

1

AN OVERVIEW OF STRESS AND IMMUNITY

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Stress occurs when environmental demands exceed the individual's adaptive capacity or ability to cope (Cohen, Kessler, & Gordon, 1995). These environmental demands are termed *stressors* and include negative life events such as family conflict, job strain, unemployment, abuse, trauma, and bereavement, as well as physical stressors. To study the process of stress, researchers measure the occurrence of the environmental stressor, behavioral and biological responses to this event, and its long-term consequences.

Stressors appear to have bidirectional effects on the immune system depending on whether they are acute or chronic (Dhabhar & McEwen, 1999; Segerstrom & Miller, 2004). Recent research indicates that acute stressors tend to activate aspects of innate immunity by increasing trafficking of immune cells to the site of challenge and by inducing long-lasting increases in immunological memory (Campisi & Fleshner, 2003; Dhabhar & McEwen, 1997, 1999; Dhabhar & Viswanathan, 2005; Viswanathan, Daugherty, & Dhabhar, 2005). In contrast, chronic stressors are more likely to suppress immune function, resulting in increased susceptibility to infections and cancers (Antoni et al., 2006; Campbell et al., 2001; Dhabhar & McEwen, 1999;

Dobbs, Vasquez, Glaser, & Sheridan, 1993; J. D. Johnson, O'Connor, Watkins, & Maier, 2004; R. R. Johnson et al., 2006; Kelley, Greenfield, Evermann, Parish, & Perryman, 1982; Padgett et al., 1998; Sheridan et al., 1998; Sieve et al., 2004; Spiegel & Giese-Davis, 2003).

HOW DOES STRESS ALTER DISEASE VULNERABILITY?

Considerable evidence suggests that stress can alter vulnerability to infectious, inflammatory, and autoimmune diseases (Ackerman et al., 2002; Backer, 2000; Chida, Sudo, & Kubo, 2005; Dowdell, Gienapp, Stuckman, Wardrop, & Whitacre, 1999; Grant et al., 1989; R. R. Johnson et al., 2006; Matyszak, 1998; McEwen et al., 1997; McGeer & McGeer, 1995, 2004; Meagher et al., 2007; Mei-Tal, Meyerowitz, & Engel, 1970; Mohr et al., 2000; Mohr, Hart, Julian, Cox, & Pelletier, 2004; Rabin, 2002; Sheridan et al., 1998; Sieve et al., 2004; Warren, Greenhill, & Warren, 1982; Warren, Warren, & Cockerill, 1991; Welsh, Meagher, & Sternberg, 2006; Whitton, 2007; R. S. Wilson et al., 2003). Stressors can indirectly alter disease risk by increasing health-compromising behaviors and maladaptive coping strategies, such as increased alcohol consumption, smoking, decreased sleep, and non-adherence to exercise, dietary, and medical regimens. Stressful events also have direct biological effects that alter disease risk. When a stressful event is perceived, the brain activates two primary outflow pathways that alter inflammation and immunity: the sympathetic system and hypothalamic–pituitary–adrenal (HPA) axis.

Sympathetic Adrenomedullary System and Parasympathetic System

The sympathetic adrenomedullary (SAM) system is an essential component of the normal acute alarm response to threat that produces the fight–flight reaction. When stressors are perceived in the limbic system, the brain sends signals through the sympathetic and parasympathetic systems, which generally act to oppose each other. The sympathetic preganglionic neurons send impulses to the adrenal medulla, releasing epinephrine and norepinephrine. Cardiac output is increased through elevated heart rate and stroke volume. Immune cells are redistributed so that they can easily reach a site of injury. Fuel sources are made available. In addition, catecholamines increase the alertness and arousal of the central nervous system (CNS). Although the SAM system predominates in the acute stress response, it can be tonically active in some individuals, that is, highly reactive to minor perturbations.

Opposing the SAM system is the parasympathetic arm of the autonomic nervous system. Vagal nerve activity may regulate allostatic load (Thayer & Sternberg, 2006). Allostasis is the changing of various physiological set points in response to chronic stress, with the effect of producing a “load” that may

contribute to pathophysiological process involved in a variety of chronic illnesses. Decreased vagal function is associated with elevated fasting glucose, increased proinflammatory cytokines and acute-phase proteins, and increased cortisol, all of which constitute allostatic load.

Hypothalamic–Pituitary–Adrenal Axis

The HPA axis is activated concomitantly with activation of the SAM system but is more gradual in its effects. Both the SAM system and the HPA axis are activated through the limbic system. HPA axis activation is initiated by release of corticotropin-releasing hormone from the hypothalamus, which stimulates the pituitary to release adrenocorticotropic hormone (ACTH). ACTH then circulates in the blood and acts on adrenal cortical cells, causing the release of glucocorticoids (GCs). Cortisol plays an important adaptive role. For example, cortisol increases food intake and causes glucose to be available as a fuel, and suppresses other functions not immediately essential, such as reproduction (Landys, Ramenofsky, & Wingfield, 2006). GCs increase the efficacy of catecholamines, thus enhancing the effects of the SAM system on cardiovascular function during stress states (McEwen, 2003).

