregiving may have long-term inflammatory consequences even after the stressor is over. These comparisons involve spouses who have been bereaved for at least 3 years, well past the usual time for adjustment to loss of their partners.

Elevated levels of C-reactive protein (CRP), IL-6, and D-dimer have been associated with greater frailty in elderly populations (Walston et al. 2002). Through general consensus, "frailty syndrome" has been characterized by the following symptoms: decrease in lean body mass, decline in walking mobility, and poor endurance with exhaustion or fatigue (Ferrucci et al. 2003). In frail individuals, inflammation is associated with muscle wasting, cognitive decline, and increased disease vulnerability (Cannon 1995; Ferrucci et al. 1999).

In a study investigating dementia caregiving and frailty, IL-6 and D-dimer were higher in caregivers than controls, but CRP levels were similar (von Kanel et al. 2006). Caregivers reported greater role overload, being overwhelmed by life's responsibilities, compared to the controls. Interestingly, role overload explained the D-dimer difference between caregivers and controls, suggesting that role overload stress may be driving the elevation in D-dimer levels. Although D-dimer is not an inflammatory marker, it can stimulate IL-6 and IL-1β production from monocytes *in vitro* (Robson et al. 1994).

In a follow-up study, the impact of sleep on inflammation was investigated in dementia caregivers and controls (von Kanel et al. 2010). As expected, caregivers reported poorer sleep and had a 3 % reduction in percent sleep as measured by actigraphy than controls. Among caregivers those who slept less had higher IL-6 and marginally higher CRP after controlling for differences in BMI, gender, and smoking. Among controls sleep was not associated with IL-6 or CRP (von Kanel et al. 2010).

A recent study assessed the consequences of caregiving for a relative with recently diagnosed brain cancer. At study entry, caregivers and controls had similar CRP levels. However, at the 4-month follow-up, caregivers' CRP was higher than controls (Rohleder et al. 2009). Mirroring the increase in CRP levels, expression of inhibitory-kappa B (I-κB), a transcription factor that produces anti-inflammatory effects, was lower in caregivers at the 4-month follow-up compared to controls (Rohleder et al. 2009). Even in a relative young sample, caregivers (N=40; age: 44.9 ± 7.4 years [±SD]) of children with autism or attention deficit hyperactivity disorder had elevated CRP levels compared to controls (N=17; age: 40.3 ± 6.4 years [±SD]) despite having similar diurnal cortisol patterns (Lovell et al. 2012).

Thus, the increase in inflammation associated with caregiving may lead to a greater propensity to frailty above and beyond the age-related increases observed in the control population. Caregivers' poorer sleep and decreased anti-inflammatory control may contribute to the greater frailty and inflammation observed in this group compared to controls.

3.6 Mechanisms Underlying Inflammation and Chronic Stress

There are several possible neuroendocrine mechanisms that may enhance the effects of chronic stress on inflammation. Stress activates the hypothalamic–pituitary–adrenal (HPA)-axis. Thus, one pathway is reduced glucocorticoid regulation of inflammation. Cortisol, a glucocorticoid produced by HPA-axis activation, inhibits immune cell activity by binding to the glucocorticoid receptor and reducing cytokine production (Barnes 1998; Brattsand and Linden 1996). However, chronically elevated cortisol can lead to glucocorticoid insensitivity, such that immune cells downregulate the expression of glucocorticoid receptors (Webster and Cidlowski 1994; Webster et al. 2002). In turn, this downregulation leads to increased inflammation because cortisol no longer has immunoregulatory properties and the immune cells are able to produce cytokines in an unregulated environment (Miller et al. 2002).

Data from one study suggested that caregivers' immune cells were less sensitive to glucocorticoids than controls'. Specifically, dementia caregivers' lymphocytes proliferated at a greater rate during an *in vitro* challenge in the presence of cortisol than did the controls' lymphocytes (Bauer et al. 2000). Caregivers also had higher cortisol levels in the morning and prior to lunchtime compared to the controls (Bauer et al. 2000). In another study, lymphocytes from parents of cancer patients produced higher IL-6 levels *in vitro* in the presence of glucocorticoids compared to lymphocytes from parents of healthy children (Miller et al. 2002). Therefore, caregivers' lymphocytes were less sensitive to cortisol's immunoregulatory effects. This lack of glucocorticoid inhibition on lymphocyte proliferation and cytokine production adds to the ammunition linking chronic stress and inflammation.

