64

Psychological Influences on Neuroendocrine and Immune Disorders

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Over the past 25 years, substantial evidence has established that psychological factors affect clinically relevant immune and neuroendocrine outcomes. In particular, psychosocial stress reliably causes immunological changes that are not only measurable, but also meaningful in terms of health. Moreover, alterations in neuroendocrine function are primary mediators of immune changes seen in response to stress.

This chapter focuses on work linking psychosocial factors with immune function among humans in three outcome areas. We first review substantial evidence linking the psychological states of stress and depression to inflammation, a key outcome because of its clinical relevance to serious health conditions. Next, we summarize research linking stress and wound healing, a clinically vital process in which inflammation plays an important role. Finally, we review effects of stress on susceptibility to infectious illness including studies of vaccination, exposure to infectious agents, and immune control of latent viruses.

This chapter focuses primarily on the immune effects of stress, although other specific psychosocial factors (including depression, hostility, and anxiety) are also discussed. Although we emphasize human studies, we also describe key animal studies, primarily those elucidating physiological mechanisms underlying links between psychosocial factors and immune outcomes. Throughout, the role of neuroendocrine mediators is highlighted. We also describe the positive effects of social support and promising interventions that target the effects of stress.

OVERVIEW OF THE IMMUNE SYSTEM

The protective physical barrier formed by the skin provides the body's first line of defense against foreign invaders. The second line of defense is the innate immune system, which responds very rapidly (within minutes to hours) but in a nonspecific manner when exogenous antigens such as bacteria and viruses are detected. The key elements of the innate immune system are neutrophils, macrophages, natural killer (NK) cells, and complement proteins.

When the innate immune system cannot effectively eliminate or control the antigen in question, the adaptive immune system provides the third line of defense. Although the adaptive immune system may take several days to mount an optimal response, its action is highly targeted. The main cell type of the adaptive immune system is the lymphocyte, which includes T-cells and B-cells. Importantly, after the adaptive immune system is exposed to a particular antigen, certain T-cells and B-cells retain memory of that antigen, which allows a stronger and more rapid response on subsequent exposure; the ability of the adaptive immune system to form memory in this way provides the basis for vaccination (see Figure 64.1).

Cytokines are soluble proteins that are involved in communication between immune cells. Cytokines also have more far-reaching effects (e.g., effects of cytokines on the brain are key to behavioral changes related to illness). Cytokines are produced by cells of both the innate and adaptive immune systems as well as several other non-lymphoid cells in the body, such as adipocytes (fat cells). Among their multiple functions, cytokines play a key role in inflammatory immune responses, which involve the recruitment of key proteins and immune cells to an affected area. Inflammation is a critical response to infection or injury; however, chronic or excessive inflammation is linked to negative health outcomes. Thus an adequate,

First Line of Defense
Skin
Key Features: Body's largest organ Prevents bacteria, viruses, and other exogenous antigens from entering

Second Line of Defense
Innate Immune System
Key Features: Rapid, but nonspecific response
Major components: Neutrophils, macrophages, natural killer cells, complement proteins

Third Line of Defense
Adaptive Immune System
Key Features: Slower, highly targeted response Formation of immunological memory
Major components: T-cells and B-cells

Figure 64.1   Divisions of the Immune System.

but not exaggerated inflammatory response to immune challenge is optimal. For more detailed coverage of the elements of the immune system, see Chapter 7, Volume 1.

EFFECTS OF HEALTH BEHAVIORS ON IMMUNE OUTCOMES

Although this chapter focuses on neuroendocrine pathways linking psychological stress and immune outcomes, behavioral pathways are another important area of investigation. In particular, heightened distress is associated with less adaptive health behavior, including more smoking and alcohol use, poorer diet, and less sleep (Steptoe, Wardle, Pollard, Canaan, & Davies, 1996; Vitaliano, Scanlan, Zhang, Savage, & Hirsch, 2002). In turn, health behaviors affect neuroendocrine function, immune function, and related health outcomes, including wound healing and response to infectious agents (Figure 64.2).

For each of the outcomes discussed in this chapter, effects of stress remain after accounting for effects of health behaviors, indicating that more direct physiological pathways exist between psychological factors and immune outcomes. However, because health behaviors may partly explain or exacerbate the effects of stress, assessing and appropriately controlling for health behaviors is an important component of research aimed at identifying and separating physiological versus behavioral pathways linking stress and immune function. Moreover, because health behaviors are modifiable, they represent a key target for interventions. One pathway by which behavioral interventions can benefit immune function is by improving physiological responses to stress.

STRESS, DEPRESSION, AND INFLAMMATION

Inflammation is an essential immune response to infection or injury. Among multiple other functions, inflammation promotes destruction (phagocytosis) and clearance of pathogens and initiates wound healing. As described, the production of cytokines, which are soluble proteins involved in communication between immune and other cells, is an important component of the inflammatory response. Cytokines can be classified as pro- or anti-inflammatory, although some cytokines demonstrate both pro- and anti-inflammatory characteristics. As the name implies, proinflammatory cytokines—including interleukin (IL)-6, IL-1, and tumor necrosis factor (TNF)-α—promote inflammation. Anti-inflammatory cytokines such as interleukin-10 (IL-10) act as important regulators of the immune response, in part by inhibiting the production of proinflammatory cytokines (Opal & DePalo, 2000; Parham, 2005).