Cortisol is immunosuppressive and anti-inflammatory, and down-regulates the excessive inflammatory and immune processes that might be activated by stressors caused by predation (i.e., injury, bleeding, and infection). By binding to receptors on immune cells, GCs normally decrease gene transcription for proinflammatory cytokines, thereby decreasing inflammation. This mechanism is thought to account in part for the immunosuppressive effects of GCs (Adcock, Ito, & Barnes, 2004).

People with depression may either have abnormally low levels of cortisol or become less sensitive to cortisol. In either case, cortisol fails to restrain the inflammatory response (Dhabhar & McEwen, 2001). Pace, Hu, and Miller (2007) noted that GC resistance has been one of the most reproducible biologic symptoms of depression, and that it occurs in up to 80% of patients with depression. GC resistance may be a result of impaired function of the GC receptors. Chronic exposure to inflammatory cytokines, from either medical illness or chronic stress, likely leads to impaired receptor function.

Without cortisol and other anti-inflammatory molecules, inflammation and tissue destruction could lead to severe and continuous tissue damage. However, excessive secretion of cortisol over a longer term may contribute to allostatic load, and thus to disease. Dysregulation of the HPA axis is a central component of allostatic load, and potentially an early indicator of allostasis. The types of perturbations include hyper- and hypocortisolemia, aberrations in the early morning awakening rise in cortisol, abnormalities in the dexamethasone suppression test, and flattened cortisol rhythms across the day (McEwen, 2003a). Conditions or situations that result in a chroni-

cally activated HPA include melancholic depression, anorexia nervosa, obsessive-compulsive disorder, panic anxiety, alcoholism, alcohol and narcotic withdrawal, excessive exercising, poorly controlled diabetes mellitus, hyperthyroidism, and childhood sexual abuse (Tsigos & Chrousos, 2002).

Cortisol is an allostatic hormone that changes on a daily basis depending on time of day, season, and reproductive state. It is now appreciated that the cortisol rise that occurs on awakening is a key determinant of adaptation to routine activities of daily living (Wust, Federenko, Hellhammer, & Kirschbaum, 2000). Even arising from bed in the morning is a sufficient stressor to require both cortisol and the SAM system in order to ensure adequate blood flow to the brain and mobilization of metabolic fuels for the energy needs of the day. It is interesting that the most frequent time for an acute myocardial infarction is in the morning, particularly Monday morning, in association with the morning rise in blood pressure and heart rate (Giles, 2005). The normal circadian rhythm and cortisol response to stressors are healthy phenomena. But prolonged exposure to cortisol is damaging to neural structures. Chronically high and low levels are considered maladaptive (the so-called U-shaped curve; Gunnar & Quevedo, 2007).

Hypocortisolemia is also seen in some chronic stress states. Atypical depression with exhaustion (Gold, Goodman, & Chrousos, 1988), posttraumatic stress disorder (PTSD; Yehuda, 1997), addiction disorders (Schuder, 2005), fibromyalgia (McBeth et al., 2005), and postpartum depression (Groër & Morgan, 2007) are characterized by hypocortisolemia. Several studies have shown that combat veterans with PTSD may have lower morning cortisol (Boscarino, 1996) and lower 24-hour cortisol levels compared with the corresponding values for men without PTSD (Yehuda, 1997). Women exposed to intimate partner violence who develop PTSD actually have higher cortisol levels across the day than do similarly exposed women without PTSD. The inability of organisms to elaborate an adequate cortisol response is an abnormality that contributes to allostatic load.

Inflammatory Cytokines and Acute-Phase Reactants

Inflammation is a rapid and nonspecific response to danger, usually provoked by pathogen-associated molecular patterns, which bind to toll-like receptors on the membranes of immune cells (Beutler, 2004). These cells are also activated by neurotransmitters and neuropeptides (Sternberg, 2006) and “danger signals,” such as complement proteins, heat shock proteins, and other products of injured or dying cells (Matzinger, 2002). The neuroimmunological axis is of particular importance in understanding how stress might activate inflammatory pathways. Recent evidence suggests that norepinephrine may play an important role in the induction of stress-induced proinflammatory cytokines within CNS and peripheral circula-

tion (Blandino, Barnum, & Deak, 2006; J. D. Johnson et al., 2005). Virtually every immune organ is innervated by sympathetic fibers; however, the density and distribution of innervation vary between organs. Likewise, immune cells have receptors for one or more of these stress hormones or neurotransmitters, thereby allowing stress response to exert regulatory control over immune function. A stress-induced autonomic–inflammatory reflex may explain how stress is involved in metabolic, vascular, and autoimmune diseases (Bierhaus, Humpert, & Nawroth, 2006).