In addition to differences in HPA-axis responses between caregivers and controls, elevated sympathetic nervous system activation primes inflammatory responses as well. Specifically, the sympathetic–adrenal–medullary (SAM)-axis stimulates the release of peripheral norepinephrine and epinephrine from the adrenal medulla within seconds of a stressor (Mason 1968). Increased norepinephrine leads to an increase in nuclear factor-kappa B (NF-κB) translocation in mononuclear cells (Bierhaus et al. 2003). NF-κB is a transcription factor that increases inflammatory gene expression, such as IL-6 and IL-8; thus, NF-κB activation results in elevated release of these cytokines (Baldwin 1996; Barnes and Karin 1997). In a recent report, dementia caregivers had a prolonged norepinephrine response to a laboratory stressor compared to controls (Aschbacher et al. 2008). If the extended norepinephrine production is an indicator of chronic sympathetic over-activation, then it could be one of the underlying mechanisms for the elevated IL-6 levels observed in caregivers compared to controls (Kiecolt-Glaser et al. 2003; von Kanel et al. 2006).

Thus, chronic stressors like caregiving may promote inflammation through alterations in neuroendocrine pathways. In addition to the health consequences of inflammation already addressed, inflammation also has implications for cell aging (Kiecolt-Glaser and Glaser 2010). Elevated inflammation promotes T-cell proliferation and differentiation, which is a characteristic of cellular aging (Aviv 2004), as described below.

3.7 Telomere Length and Aging of Immune Cells

A telomere is a group of nucleoprotein complexes that cap chromosomes to protect and stabilize their integrity across the lifespan (Blackburn 2001). Telomere length indicates a cell's ability to replicate; because cell replication naturally shortens the length of a telomere, once a critical length is reached, the cell no longer divides and dies (Blackburn 2001). Therefore, telomere length is a proxy for measuring the biological age of the cell. Telomerase is an enzyme responsible for the production of the telomere cap after cell division (Blackburn 2001). Greater telomerase activity leads to longer telomeres. Thus, both telomerase activity and telomere length can provide insight into how cells age and what factors may expedite or impede the aging process at a molecular level. Further details of the association between telomeres and aging can be found in Chap. 8.

A growing body of literature suggests that chronic stress accelerates telomere shortening (Damjanovic et al. 2007; Epel et al. 2004, 2010; Simon et al. 2006). In a seminal study of mothers (age: 38 ± 6.5 years) who were caregivers for a chronically ill child, women who served as caregivers for a longer period of time had shorter telomeres, lower telomerase activity, and higher oxidative stress than those who were caregivers for a shorter period of time (Epel et al. 2004). These findings suggest that duration of stress affects cell aging and may lead to a decline in immune function and earlier onset of age-related diseases. In addition, although there were no differences between caregivers and controls overall, more stressed women in both groups had shorter telomeres (Epel et al. 2004). Further work that investigated telomere length of T cells and monocytes in dementia caregivers and age-matched controls showed that caregivers' telomeres were shorter than those of controls' (Damjanovic et al. 2007).

The evidence linking chronic stress and telomere shortening provides additional biological pathways connecting stress and aging (Kiecolt-Glaser and Glaser 2010). In addition to shorter telomeres, caregivers had greater inflammation measured by serum TNF-α levels compared to controls (Damjanovic et al. 2007). Higher levels of inflammation activates T-cell proliferation, which leads to shorter telomeres due to increased replication (Aviv 2004). Chronic stress also increases oxidative stress (Epel et al. 2004), which promotes telomere erosion during replication (Aviv 2004). Therefore, the combined effects of stress and inflammation on cellular aging have major implications for the immune system, especially in older individuals.

3.8 Conclusion

The chronic stress of caregiving impairs immune and cellular functions locally and systemically consistent with accelerated aging. Caregivers' wounds heal more slowly than controls' (Kiecolt-Glaser 1995), show more frequent latent herpesviruses reactivation (Glaser and Kiecolt-Glaser 1997; Kiecolt-Glaser et al. 1991), and poor vaccine responses (Gallagher et al. 2009a, b; Glaser et al. 2000; Kiecolt-Glaser et al. 1996;

Vedhara et al. 1999). Furthermore, caregivers have greater inflammation than controls (Damjanovic et al. 2007; Kiecolt-Glaser et al. 2003; Rohleder et al. 2009; von Kanel et al. 2010, 2006), a major predictor for frailty, cognitive decline, and all-cause mortality. Finally, caregivers' immune cells have shorter telomeres, suggesting they age more quickly compared to controls' (Damjanovic et al. 2007; Epel et al. 2004).