A local inflammatory response involves increased vascular permeability and the recruitment of key proteins and immune cells to the affected area. It can be characterized by redness, swelling, pain, and fever (Rabin, 1999). In the case of infection or injury, inflammation is beneficial, as it aids recovery. In fact, proinflammatory cytokines are administered therapeutically to treat hepatitis and some cancers (Capuron & Miller, 2004; Dantzer & Kelley, 2007). However, exaggerated or chronic inflammation is detrimental to health. Chronic inflammation has been implicated in serious medical conditions including cardiovascular disease, arthritis, diabetes, inflammatory bowel disease, periodontal disease, certain cancers, and age-related functional decline (Black & Garbutt, 2002; Bruunsgaard, Pedersen, & Pedersen, 2001; Ershler & Keller, 2000; Hamerman, Berman, Albers, Brown, & Silver, 1999; Ishihara & Hirano, 2002). An insufficient anti-inflammatory response can contribute to excessive inflammation. Relatedly, the administration of anti-inflammatory cytokines has been implicated as a useful therapeutic strategy for diseases marked by inflammation, particularly rheumatoid arthritis (Opal & DePalo, 2000). Excessive anti-inflammatory control can overly inhibit inflammation, resulting in increased risk for infection and illness (Opal & DePalo, 2000). Thus, an appropriate balance of inflammatory and anti-inflammatory function is necessary for optimal health.

Conceptualizing Stress and Depression

Although conceptually distinct, stress and depression are similar in that they involve negative mood, activation of the hypothalamic-pituitary-adrenal (HPA) axis, and associated negative health outcomes (Anisman & Merali, 2003;
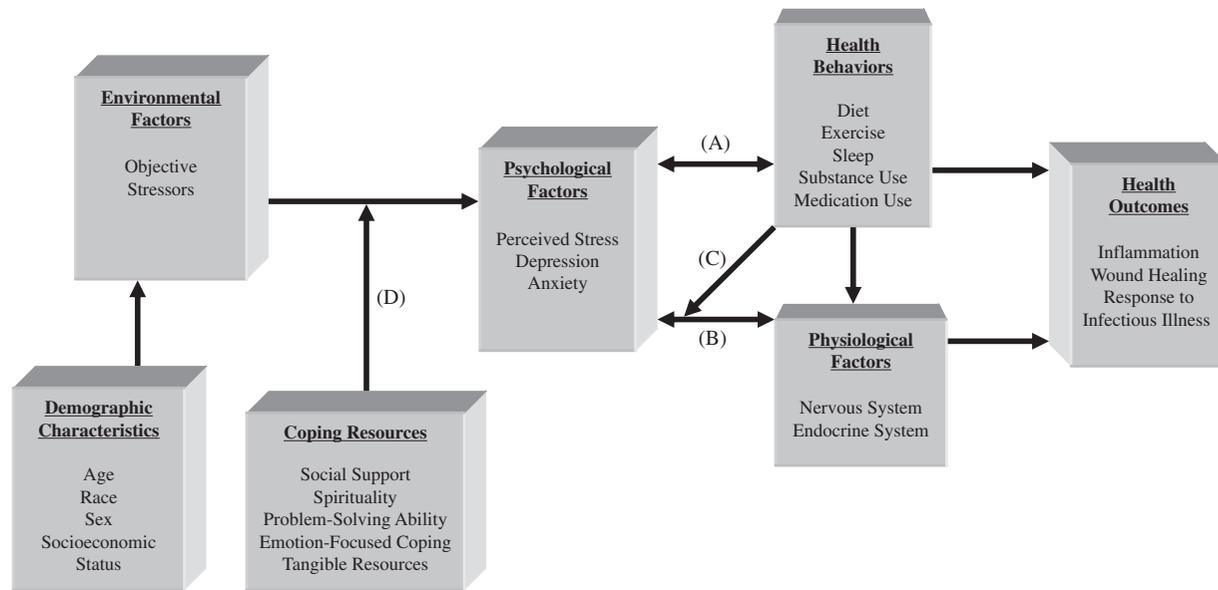
Figure 64.2   Pathways by which psychological factors affect health outcomes.

Note: An important pathway by which psychological factors affect health is health behaviors (A). Thus, appropriate control for health behaviors is important to research aiming to delineate physiological pathways linking psychological factors to health. Effects of psychological factors on health outcomes remain after accounting for effects of health behaviors, indicating that more direct physiological pathways between psychological factors and health outcomes exist (B). Importantly, health behaviors are modifiable and can moderate physiological responses to stress (C). Thus, health behaviors represent a key target for intervention. Another important target of interventions is coping resources, which moderate effects of environmental stressors on psychological responses (D).

Connor & Leonard, 1998). Stress can be defined and measured in many ways. Objective definitions generally focus on characteristics of the stressor experienced. Completing a 10-minute speech task can be defined as a mild acute stressor. In contrast, subjective measures of stress reflect an individual's perceptions of stress in their lives as well as their perceived ability to cope with that stress. In this way, subjective measures can capture important individual differences in how people react to the same stressor.

Common depressive symptoms include negative mood, loss of interest or pleasure, difficulty concentrating, changes in appetite, sleep disturbance, and thoughts of death. Importantly, psychological stress is a frequent precursor of clinical depression (Kendler, Karkowski, & Prescott, 1999). Moreover, as will be reviewed briefly, stress-associated overactivation of the sympathetic nervous system and HPA axis may play a causal role in the development of depression (also see Chapters 6 and 7, Volume 1; and Chapters 55 and 62, this Volume).

Stress and Inflammation

Using various stressors, both animal and human models have demonstrated effects of stress on inflammation. In terms of animal studies, acute stress in the form of exposure to a novel environment or foot/tail shock induces increases in plasma IL-6 levels in rats (LeMay, Vander, &

Kluger, 1990; Zhou, Kusnecov, Shurin, DePaoli, & Rabin, 1993). For example, rats exposed to foot shock exhibited heightened plasma IL-6. Moreover, IL-6 rose as an increasing number of foot shocks were administered (Zhou et al., 1993). Notably, this physiological response to stress can be conditioned; after repeated shocking, exposure to stimuli (e.g., auditory tones) that were present when shocks were administered also elicited increases in IL-6 (Johnson et al., 2002; Zhou et al., 1993).