Inflammatory mediators are capable of tissue damage if not controlled. To prevent such damage, anti-inflammatory processes normally suppress inflammation. These anti-inflammatory molecules include cortisol and cytokines such as interleukin-10 (IL-10) and transforming growth factor- β . The inflammatory response, if inappropriate, excessive, or long-lasting, becomes the underpinning of many human diseases, such as coronary heart disease (CHD).

Inflammatory cytokines are released by many cell types (e.g., macrophages, endothelium, fat cells, muscle cells, liver) in response to danger signals. The action of the proinflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor- α (TNF- α), is to provoke inflammatory changes locally and act on other systems such as the brain and liver at a distance. One of the most important primary mediators of allostasis is IL-6, an endogenous proinflammatory cytokine produced by adipose tissue, macrophages, adipocytes, T cells, and endothelium. IL-6 stimulates sickness behaviors, fever, fatigue, hematopoiesis, and immune responses; it leads to the acute-phase inflammatory response and controls the hepatic acute-phase response. When exposed to IL-6, hepatocytes augment expression of proteins of the acute-phase response, including fibrinogen and C-reactive protein (CRP). IL-6 has been correlated with measures of CHD and insulin resistance. It is increased in individuals who are obese (Brunn et al., 2003).

CRP is an acute-phase reactant released in response to acute injury, infection, and other inflammatory stimuli, such as inflammatory diseases, necrosis, and trauma (A. Wilson, Ryan, & Boyle, 2006). Largely produced in the liver and synthesized in response to cytokines (predominantly IL-6 and TNF- α), CRP is a marker of low-grade inflammation. High levels of CRP have been associated with obesity, insulin resistance, and an increased risk of developing Type 2 diabetes (Kip et al., 2004; A. Wilson et al., 2006). The usefulness of CRP as a marker of allostatic load in predicting cardiovascular risk has been demonstrated. Cook, Buring, and Ridker (2006) found that adding CRP to a global risk prediction model improved cardiovascular risk classification in participants in the Women's Health Study, particularly for those with a 10-year risk of 5% to 20%. High body mass index showed stronger associations with CRP than did physical activity (Mora, Lee, Buring, & Ridker, 2006).

BIDIRECTIONAL COMMUNICATION BETWEEN BRAIN AND IMMUNE SYSTEM

Communication between the CNS and immune system is bidirectional in nature. For example, the immune system is able to alter the functioning of the CNS through the release of proinflammatory cytokines (Dantzer & Kelley, 2007; Maier & Watkins, 1998). Cytokines, such as interleukins, are regulatory proteins that are released by cells of the immune system and CNS. Not only do they act as intercellular messengers to alter inflammation and immunity, but cytokines can also influence CNS function and behavior (Maier & Watkins, 1998; Watkins & Maier, 2000). For example, proinflammatory cytokine expression increases in the brain and in the periphery following either immune challenge or exposure to stress. A variety of stressors have also been shown to increase circulating and central levels of proinflammatory cytokines, such as IL-1 β and IL-6 (Huang, Takaki, & Arimura, 1997; LeMay, Otterness, Vander, & Kluger, 1990; LeMay, Vander, & Kluger, 1990; Maes, 2001; Shizuya et al., 1997, 1998; Steptoe, Willemson, Owen, Flower, & Mohamed-Ali, 2001; Takaki, Huang, Somogyvari-Vigh, & Arimura, 1994; Zhou, Kusnecov, Shurin, DePaoli, & Rabin, 1993).

Within the CNS, IL-1 β and IL-6 can regulate the stress response by binding to receptors that can activate the HPA axis during either an immune or stress response (Bethin, Vogt, & Muglia, 2000; Turnbull & Rivier, 1999). In addition, proinflammatory cytokines have been shown to mediate the sickness syndrome observed following both infection and stress (Bluthe, Michaud, Poli, & Dantzer, 2000; Dantzer & Kelley, 2007; Maier & Watkins, 1998; Watkins & Maier, 2000). Sickness syndrome includes a range of behavioral and physiological changes that have evolved to conserve metabolic resources during periods of challenge, including loss of appetite and consequent weight loss, decreased behavioral activity, loss of interest in pleasurable activities (anhedonia), and enhanced pain sensitivity (hyperalgesia and allodynia).