Taken together, the accelerated aging of the immune system leaves caregivers open to health problems above and beyond that of their non-caregiving counterparts. For example, caregiving has been categorized as a risk factor for mortality; strained caregivers were 63 % more likely to die over a 4-year period than controls (Schulz and Beach 1999). Another study showed that caregivers were more likely to develop heart disease than controls (Shaw et al. 1999). Furthermore, in the Nurses' Health Study, caring for an ill spouse increased the risk of developing coronary heart disease (Lee et al. 2003). The studies reviewed here clearly demonstrate that caregiving may accelerate the natural decline of the immune system, which may form a key pathway increasing the risk of disease and possibly premature death.

Acknowledgments Work on this chapter was supported in part by the following grants: National Institute on Aging (AG029562), National Institute of Dental & Craniofacial Research (DE014320), and National Cancer Institute (CA126857 and CA131029). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health or any division providing financial support.

References

Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G (2006) Inflammation and cancer: How hot is the link? Biochem Pharmacol 72:1605–1621

Allen SM (1994) Gender differences in spousal caregiving and unment need for care. J Gerontol Soc Sci 49:S187–S195

Aschbacher K, Mills PJ, von Kanel R, Hong S, Mausbach BT, Roepke SK et al (2008) Effects of depressive and anxious symptoms on norepinephrine and platelet P-selectin responses to acute psychological stress among elderly caregivers. Brain Behav Immun 22:493–502

Aviv A (2004) Telomeres and human aging: Facts and fibs. Sci Aging Knowledge Environ 51:pe43

Baldwin AS (1996) The NF-kappa B and I kappa B proteins: New discoveries and insights. Ann Rev Immunol 14:649–683

Barnes PJ (1998) Anti-inflammatory actions of glucocorticoids: molecular mechanisms. Clin Sci 94:557–572

Barnes PJ, Karin M (1997) Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. New Engl J Med 336:1066–1071

Bauer ME, Vedhara K, Perks P, Wilcock GK, Lightman SL, Shanks N (2000) Chronic stress in caregivers of dementia patients is associated with reduced lymphocyte sensitivity to glucocorticoids. J Neuroimmunol 103:84–92

Bierhaus A, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D et al (2003) A mechanism converting psychosocial stress into mononuclear cell activation. Proc Natl Acad Sci USA 100:1920–1925

Black PH, Garbutt LD (2002) Stress, inflammation and cardiovascular disease. J Psychosom Res 52:1–23

Blackburn EH (2001) Switching and signaling at the telomere. Cell 106:661–673

Bloomberg GR, Chen E (2005) The relationship of psychologic stress with childhood asthma. Immunol Allergy Clin 25:83–105