Proinflammatory cytokines also rise in response to acute stressors such as public speaking and mental arithmetic (Brydon, Edwards, Mohamed-Ali, & Steptoe, 2004; Steptoe, Willemsen, Owen, Flower, & Mohamed-Ali, 2001). Circulating IL-6 and IL-1 receptor antagonist (IL-1ra) increased two hours after completion of Stroop and mirror-tracing tasks, while control participants did not change (Steptoe et al., 2001). This time lag between acute stressors and cytokine responses in humans has been reported in other studies. Some null findings (e.g., Heesen et al., 2002; Lutgendorf, Logan, Costanzo, & Lubaroff, 2004) may be explained by the fact that samples were taken at time points that were too close to the stressor. It is also notable that the magnitude of inflammation seen in response to objective stressors is not necessarily predicted by perceived stress (e.g., Brydon et al., 2004). This is consistent with evidence that subjective evaluations are often poor predictors of cardiovascular reactivity to acute stressors (e.g., Christian & Stoney, 2006).

Importantly, repeated exposure to a stressor may not lead to habituation of inflammatory responses. A sample of 21 healthy middle-aged men completed the Trier Social Stress Test (a combined speech and mental arithmetic task; see Kirschbaum, Pirke, & Hellhammer, 1993) three times with 1-week intervals between sessions. As expected, the stressor resulted in increases in plasma IL-6. Notably, although participants demonstrated habituation of cortisol and systolic blood pressure reactivity to the task between weeks 1 and 3, they demonstrated similar stress-induced elevations in IL-6 across visits (von Kanel, Kudielka, Preckel, Hanebuth, & Fischer, 2005). If such lack of habituation also occurs in naturalistic settings, inflammatory responses to relatively minor but recurrent stress in daily life may contribute to morbidity and mortality.

Given the effects demonstrated in response to acute stress, it would be expected that chronic stress could have an even greater impact on inflammation. Caregiving provides an excellent 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 ongoing stress, significant life change, and social isolation. Relatedly, caregivers experience heightened risk of negative mental and physical health outcomes, including depressive symptoms, infectious illness, and poorer response to vaccination (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991; Pinquart & Sorensen, 2004; Vitaliano, Zhang, & Scanlan, 2003). Notably, Schulz and Beach (1999) found that strained caregivers experienced 63% greater risk of mortality over a 4-year time frame compared with noncaregiving control participants.

Inflammation from chronic stress may contribute to morbidity and mortality among caregivers. Older women caregivers had higher levels of IL-6 compared with older women undergoing moderate stress (housing relocation) and low stress (Lutgendorf et al., 1999). Additional research with caregivers has demonstrated that caregiving exacerbates typical age-related increases in IL-6; caregivers experienced fourfold greater increases in IL-6 over a 6-year follow-up period compared with controls (Kiecolt-Glaser et al., 2003). These data suggest that the experience of chronic stress can accelerate the aging process. Notably, although caregivers reported greater perceived stress, depressive symptoms, and loneliness than controls, the effects of caregiver status on inflammation were not accounted for by these factors. Thus, effects of chronic stress on inflammation were not simply a reflection of greater stress, depression, or loneliness.

Depression and Inflammation

Relationships between depression and inflammation are seen across the life span. Among young adults who were 30 years old on average, those experiencing major depression had significantly higher circulating levels of inflammatory markers than controls with no psychiatric history (Maes et al., 1995). These markers included IL-6 and the soluble receptor of IL-6 (IL-6sR), which can widen the action of IL-6 (Jones, Horiuchi, Topley, Yamamoto, & Fuller, 2001). Similarly, among middle-aged adults, those with major depression had elevated serum levels of IL-6, IL-6sr, as well as the receptor antagonist for IL-1 (IL-1ra); IL-1ra is often elevated in individuals with diseases marked by inflammation (Maes et al., 1997).

These effects are also seen in older adults. In a sample of adults over 60 years of age compared with individuals with no prior history of psychiatric disorder, those who met criteria for clinical depression had 171% higher serum levels of IL-1β (Thomas et al., 2005). Moreover, among the depressed individuals, depression severity was positively correlated with IL-1β, levels. Along with other proinflammatory cytokines, IL-1β, is implicated in sickness behavior. Similarly, in a study of 1,686 participants over 70 years of age, those who exceeded a clinical cutoff on the Center for Epidemiologic Studies Depression scale (CES-D) had higher levels of IL-6 compared with individuals reporting fewer depressive symptoms, a relationship that held after controlling for age, race, and gender (Dentino et al., 1999). In addition, in a sample of 3,024 adults ages 70 to 79 years, those who exceeded a clinical cutoff on the CES-D had higher levels of IL-6 as well as TNF-α and C-reactive protein (CRP; Penninx et al., 2003). CRP is an inflammatory marker that is an emerging risk factor for cardiovascular disease (Hackam & Anand, 2003). These studies demonstrate associations between depressive symptoms and inflammatory markers across the life span.