There is increasing evidence that cross-sensitization can occur between stress-induced and immune-induced proinflammatory cytokines, resulting in the potentiation of CNS cytokine responses (Cunningham, Wilcockson, Campion, Lunnon, & Perry, 2005; Frank, Baratta, Sprunger, Watkins, & Maier, 2007; J. D. Johnson et al., 2002, 2004; Perry, Newman, & Cunningham, 2003; Quan et al., 2001). For example, prior exposure to stress leads to an exacerbation of brain cytokine synthesis after peripheral inflammatory challenge (J. D. Johnson et al., 2002; J. D. Johnson, O'Connor, Watkins, & Maier, 2004; Quan et al., 2001). Other evidence suggests that prior exposure to proinflammatory cytokines can sensitize neuronal, hormonal, cytokine, and behavioral responses to subsequent stress and immune challenges. For example, two prior administrations of IL-6 increased expression of IL-6 in the hypothalamus after a forced swim stress challenge without affecting circulat-

ing cytokines, whereas exposure to the forced swim stress alone had no impact (Matsumoto et al., 2006). It appears that prior exposure to IL-6 sensitized the hypothalamic IL-6 response to the subsequent stress challenge. In a similar way, central administration of IL-1 β in nonstressed rats results in sensitization of IL-1 β responses in the hypothalamus, hippocampus, and cortex to subsequent lipopolysaccharide challenge, without affecting circulating cytokines (J. D. Johnson et al., 2004). Furthermore, prior exposure to IL-1 β and TNF- α sensitizes subsequent endocrine, behavioral, and neurochemical responses to the same cytokine or to foot-shock stress (Merali, Lacosta, & Anisman, 1997; Schmidt, Janszen, Wouterlood, & Tilders, 1995).

The phenomenon of cross-sensitization suggests that a shared neural substrate may be primed by either stress or immune activation. Recent evidence suggests that microglia may function as the shared cellular substrate mediating these priming effects of proinflammatory cytokines in the CNS (Cunningham et al., 2005; Frank et al., 2007; Nair & Bonneau, 2006; Perry et al., 2003). Microglia function as the primary immune effector cell in the nervous system and release proinflammatory cytokines. Exposure to stress can activate microglia, resulting in priming or sensitization of microglia to subsequent proinflammatory challenges. Upon subsequent immune challenge, the primed microglia exhibit a potentiated proinflammatory response (Frank et al., 2007). Researchers are just beginning to elucidate the molecular mechanisms that mediate the cross-sensitization of cytokine synthesis (Frank et al., 2007). Whatever the underlying mechanisms may be, cross-sensitization provides a mechanism explaining how stress exacerbates inflammatory disease processes.

SUMMARY

Stressful events, particularly if chronic, can increase the risk of disease. Some of this increased risk is due to psychosocial and behavioral factors, such as smoking and alcohol use. However, there is increasing evidence that stress has a direct biological effect on disease risk, involving the sympathetic nervous system, HPA axis, and inflammatory response system. Communication between the brain and immune system is bidirectional, meaning that stress can cause the brain to trigger the immune response, and the immune response can induce changes in the CNS, resulting in a constellation of behaviors known as sickness syndrome. Chronic stress and immune response become mutually maintaining conditions, increasing the risk of inflammatory, neurodegenerative, and autoimmune diseases.

KEY POINTS

- Stressful events have direct biological effects that increase the risk of disease.

- When the brain perceives danger, it activates the sympathetic nervous system and HPA axis.
- Inflammation increases in response to perceived danger.
- When stress chronically activates these systems, the risk of illnesses such as coronary heart disease, diabetes, neurodegenerative diseases and autoimmunity, is increased.
- Communication between the brain and the immune system is bidirectional.