Brattsand R, Linden M (1996) Cytokine modulation by glucocorticoids: mechanisms and actions in cellular studies. Aliment Pharm Therap 10:81–90
Brown SL, Smith DM, Schulz R, Kabeto MU, Ubel PA, Poulin M et al (2009) Caregiving behavior is associated with decreased mortality risk. Psychol Sci 20:488–494
Brummett B, Babyak M, Siegler I, Vitaliano P, Ballard E, Gwyther L et al (2006) Associations among perceptions of social support, negative affect, and quality of sleep in caregivers and noncaregivers. Health Psychol 25:220–225
Bruunsgaard H, Pedersen BK (2003) Age-related inflammatory cytokines and disease. Immunol Allergy Clin 23:15–39
Cannon J (1995) Cytokines in aging and muscle homeostasis. J Gerontol: Series A, Biol Sci Med Sci 50:120–123
Christian LM, Graham JE, Padgett DA, Glaser R, Kiecolt-Glaser JK (2006) Stress and wound healing. Neuroimmunomodulation 13:337–346
Clipp EC, George LK (1990) Caregiver needs and patterns of social support. J Gerontol 45:102–222
Clyburn L, Stones M, Hadjistavropoulos T, Tuokko H (2000) Predicting caregiver burden and depression in Alzheimer's disease. J Gerontol Series B: Psychol Sci Soc Sci 55:S2
Cohen S, Herbert TB (1996) Health psychology: psychological factors and physical disease from the perspective of human psychoneuroimmunology. Ann Rev Psychol 47:113–142
Cooper C, Balamurali TBS, Livingston G (2007) A systematic review of the prevalence and covariates of anxiety in caregivers of people with dementia. Intl Psychogeriatrics 19:175–195
Croen KD (1991) Latency of the human herpesviruses. Ann Rev Med 42:61–67
Damjanovic AK, Yang Y, Glaser R, Kiecolt-Glaser JK, Nguyen H, Laskowski B et al (2007) Accelerated telomere erosion is associated with a declining immune function of caregivers of Alzheimer's disease patients. J Immunol 179:4249–4254
De Martinis M, Franceschi C, Monti D, Ginaldi L (2006) Inflammation markers predicting frailty and mortality in the elderly. Exper Molec Pathol 80:219–227
Donelan K, Hill CA, Hoffman C, Scoles K, Feldman PH, Levine C et al (2002) Challenged to care: Informal caregivers in a changing health system. Health Affairs 21:222–231
Elenkov IJ, Chrousos GP (2002) Stress hormones, proinflammatory and anti-inflammatory cytokines, and autoimmunity. Ann NY Acad Sci 966:290–303
Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD et al (2004) Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci USA 101:17312–17315
Epel ES, Lin J, Dhabhar FS, Wolkowitz OM, Puterman E, Karan L et al (2010) Dynamics of telomerase activity in response to acute psychological stress. Brain Behav Immun 24:531–539
Ershler W, Keller E (2000) Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Ann Rev Med 51:245–270
Ferrucci L, Guralnik JM, Cavazzini C, Bandinelli S, Lauretani F, Bartali B et al (2003) The frailty syndrome: a critical issue in geriatric oncology. Crit Rev Oncol/Hematol 46:127–137
Ferrucci L, Harris T, Guralnik J, Tracy R, Corti M, Cohen H et al (1999) Serum IL-6 level and the development of disability in older persons. J Am Geriatr Soc 47:639–646
Gallagher D, Rose J, Rivera P, Lovett S, Thompson LW (1989) Prevalence of depression in family caregivers. Gerontologist 29:449–456
Gallagher S, Phillips AC, Drayson MT, Carroll D (2009a) Caregiving for children with developmental disabilities is associated with a poor antibody response to influenza vaccination. Psychosom Med 71:341–344
Gallagher S, Phillips AC, Drayson MT, Carroll D (2009b) Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. Brain Behav Immun 23:338–346
Glaser R, Kiecolt-Glaser JK (1994) Stress-associated immune modulation and its implications for reactivation of latent herpesviruses. In Glaser R, Jones J (eds) Human herpesvirus infections, Dekker, New York, p 245–270
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 (2005) Stress-induced immune dysfunction: Implications for health. Nature Rev Immunol 5:243–251

Glaser R, Kiecolt-Glaser PK, Marucha PT, MacCallum RC, Laskowski, BF, Malarkey WB (1999) Stress-related changes in proinflammatory cytokine production in wounds. Arch Gen Psychiatr 56:450–456

Glaser R, Sheridan J, Malarkey WB, MacCallum RC, Kiecolt-Glaser JK (2000) Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. Psychosom Med 62:804–807

Godbout JP, Glaser R (2006) Stress-induced immune dysregulation: Implications for wound healing, infectious disease and cancer. J Neuroimmune Pharmacol 1:421–427

Harris TB, Ferrucci L, Tracy RP, Corti MC, Wacholder S, Ettinger WH, Jr et al (1999) Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am J Med 106:506–512

Kiecolt-Glaser J (2009) Psychoneuroimmunology: Psychology's gateway to the biomedical future. Perspect Psychol Sci 4(367)

Kiecolt-Glaser J, Dura J, Speicher C, Trask O, Glaser R (1991) Spousal caregivers of dementia victims: Longitudinal changes in immunity and health. Psychosom Med 53:345

Kiecolt-Glaser J, Glaser R (1995) Psychoneuroimmunology and health consequences: Data and shared mechanisms. Psychosom Med 57(269)

Kiecolt-Glaser J, Glaser R, Shuttleworth E, Dyer C, Ogrocki P, Speicher C (1987) Chronic stress and immunity in family caregivers of Alzheimer's disease victims. Psychosom Med 49(523)

Kiecolt-Glaser JK, Glaser R (2010) Psychological stress, telomeres, and telomerase. Brain Behav Immun 24:529–530

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, Marucha PT, Malarkey WB, Mercado AM, Glaser R (1995) Slowing of wound healing by psychological stress. Lancet 346:1194–1196

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, 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

Lee S, Colditz GA, Berkman LF, Kawachi I (2003) Caregiving and risk of coronary heart disease in US women—a prospective study. Am J Prevent Med 24:113–119

Levine M, Beattie BL, McLean DM, Corman D (1987) Characterization of the immune response to trivalent influenza vaccine in elderly men. J Am Geriatr Soc 35:609–615