In the preceding studies that examined depressive symptoms and inflammatory markers, perceived stress was not measured or statistically controlled. This may be an important consideration, however, because perceived stress tends to covary with depressive symptoms. McDade, Hawkley, and Cacioppo (2006) found that perceived stress was a more robust predictor of CRP than depressive symptoms in a population-based study of middle-aged and older adults. Moreover, the association between depressive symptoms and CRP was attenuated after controlling for perceived stress. Future research should aim to clarify the predictive value of perceived stress versus depressive symptoms in the context of clinical depression as well as milder depressive symptomatology. Relatedly, depressive symptomatology may be an important moderator of physiological responses to objective stressors (e.g., Miller, Freedland, & Carney, 2005). Thus, the specific and interactive effects of objective stressors, perceived stress, and depressive symptomatology warrant further investigation.
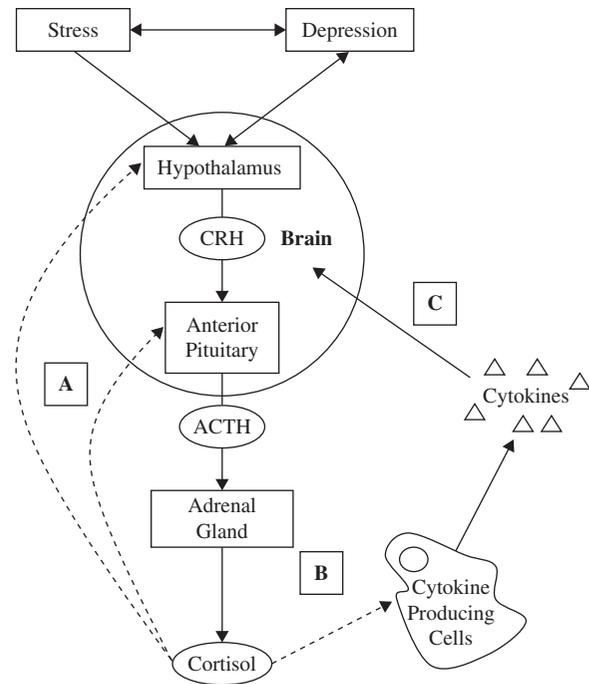
Physiological Mechanisms Linking Stress, Depression, and Inflammation

The experience of life stress is a common precursor of depression and inflammatory responses to stressors may play a causal role in this relationship. Stress-induced activation of the sympathetic-adrenal-medullary (SAM) and HPA axes provokes the release of stress hormones (e.g., epinephrine and norephinephrine) that stimulate the release of inflammatory markers, including cytokines, that affect the CNS. It is well documented that cytokines elicit sickness behaviors (e.g., lethargy and withdrawal) that parallel symptoms of depression (Dantzer et al., 2007).

Cytokines can affect the brain by entering from the periphery or via neural pathways that induce cytokine production within the brain. Although transfer of cytokines from peripheral circulation to the brain is largely prevented by the blood-brain-barrier, cytokines can enter the brain via weaker areas of the blood-brain-barrier as well as through active cytokine transporters (Raison, Capuron, & Miller, 2006). In addition, a key proposed route by which peripheral inflammation can affect the brain is via stimulation of peripheral afferent vagal nerves that innervate organs of the abdominal cavity (Konsman, Parnet, & Dantzer, 2002). Notably, cytokine receptors, including those for IL-1, IL-6, and TNF, are located throughout the brain. In particular, IL-1 has significant effects on the hypothalamus and hippocampus, which are key regulators of sickness behaviors (Bailey, Engler, Hunzeker, & Sheridan, 2003; Konsman et al., 2002).

In addition to direct action via cytokine receptors in the brain, cytokines also affect mood and behavior by altering function of neurotransmitters including dopamine, norepinephrine, and serotonin, which are known to affect depressive symptomatology. In particular, a clear causal pathway linking inflammation to decreased serotonin (5-HT) availability has been described. Specifically, heightened levels of proinflammatory cytokines reduce the availability of tryptophan (TRP), the precursor of 5-HT synthesis (Schiepers, Wichers, & Maes, 2005).

For healthy individuals, mechanisms exist that help to self-limit stress responses. Normally cortisol, a key hormone for the regulation of inflammation and stress responses, is released by the HPA axis during stress responses and then signals back to the HPA axis, eliciting termination of HPA stress responses (Figure 64.3). In addition, cortisol has robust anti-inflammatory effects on cytokine-producing cells. However, extended exposure to elevated levels of glucocorticoids (GC), such as that seen in conditions of repeated or chronic stress, may produce GC insensitivity at the level of both cytokine-producing cells and the HPA axis (Sapolsky & McEwen, 1985; Spencer, Miller, Stein, & McEwen, 1991). GC insensitivity is marked by

Figure 64.3 Physiological pathways linking stress, depression, and inflammation.

Note: Stress-induced activation of the HPA axis results in the release of cortisol which signals back to the hypothalamus and pituitary (A), eliciting termination of HPA stress responses. Cortisol also has powerful anti-inflammatory effects on cytokine-producing cells (B). However, extended exposure to elevated cortisol can produce glucocorticoid insensitivity in the HPA axis and cytokine-producing cells, provoking greater production of proinflammatory cytokines. Cytokines can affect the brain via transfer across the blood-brain-barrier from peripheral circulation as well as via stimulation of afferent vagal nerves. In addition, inflammation can affect mood by reducing the availability of tryptophan, a precursor of serotonin (5-HT) (C). ACTH = Adrenocorticotropic hormone. Solid lines indicate a stimulatory association. CRH = Corticotropin releasing hormone. Dashed lines = An inhibitory relationship.

a diminished ability of the HPA axis and cytokine producing cells to respond to cortisol, resulting in more sustained HPA axis responses and greater production of inflammatory markers. Thus, the development of GC resistance and resulting elevations in inflammatory markers has been proposed as an important pathway by which stress can contribute to depressive symptomatology (Raison & Miller, 2003). Clinical depression is frequently characterized by GC resistance, as evidenced by a reduced capacity to suppress HPA axis secretion of cortisol after administration of dexamethasone, a synthetic glucocorticoid (Modell, Yassouridis, Huber, & Holsboer, 1997).