REFERENCES

- Ackerman, K. D., Heyman, R., Rabin, B. S., Anderson, B. P., Houck, P. R., Frank, E., & Baum, A. (2002). Stressful life events precede exacerbations of multiple sclerosis. *Psychosomatic Medicine*, *64*, 916–920.
- Adcock, I. M., Ito, K., & Barnes, P. J. (2004). Glucocorticoids: Effects on gene transcription. *Proceedings of the American Thoracic Society*, *1*, 247–254.
- Antoni, M. H., Lutgendorf, S. K., Cole, S. W., Dhabhar, F. S., Sephton, S. E., McDonald, P. G., et al. (2006). The influence of bio-behavioural factors on tumour biology: Pathways and mechanisms. *Nature Reviews: Cancer*, *6*, 240–248.
- Backer, J. H. (2000). Stressors, social support, coping, and health dysfunction in individuals with Parkinson's disease. *Journal of Gerontological Nursing*, *26*(11), 7–16.
- Bethin, K. E., Vogt, S. K., & Muglia, L. J. (2000). Interleukin-6 is an essential, corticotropin-releasing hormone-independent stimulator of the adrenal axis during immune system activation. *Proceedings of the National Academy of Sciences USA*, *97*, 9317–9322.
- Beutler, B. (2004). Innate immunity: An overview. *Molecular Immunology*, *40*, 845–859.
- Bierhaus, A., Humpert, P., & Nawroth, P. (2006). Linking stress to inflammation. *Anesthesiology Clinics*, *24*, 325–340.
- Blandino, P., Jr., Barnum, C. J., & Deak, T. (2006). The involvement of norepinephrine and microglia in hypothalamic and splenic IL-1beta responses to stress. *Journal of Neuroimmunology*, *173*, 87–95.
- Bluthe, R. M., Michaud, B., Poli, V., & Dantzer, R. (2000). Role of IL-6 in cytokine-induced sickness behavior: A study with IL-6 deficient mice. *Physiology & Behavior*, *70*, 367–373.
- Boscarino, J. (1996). Posttraumatic stress disorder, exposure to combat, and lower plasma cortisol among Vietnam veterans: Findings and clinical implications. *Journal of Consulting and Clinical Psychology*, *64*, 191–201.
- Brunn, J. M., Lihn, A. S., Verdich, C., Pedersen, S. B., Toubro, S., Astrup, A., et al. (2003). Regulation of adiponectin by adipose tissue-derived cytokines: In vivo

- and in vitro investigations in humans. *American Journal of Physiology, Endocrinology and Metabolism*, 285, E527–E533.
- Campbell, T., Meagher, M. W., Sieve, A., Scott, B., Storts, R., Welsh, T. H., & Welsh, C. J. R. (2001). The effects of restraint stress on the neuropathogenesis of Theiler's virus infection: I. Acute disease. *Brain, Behavior, and Immunity*, 15, 235–254.
- Campisi, J., & Fleshner, M. (2003). The role of extracellular HSP72 in acute stress-induced potentiation of innate immunity in physically active rats. *Journal of Applied Physiology*, 94, 43–52.
- Chida, Y., Sudo, N., & Kubo, C. (2005). Social isolation stress exacerbates autoimmune disease in MRL/lpr mice. *Journal of Neuroimmunology*, 158, 138–144.
- Cohen, S., Kessler, R. C., & Gordon, U. L. (1995). Strategies for measuring stress in studies of psychiatric and physical disorder. In S. Cohen, R. C. Kessler, & U. L. Gordon (Eds.), *Measuring stress: A guide for health and social scientists* (pp. 3–26). New York: Oxford University Press.
- Cook, N., Buring, J., & Ridker, P. (2006). The effect of including C-reactive protein in cardiovascular risk prediction models for women. *Annals of Internal Medicine*, 145, 21–29.
- Cunningham, C., Wilcockson, D. C., Campion, S., Lunnon, K., & Perry, V. H. (2005). Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. *Journal of Neuroscience*, 25, 9275–9284.
- Dantzer, R., & Kelley, K. W. (2007). Twenty years of research on cytokine-induced sickness behavior. *Brain, Behavior, and Immunity*, 21, 153–160.
- Dhabhar, F. S., & McEwen, B. S. (1997). Acute stress enhances while chronic stress suppresses immune function in vivo: A role for leukocyte trafficking. *Brain, Behavior, and Immunity*, 11, 286–306.
- Dhabhar, F. S., & McEwen, B. S. (1999). Enhancing versus suppressive effects of stress hormones on skin immune function. *Proceedings of the National Academy of Sciences USA*, 96, 1059–1064.
- Dhabhar, F. S., & McEwen, B. S. (2001). Bidirectional effects of stress and glucocorticoid hormones on immune function: Possible explanations for paradoxical observations. In R. Ader, D. L. Felten, & N. Cohen (Eds.), *Psychoneuroimmunology* (3rd ed., Vol. 1, pp. 301–338). New York: Academic Press.
- Dhabhar, F. S., & Viswanathan, K. (2005). Short-term stress experienced at time of immunization induces a long-lasting increase in immunologic memory. *American Journal of Physiology—Regulatory, Integrative and Comparative Physiology*, 289, R738–R744.
- Dobbs, C. M., Vasquez, M., Glaser, R., & Sheridan, J. F. (1993). Mechanisms of stress-induced modulation of viral pathogenesis and immunity. *Journal of Neuroimmunology*, 48, 151–160.
- Dowdell, K. C., Gienapp, I. E., Stuckman, S., Wardrop, R. M., & Whitacre, C. C. (1999). Neuroendocrine modulation of chronic relapsing experimental autoim-