Libby P (2002) Inflammation in atherosclerosis. Nature 420:868–874

Lovell B, Moss M, Wetherell M (2012) The psychosocial, endocrine and immune consequences of caring for a child with autism or ADHD. Psychoneuroendocrinology 37:534–542

Lowry SF (1993) Cytokine mediators of immunity and inflammation. Arch Surg 28:1235–1241

Mahoney R, Regan C, Katona C, Livingston G (2005) Anxiety and depression in family caregivers of people with Alzheimer disease: the LASER-AD study. Am J Geriatr Psychiatry 13:795

Mason J (1968) A review of psychoendocrine research on the sympathetic-adrenal medullary system. Psychosom Med 30:631

Miller G, Cohen S, Ritchey A (2002) Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. Health Psychol 21:531–541

Mohamed-Ali V, Pinkney J, Coppack S (1998) Adipose tissue as an endocrine and paracrine organ. Intl J Obes 22:1145–1158

Nahmias A, Roizman B (1973) Infection with herpes-simplex viruses 1 and 2. New Engl Jf Med 289:781–789

Padgett DA, Marucha PT, Sheridan JF (1998) Restraint stress slows cutaneous wound healing in mice. Brain Behav Immun 12:64–73

Pawelec G, Derhovanessian E, Larbi A, Strindhall J, Wikby A (2009) Cytomegalovirus and human immunosenescence. Rev Med Virol 19:47–56

Pawelec G, Solana R (1997) Immunosenescence. Immunol Today 18:514–516

Pedersen BK, Febbraio MA (2008) Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev 88:1379–1406

Robson SC, Shephard EG, Kirsch RE (1994) Fibrin degradation product D-dimer induces the synthesis and release of biologically-active IL-1-beta, IL-6 and plasminogen-activator inhibitros from monocytes in-vitro. [Article]. Brit J Haematol 86:322–326

Rohleder N, Marin TJ, Ma R, Miller GE (2009) Biologic cost of caring for a cancer patient: Dysregulation of pro- and anti-inflammatory signaling pathways. J Clin Oncol 27:2909–2915

Schulz R, Beach S (1999) Caregiving as a risk factor for mortality: the caregiver health effects study. J Am Med Assoc 282:2215

Shaw WS, Patterson TL, Ziegler MG, Dimsdale JE, Semple SJ, Grant I (1999) Accelerated risk of hypertensive blood pressure recordings among Alzheimer caregivers. J Psychosom Res 46:215–227

Simon NM, Smoller JW, McNamara KL, Maser RS, Zalta AK, Pollack MH et al (2006) Telomere shortening and mood disorders: preliminary support for a chronic stress model of accelerated aging. Biol Psychiatr 60:432–435

Smith NM, Bresee JS, Shay DK, Uyeki TM, Cox NJ, Strikas RA (2006) Prevention and control of influenza: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep 55:1–42

Taylor Jr D, Ezell M, Kuchibhatla M, Østbye T, Clipp E. (2008) Identifying trajectories of depressive symptoms for women caring for their husbands with dementia. J Am Geriatr Soc 56:322–327

Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ et al (2003) Mortality associated with influenza and respiratory syncytial virus in the United States. J Am Med Assoc 289:179–186

Vedhara K, Cox NK, Wilcock GK, Perks P, Hunt M, Anderson S et al (1999) Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. Lancet 353:627–631

von Kanel R, Ancoli-Israel S, Dimsdale JE, Mills PJ, Mausbach BT, Ziegler MG et al (2010) Sleep and biomarkers of atherosclerosis in elderly Alzheimer caregivers and controls. Gerontology 56:41–50

von Kanel R, Dimsdale JE, Mills PJ, Ancoli-Israel S, Patterson TL, Mausbach BT et al (2006) Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C-reactive protein, and D-dimer. J Gerontol A 61:963–969

Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, Hirsch CH et al (2002) Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the cardiovascular health study. Arch Intern Med 162:2333–2341

Webster JC, Cidlowski JA (1994) Downregulation of the glucocorticoid receptor. A mechanism for physiological adaptation to hormones. Ann NY Acad Sci 746:216–220

Webster JI, Tonelli L, Sternberg EM (2002) Neuroendocrine regulation of immunity. Ann Rev Immunol 20:125–163

Wimo A, von Strauss E, Nordberg G, Sassi F, Johansson L (2002) Time spent on informal and formal care giving for persons with dementia in Sweden. Health Policy 61:255–268

Zarit SH, Reever KE, Bach-Peterson J (1980) Relatives of the impaired elderly: Correlates of feelings of burden. Gerontologist 20:649–655