In humans, the best evidence that inflammation can play a causal role in the development of depression comes from studies in which cytokines are administered therapeutically. In particular, the proinflammatory cytokine interferon-alpha is used with some cancers as well as some infectious illnesses (e.g., hepatitis). This treatment produces significant depressive symptomatology in a high percentage of

individuals (Capuron & Miller, 2004; Dantzer & Kelley, 2007). Interferon treatment can also increase circulating IL-6 and TNF-α, alter in HPA axis function, and dysregulate serotonin metabolism (Capuron & Miller, 2004; Dantzer & Kelley, 2007). Thus, studies of interferon treatment support the proposition that inflammation can play a causal role in the development of depression. For additional coverage of physiological pathways underlying the link between stress and depression, please refer to Chapters 6 and 7, Volume 1; and Chapters 55 and 62, this Volume.

Interventions Targeting Stress, Depression, and Inflammation

Certain interventions may help to break the negative cycle of stress, depression, and inflammation. For one, interventions targeting social support may be helpful. Among female cancer patients, greater social support has predicted lower levels of inflammatory markers in circulating blood and ascitic fluid (Costanzo et al., 2005; Lutgendorf, Anderson, Sorosky, Buller, & Lubaroff, 2000; Lutgendorf et al., 2002). Relatedly, religious participation, a key source of social support for many people, has predicted lower levels of IL-6 among community-based samples (Koenig et al., 1997; Lutgendorf, Russell, Ullrich, Harris, & Wallace, 2004). Interventions aimed at improving the availability and utilization of social support warrant investigation, particularly for individuals experiencing both significant stress and lack of support.

Other interventions targeting stress include yoga, tai chi, and meditation. Participation in both tai chi and yoga is associated with improved mood (Waelde, Thompson, & Gallagher-Thompson, 2004; Woolery, Myers, Sternlieb, & Zeltzer, 2004); however, limited research has attempted to link such activities with changes in inflammatory activity. One study examined effects of mindfulness based stress reduction, which included elements of meditation and gentle yoga among breast cancer patients. Results demonstrated improvements in mood, reductions in perceived stress, and beneficial immunological changes including decreased production of interferon (IFN)—ψ and increased production of IL-4, an anti-inflammatory cytokine, by stimulated T-cells (Carlson, Speca, Patel, & Goodey, 2003). Notably, regular physical activity is associated with reductions in circulating inflammatory markers (e.g., Ford, 2002). Therefore, further investigation of activities such as tai chi and yoga that involve elements of both meditation and physical activity holds promise.

In terms of clinical depression, both antidepressant medication and cognitive-behavioral therapy have been associated with reductions in inflammatory markers (Basterzi et al., 2005; Doering, Cross, Vredevoe, Martinez-Maza, & Cowan, 2007; Sharpe et al., 2001; Tuglu, Kara, Caliyurt,

Vardar, & Abay, 2003). Such antiinflammatory effects may contribute to the efficacy of these treatments. Indeed, the depressive symptoms induced by interferon treatment can largely be prevented or reversed by treatment with antidepressant medications (Hauser et al., 2002; Musselman et al., 2001).

Accumulating research also speaks to the importance of omega-3 (*n*-3) polyunsaturated fatty acids (PUFAs) for both mental health and inflammatory processes. Specifically, low plasma levels of *n*-3 PUFA as well as high omega-6 (*n*-6) to *n*-3 ratios have been associated with the presence and severity of depressive symptoms in several studies (e.g., Frasure-Smith, Lesperance, & Julien, 2004; Hibbeln, 1998; Kiecolt-Glaser et al., 2007; Maes & Smith, 1998). PUFAs inhibit the release of proinflammatory cytokines including IL-6, IL-1β, and TNF-α(Logan, 2003). Consistent with this evidence, higher circulating levels of *n*-3 PUFAs are related to lower levels of circulating proinflammatory cytokines (Ferrucci et al., 2006; Kiecolt-Glaser et al., 2007). Moreover, a number of studies have demonstrated that *n*-3 PUFA supplementation decreases depressive symptoms (for review, see Parker et al., 2006), supporting the argument that interventions targeting inflammation are a promising direction for depression treatment.

STRESS AND WOUND HEALING

Psychological stress and psychosocial factors have also been linked with wound healing (Christian, Graham, Padgett, Glaser, & Kiecolt-Glaser, 2007), a clinically critical outcome. The skin is the body's largest organ and primary immune defense, preventing bacteria, viruses, and other exogenous antigens from entering (Elias, 2005) and limiting the movement of water in and out of the body (Marks, 2004). As such, the skin's ability to heal wounds effectively is essential to good health. The effects of stress on healing have important implications in the context of surgery and naturally occurring wounds, particularly among at-risk and chronically ill populations.

The Wound-Healing Process

When tissue damage occurs in healthy individuals, healing progresses sequentially through three overlapping phases: inflammation, proliferation, and remodeling (see Baum & Arpey, 2005, figure 2; Singer & Clark, 1999). Success in later phases is highly dependent on preceding phases. The inflammatory phase, which typically lasts 5 to 7 days, is marked by vasoconstriction, blood coagulation, platelet activation, and the release of substances that attract cells to clean the area, that is, remove bacteria (Singer et al., 1999;

Van De Kerkhof, Van Bergen, Spruijt, & Kuiper, 1994). The proliferative phase is characterized by recruitment and replication of cells necessary for tissue regeneration and capillary regrowth. The final stage, which may continue for weeks or months, involves contraction and tissue remodeling (see Figure 64.4). The sequence and mechanisms described here apply best to acute wounds: The molecular mechanisms by which stress affects chronic wounds, such as diabetic foot ulcers, are less well understood and are complicated by other factors (Vileikyte, 2007).