- immune encephalomyelitis: A critical role for the hypothalamic–pituitary–adrenal axis. *Journal of Neuroimmunology*, 100, 243–251.
- Frank, M. G., Baratta, M. V., Sprunger, D. B., Watkins, L. R., & Maier, S. F. (2007). Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS pro-inflammatory cytokine responses. *Brain, Behavior, and Immunity*, 21, 47–59.
- Giles, T. (2005). Relevance of blood pressure variation in the circadian onset of cardiovascular events. *Journal of Hypertension*, 23(Suppl. 1), S35–S39.
- Gold, P., Goodman, F., & Chrousos, G. (1988). Clinical and biochemical manifestations of depression: Relation to the neurobiology of stress (1). *The New England Journal of Medicine*, 319, 348–353.
- Grant, I., Brown, G. W., Harris, T., McDonald, W. I., Patterson, T., & Trimble, M. R. (1989). Severely threatening events and marked life difficulties preceding onset or exacerbation of multiple sclerosis. *Journal of Neurology, Neurosurgery, & Psychiatry*, 52, 8–13.
- Groër, M. W., & Morgan, K. (2007). Immune, health and endocrine characteristics of depressed postpartum mothers. *Psychoneuroendocrinology*, 32, 133–139.
- Gunnar, M., & Quevedo, K. (2007). The neurobiology of stress and development. *Annual Review of Psychology*, 58, 145–173.
- Huang, Q. H., Takaki, A., & Arimura, A. (1997). Central noradrenergic system modulates plasma interleukin-6 production by peripheral interleukin-1. *American Journal of Physiology—Regulatory, Integrative and Comparative Physiology*, 273, R731–R738.
- Johnson, J. D., Campisi, J., Sharkey, C. M., Kennedy, S. L., Nickerson, M., Greenwood, B. N., & Fleshner, M. (2005). Catecholamines mediate stress-induced increases in peripheral and central inflammatory cytokines. *Neuroscience*, 135, 1295–1307.
- Johnson, J. D., O'Connor, K. A., Deak, T., Stark, M., Watkins, L. R., & Maier, S. F. (2002). Prior stressor exposure sensitizes LPS-induced cytokine production. *Brain, Behavior, and Immunity*, 16, 461–476.
- Johnson, J. D., O'Connor, K. A., Watkins, L. R., & Maier, S. F. (2004). The role of IL-1 β in stress-induced sensitization of proinflammatory cytokine and corticosterone responses. *Neuroscience*, 127, 569–577.
- Johnson, R. R., Prentice, T., Bridegam P., Young, C. R., Steelman, A. J., Welsh, T. H., et al. (2006). Social stress alters the severity and onset of the chronic phase of Theiler's virus infection. *Journal of Neuroimmunology*, 175, 39–51.
- Kelley, K. W., Greenfield, R. E., Evermann, J. F., Parish, S. M., & Perryman, L. E. (1982). Delayed-type hypersensitivity, contact sensitivity, and phytohemagglutinin hemagglutinin skin-test responses of heat- and cold-stressed calves. *American Journal of Veterinary Research*, 43, 775–779.
- Kip, K., Marroquin, O., Kelley, D., Johnson, B., Kelsey, S., Shaw, L., et al. (2004). Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: A report from the Women's Ischemia Syndrome Evaluation (WISE) study. *Circulation*, 109, 706–713.