A key pathway by which stress affects healing is via inflammatory processes at the site of the wound. Although prolonged or exaggerated inflammation is detrimental to health, inflammatory cytokines play a critical role in the healing cascade and a robust localized inflammatory response is ideal. Inflammatory cytokines help prevent infection, prepare injured tissue for repair, enhance recruitment and activation of additional phagocytic cells, and regulate the ability of cells to remodel damaged tissue (Lowry, 1993). Stress-induced elevations in glucocorticoids can transiently suppress proinflammatory cytokine production in humans (DeRijk et al., 1997). Moreover, mice treated with glucocorticoids showed impairment in the induction of IL-1 and TNF, as well as deficient wound repair (Hübner et al., 1996). Although other mechanisms are implicated in the link between stress and healing, the interactive roles of proinflammatory cytokines and glucocorticoid hormones are the best delineated to date. Further evidence of their role is demonstrated in the studies described in the following subsection.

Effects of Stress on Wound Healing

The first human study to demonstrate the effects of stress on healing examined women experiencing the chronic stress of caregiving for a loved one with dementia. In this study, caregivers took 24% longer to heal a small standardized punch biopsy wound than did well-matched controls (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995). Healing rate was determined using photographs to compare wound size to a standard dot. The same study revealed that circulating peripheral blood leukocytes (PBLs) from caregivers expressed less IL-1β in messenger RNA (mRNA) in response to lipopolysaccharide (LPS) stimulation than did cells from controls (Kiecolt-Glaser et al., 1995). As described earlier, a strong IL-1β response is desirable in the context of healing.
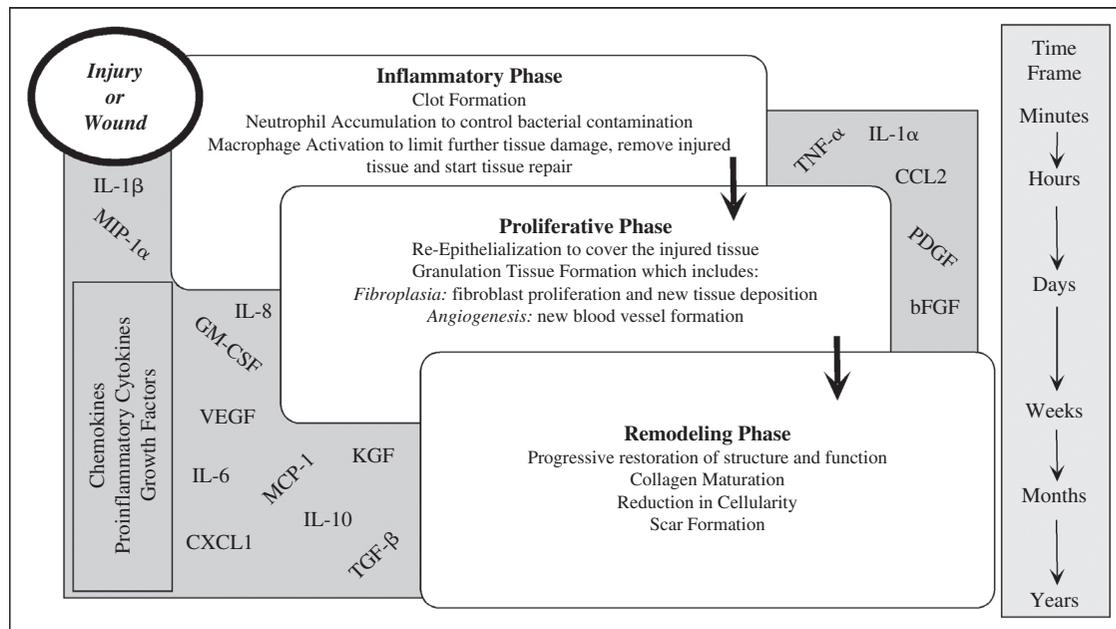
Figure 64.4 Stages of wound healing.

Note: In healthy individuals, healing progresses sequentially through three overlapping phases: (1) inflammatory phase, (2) proliferative phase, and (3) remodeling phase. Stress can affect progression through these stages via multiple immune and neuroendocrine pathways. This chapter focuses on the interactive role of glucocorticoids and cytokines (e.g., IL-8, IL-1α, IL-1β, IL-6, and TNF-α). However, additional cytokines, chemokines, and growth factors are important to healing. These include CXC-chemokine ligand 1 (CXCL1), CC-chemokine ligand 2 (CCL2), granulocyte macrophage colony-stimulating factor (GM-CSF), monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protien-1 alpha (MIP-1α), vascular endothelial growth factor (VEGF), transforming growth factor-β, (TGF-β,), keratinocyte growth factor (KGF), platelet derived growth factor (PDGF), and basic fibroblast growth factor (bFGF). For a broader review of physiological mechanisms relevant to wound healing, see Werner and Grose (2003). From "Stress and Wound Healing," by L. M. Christian, J. E. Graham, D. A. Padgett, R. Glaser, and J. K. Kiecolt-Glaser, 2007, *Neuroimmunomodulation, 13,* p. 338. Reprinted with permission.

Subsequent research demonstrated that milder stress also impairs healing. In a sample of 11 dental students, mucosal punch biopsy wounds placed in the hard palate healed an average of 40% more slowly during an examination period than during a vacation period, which was rated as less stressful by participants (Marucha, Kiecolt-Glaser, & Favagehi, 1998). This effect was remarkably reliable: Every student in the study healed more slowly during exams than during vacation. Moreover, in concordance with studies on caregiving stress, production of IL-1β mRNA by LPS-stimulated peripheral blood leukocytes (PBLs) was reduced in every student during the examination period compared with the vacation period.