- Landys, M., Ramenofsky, M., & Wingfield, J. C. (2006). Actions of glucocorticoids at a seasonal baseline as compared to stress-related levels in the regulation of periodic life processes. *General and Comparative Endocrinology*, *148*, 132–149.
- LeMay, L. G., Otterness, I. G., Vander, A. J., & Kluger, M. J. (1990). In vivo evidence that the rise in plasma IL 6 following injection of a fever-inducing dose of LPS is mediated by IL 1 beta. *Cytokine*, *2*, 199–204.
- LeMay, L. G., Vander, A. J., & Kluger, M. J. (1990). The effects of psychological stress on plasma interleukin-6 activity in rats. *Physiology & Behavior*, *47*, 957–961.
- Maes, M. (2001). Psychological stress and the inflammatory response system. *Clinical Science*, *101*, 193–194.
- Maier, S. F., & Watkins, L. R. (1998). Cytokines for psychologists: Bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychological Review*, *105*, 83–107.
- Matsumoto, T., Komori, T., Yamamoto, M., Shimada, Y., Nakagawa, M., Shiroyama, T., et al. (2006). Prior intraperitoneal injection of rat recombinant IL-6 increases hypothalamic IL-6 contents in subsequent forced swim stressor in rats. *Neuropsychobiology*, *54*, 186–194.
- Matyszak, M. K. (1998). Inflammation in the CNS: Balance between immunological privilege and immune responses. *Progress in Neurobiology*, *56*, 19–35.
- Matzinger, P. (2002, April 12). The danger model: A renewed sense of self. *Science*, *296*, 301–305.
- McBeth, J., Chiu, Y. H., Silman, A., Ray, D., Morriss, R., Dickens, C., et al. (2005). Hypothalamic–pituitary–adrenal stress axis function and the relationship with chronic widespread pain and its antecedents. *Arthritis Research and Therapeutics*, *7*, R992–R1000.
- McEwen, B. S. (2003). Interacting mediators of allostasis and allostatic load: Towards an understanding of resilience in aging. *Metabolism*, *52*, 10–16.
- McEwen, B. S., Biron, C. A., Brunson, K. W., Bulloch, K., Chambers, W. H., Dhabhar, F. S., et al. (1997). The role of adrenocorticoids as modulators of immune function in health and disease: Neural, endocrine and immune interactions. *Brain Research Review*, *23*, 79–133.
- McGeer, P. L., & McGeer, E. G. (1995). The inflammatory response system of brain: Implications for therapy of Alzheimer and other neurodegenerative diseases. *Brain Research Review*, *21*, 195–218.
- McGeer, P. L., & McGeer, E. G. (2004). Inflammation and the degenerative diseases of aging. *Annals of the New York Academy of Sciences*, *1035*, 104–116.
- Meagher, M. W., Johnson, R. R., Young, E. E., Vichaya, E. G., Lunt, S., Harden, E., et al. (2007). Interleukin-6 as a mechanism for the adverse effects of social stress on acute Theiler's virus infection. *Brain, Behavior, and Immunity*, *21*, 1083–1095.
- Mei-Tal, V., Meyerowitz, S., & Engel, G. L. (1970). The role of psychological process in a somatic disorder: Multiple sclerosis: 1. The emotional setting of illness onset and exacerbation. *Psychosomatic Medicine*, *32*, 67–86.

- Merali, Z., Lacosta, S., & Anisman, H. (1997). Effects of interleukin-1beta and mild stress on alterations of norepinephrine, dopamine and serotonin neurotransmission: A regional microdialysis study. *Brain Research*, 761, 225–235.
- Mohr, D. C., Goodkin, D. E., Bacchetti, P., Boudewyn, A. C., Huang, L., Marrietta, P., et al. (2000). Psychological stress and the subsequent appearance of new brain MRI lesions in MS. *Neurology*, 55, 55–61.
- Mohr, D. C., Hart, S. L., Julian, L., Cox, D., & Pelletier, D. (2004, March 27). Association between stressful life events and exacerbation in multiple sclerosis: A meta-analysis. *BMJ*, 328, 731–735.
- Mora, S., Lee, I., Buring, J., & Ridker, P. (2006). Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women. *JAMA*, 295, 1412–1419.
- Nair, A., & Bonneau, R. H. (2006). Stress-induced elevation of glucocorticoids increases microglia proliferation through NMDA receptor activation. *Journal of Neuroimmunology*, 171, 72–85.
- Pace, T. W., Hu, F., & Miller, A. H. (2007). Cytokine-effects on glucocorticoid receptor function: Relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain, Behavior, and Immunity*, 21, 9–19.
- Padgett, D. A., Sheridan, J. F., Dorne, J., Berntson, G. G., Candelora, J., & Glaser, R. (1998). Social stress and the reactivation of latent herpes simplex virus Type 1. *Proceedings of the National Academy of Sciences USA*, 95, 7231–7235.
- Perry, V. H., Newman, T. A., & Cunningham, C. (2003). The impact of systemic infection on the progression of neurodegenerative disease. *Nature Reviews: Neuroscience*, 4, 103–112.
- Quan, N., Avitsur, R., Stark, J. L., He, L., Shah, M., Caliguiri, M., et al. (2001). Social stress increases the susceptibility to endotoxic shock. *Journal of Neuroimmunology*, 115, 36–45.
- Rabin, B. S. (2002). Can stress participate in the pathogenesis of autoimmune disease? *Journal of Adolescent Health*, 30, 71–75.
- Schmidt, E. D., Janszen, A. W., Wouterlood, F. G., & Tilders, F. J. (1995). Interleukin-1-induced long-lasting changes in hypothalamic corticotropin-releasing hormone (CRH)-neurons and hyperresponsiveness of the hypothalamic–pituitary–adrenal axis. *Journal of Neuroscience*, 15, 7417–7426.
- Schuder, S. (2005). Stress-induced hypocortisolemia diagnosed as psychiatric disorders responsive to hydrocortisone replacement. *Annals of the New York Academy of Sciences*, 1057, 466–478.
- Segerstrom, S. C., & Miller, G. E. (2004). Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin*, 13, 601–630.
- Sheridan, J. F., Dobbs, C., Jung, J., Chu, X., Konstantinos, A., Padgett, D. A., & Glaser, R. (1998). Stress-induced neuroendocrine modulation of viral pathogenesis and immunity. *Annals of the New York Academy of Sciences*, 840, 803–808.