Further research has examined cytokine production at the local wound site. In a study of 36 women, blister wounds were created using a suction blister device that produced 8 sterile 8mm blister wounds (Glaser, Kiecolt-Glaser, et al., 1999). A plastic template with 8 wells was placed over the blister wounds and each well was filled with the woman's serum and a salt solution, allowing cells to migrate into the blister chambers. Women reporting greater stress had significantly lower levels of two key cytokines (IL-1α and IL-8) at the wound site (Glaser, Kiecolt-Glaser, et al., 1999). By demonstrating an association between stress and local cytokine production, this study significantly extended previous data linking stress and mechanisms associated with healing.

Dramatically, even a single 30-minute marital conflict discussion in a laboratory setting can slow wound healing: Married couples healed standardized blister wounds more slowly after a conflictive interaction than after a supportive interaction (Kiecolt-Glaser et al., 2005). Decreased production of three key cytokines—IL-6, IL-1β, and TNF-α—was observed at the wound site following conflict compared with a supportive interaction. Furthermore, couples who demonstrated consistently high levels of hostile behavior during both conflictive and supportive interactions healed wounds at 60% of the rate of low hostile couples.

Other research has examined relationships between wound healing and subjective stress. Among healthy males, greater perceived stress predicted slower healing of a punch biopsy wound from 7 to 21 days postwounding (Ebrecht et al., 2004). Healing was also significantly related to cortisol levels: Greater morning increases in cortisol predicted slower healing. Healing in this study was assessed with ultrasound biomicroscopy, a relatively new imaging technique that uses high-resolution ultrasound scanning to measure wound depth as well as circumference. This approach provides an assessment of healing in deep tissue layers and enables measurement of wound circumference that is not impeded by scab formation (Dyson et al., 2003).

Stress also has measurable effects on healing outside a controlled laboratory setting. Depression and anxiety were associated with healing among elderly men and women with chronic leg ulcers: Those reporting greater than average symptoms of depression or anxiety were four times more likely to be categorized as slow healers compared with those reporting less distress (Cole-King & Harding, 2001). Similarly, in a sample of adults undergoing hernia surgery, self-reported worry about surgery predicted slower healing time, even after controlling for age, gender, and type of anesthetic (Broadbent, Petrie, Alley, & Booth, 2003). Moreover, greater preoperative stress predicted lower levels of IL-1 in the wound fluid, while greater worry about surgery was related to lower matrix metalloproteinase-9 (MMP-9) in the wound fluid (Broadbent et al., 2003). MMP-9, which is regulated by cytokines IL-1 and IL-6, facilitates cellular migration within the wound area, and thus aids in tissue remodeling (Pajulo et al., 1999).

Animal models support and extend findings related to causal mechanisms linking stress and healing. Mice exposed to periods of restraint stress for 3 days before and 5 days following wounding healed punch biopsy wounds 27% more slowly than did nonstressed controls (Padgett, Marucha, & Sheridan, 1998). Restraint-stressed mice also had reduced cellularity in the margins of their punch biopsy wounds, particularly early in the healing process and significantly higher levels of serum corticosterone compared with unstressed controls. Notably, when the stressed animals were treated with the glucocorticoid receptor antagonist RU40555, their healing rates were equivalent to nonstressed animals (Padgett et al., 1998). Thus, results from animal models confirm that the suppressive effects of glucocorticoids on inflammatory activity play an important role in stress-induced delays in healing.

Thus, the effects of stress on glucocorticoid functioning and subsequent effects on decreases in localized inflammatory responses to injury represent a primary pathway by which stress impairs wound healing (Figure 64.5). Glucocorticoids have multiple effects that can disrupt the inflammatory stage of healing, particularly early on. These effects include (a) suppression of immune cell differentiation and proliferation, (b) reduced expression of cell adhesion molecules that play an important role in trafficking cells to the site of the wound, (c) decreases in nuclear factor kappa B (NFκ-B) activity, which results in decreased proinflammatory gene expression (for review, see Glaser & Kiecolt-Glaser, 2005; Godbout & Glaser, 2006; Padgett & Glaser, 2003). In addition, disruption of inflammatory processes can prevent the proper cleaning and clearance of bacteria from a wound site, resulting in greater risk for infection, which is also associated with delayed healing.

Dysregulation of the inflammatory stage of healing is important because the stages of healing are overlapping and interdependent. Therefore, delay in the early inflammatory
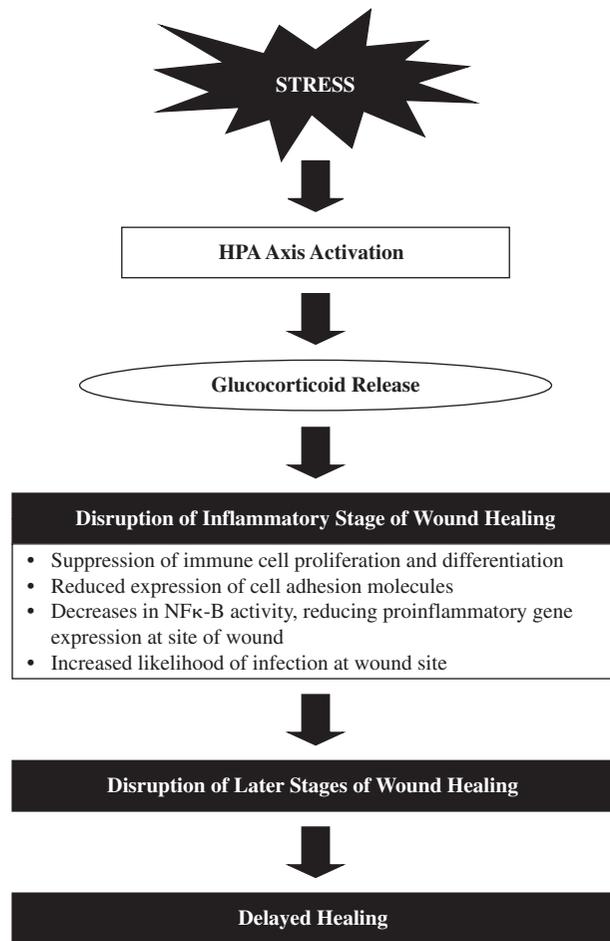
Figure 64.5 Physiological pathways linking stress to wound healing.