- Shizuya, K., Komori, T., Fujiwara, R., Miyahara, S., Ohmori, M., & Nomura, J. (1997). The influence of restraint stress on the expression of mRNAs for IL-6 and the IL-6 receptor in the hypothalamus and midbrain of the rat. *Life Science*, 61, 135–140.
- Shizuya, K., Komori, T., Fujiwara, R., Miyahara, S., Ohmori, M., & Nomura, J. (1998). The expressions of mRNAs for interleukin-6 (IL-6) and the IL-6 receptor (IL-6R) in the rat hypothalamus and midbrain during restraint stress. *Life Science*, 62, 2315–2320.
- Sieve, A. N., Steelman, A. J., Young, C. R., Storts, R., Welsh, T. H., Welsh, C. J. R., & Meagher, M. W. (2004). Chronic restraint stress during early Theiler's virus infection exacerbates the subsequent demyelinating disease in SJL mice. *Journal of Neuroimmunology*, 155, 103–118.
- Spiegel, D., & Giese-Davis, J. (2003). Depression and cancer: Mechanisms and disease progression. *Biological Psychiatry*, 54, 269–282.
- Steptoe, A., Willemsen, G., Owen, N., Flower, L., & Mohamed-Ali, V. (2001). Acute mental stress elicits delayed increases in circulating inflammatory cytokine levels. *Clinical Sciences*, 101, 185–192.
- Sternberg, E. (2006). Neural regulation of innate immunity: A coordinated nonspecific host response to pathogens. *Nature Reviews: Immunology*, 6, 318–328.
- Takaki, A., Huang, Q.-H., Somogyvari-Vigh, A., & Arimura, A. (1994). Immobilization stress may increase plasma interleukin (IL)-6 via central and peripheral catecholamines. *Neuroimmunomodulation*, 1, 335–342.
- Thayer, J., & Sternberg, E. (2006). Beyond heart rate variability: Vagal regulation of allostatic systems. *Annals of the New York Academy of Sciences*, 1088, 361–372.
- Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research*, 53, 865–871.
- Turnbull, A. V., & Rivier, C. L. (1999). Regulation of the hypothalamic–pituitary–adrenal axis by cytokines: Actions and mechanisms of action. *Physiological Reviews*, 79, 1–71.
- Viswanathan, K., Daugherty C., & Dhabhar, F. S. (2005). Stress as an endogenous adjuvant: Augmentation of the immunization phase of cell-mediated immunity. *International Immunology*, 17, 1059–1069.
- Warren, S., Greenhill, S., & Warren, K. G. (1982). Emotional stress and the development of multiple sclerosis: Case-control evidence of a relationship. *Journal of Chronic Disease*, 35, 821–831.
- Warren, S., Warren, K. G., & Cockerill, R. (1991). Emotional stress and coping in multiple sclerosis (MS) exacerbations. *Journal of Psychosomatic Research*, 35, 37–47.
- Watkins, L. R., & Maier, S. F. (2000). The pain of being sick: Implications of immune-to-brain communication for understanding pain. *Annual Review of Psychology*, 51, 29–57.
- Welsh, C. J. R., Meagher, M. W., & Sternberg, E. M. (2006). *Neural and neuroendocrine mechanisms in host defense and autoimmunity*. New York: Springer.

- Whitton, P. S. (2007). Inflammation as a causative factor in the aetiology of Parkinson's disease. *British Journal of Pharmacology*, 150, 963–976.
- Wilson, A., Ryan, M., & Boyle, A. (2006). The novel role of C-reactive protein in cardiovascular disease: Risk marker or pathogen. *International Journal of Cardiology*, 106, 291–297.
- Wilson, R. S., Evans, D. A., Bienias, J. L., Mendes de Leon, C. F., Schneider, J. A., & Bennett, D. A. (2003). Proneness to psychological distress is associated with risk of Alzheimer's disease. *Neurology*, 61, 1479–1485.
- Wust, S., Federenko, I., Hellhammer, D., & Kirschbaum, C. (2000). Genetic factors, perceived chronic stress, and the free cortisol response to awakening. *Psychoneuroendocrinology*, 25, 707–720.
- Yehuda, R. (1997). Sensitization of the hypothalamic–pituitary–adrenal axis in post-traumatic stress disorder. *Annals of the New York Academy of Sciences*, 821, 57–75.
- Zhou, D., Kusnecov, A. W., Shurin, M. R., DePaoli, M., & Rabin, B. S. (1993). Exposure to physical and psychological stressors elevates plasma interleukin 6: Relationship to the activation of hypothalamic–pituitary–adrenal axis. *Endocrinology*, 133, 2523–2530.