Note: Stress delays wound healing by affecting early inflammatory processes via glucocorticoids. Delays in the inflammatory stage of healing causes dysregulation of later stages, resulting in delayed healing.

stage disrupts progression of subsequent stages of healing, ultimately resulting in increased time to healing. This in turn, can have important clinical implications for recovery from surgery and naturally occurring wounds.

Interventions for Enhancing Wound Healing

Exercise and social contact are two interventions that have been used to target stress or the effects of stress with the goal of improving healing. First, recent data demonstrate that regular physical activity can speed healing. Older adults who completed a 4-week exercise intervention healed standard punch biopsy wounds 25% more quickly than did their less active counterparts (Emery, Kiecolt-Glaser, Glaser, Malarkey, & Frid, 2005). These effects were notable because of the low self-reported stress across the sample; effects may be even greater among individuals reporting more distress. In this study, exercise did not result

in changes in resting cortisol levels or perceived stress over time. Further research is needed to examine mechanistic pathways by which exercise may benefit healing.

Animal work suggests that social contact may mitigate effects of stress on healing. Among hamsters subjected to restraint stress, those who were individually housed (isolated) showed significant impairment of cutaneous wound healing, whereas those who were pair-housed did not (Detillion, Craft, Glasper, Prendergast, & DeVries, 2004). The adverse effect on healing observed in isolated hamsters was driven by stress-induced increases in serum cortisol; socially housed hamsters had significantly lower serum cortisol concentrations than their isolated counterparts. The protective effects of social housing in this study appeared to be at least partly mediated by oxytocin, a hormone that is released during social contact and that may facilitate social bonding. The administration of an oxytocin antagonist to socially housed animals delayed healing and treatment of isolated animals with oxytocin attenuated their stress-induced cortisol increases and speeded healing (Detillion et al., 2004). Thus, these data support the notion that cortisol plays a key role in the stress-healing link.

STRESS AND INFECTIOUS AGENTS

Turning to other models used to study effects of stress on immune-relevant outcomes, stress has been linked to impaired response to infectious illness in three related areas: vaccination, experimental exposure to infectious illness, and latent viruses. Each of these models has its own strengths, and each provides clinically relevant information about immune function in a unique manner (see Figure 64.6). These models are useful, in part, because there is unexplained variability in immune responses to each type of challenge. Individuals demonstrate varying degrees of susceptibility to infection on exposure to the same infectious agent. In addition, among those who do become infected, there is a significant range of severity and duration of illness experienced. Stress contributes to such variability in response to infectious agents.

Vaccination

Measuring Immune Responses to Vaccination

Studies of immune responses to vaccination provide clinically relevant information in at least two ways. First, an adequate immune response to vaccination is required for the vaccine to provide protection against the antigen in question. Second, immune responses to vaccination serve as a proxy measure of how well an individual's immune system would respond if he or she were exposed to the actual

Vaccination	
Outcomes	• Cellular and humoral immune responses
Strengths	• Highly ethical model for studying immune response in humans
Clinical relevance	• An adequate immune response is required for a vaccine to confer immunity • Responses to vaccination provide a proxy for responses to naturally occurring antigens
Infectious Illness	
Outcomes	• Infection and clinical symptoms, cellular and humoral immune responses
Strengths	• Laboratory exposure provides excellent control of possible confounding variables
Clinical relevance	• Evidence of effects of stress on both susceptibility to and severity of infectious illness
Latent Viruses	
Outcomes	• Antibody titers, cellular immune responses
Strengths	• Study of common latent viruses does not require exposure to an infectious agent
Clinical relevance	• Poor control of latent viruses indicates impaired cellular immune function • Latent virus reactivation contributes to morbidity and mortality among immunocompromised

Figure 64.6   Models for studying immune responses to infectious agents.

infectious agent (Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996). Consistent with this notion, poorer immune responses to vaccination are predictive of greater likelihood of experiencing clinical illness (Plotkin, 2001). A notable strength of this methodology is that vaccination is beneficial to people, with some vaccines being highly recommended for at-risk populations (e.g., influenza vaccination among the elderly). Therefore, vaccination provides a highly ethical methodology for studying clinically relevant immune outcomes in humans.

As described, the immune system can be broadly divided into two arms: the innate immune system (the rapid nonspecific defense against an antigen), and the adaptive immune system, which mounts a slower, antigen-specific response. Studies of vaccine response examine the ability of the adaptive immunity to form and maintain immunological memory after exposure to an antigen.

Effective responses to vaccination involve activation of both the humoral and cellular arms of the adaptive immune system. The humoral immune response is governed by B-cells and marked by antibody production. Antigen-specific antibodies, produced by B-lymphocytes, can opsonize the antigen (tag it for destruction by other immune cells), and neutralize it by preventing it from further interacting with the host's cells. Therefore, it is beneficial for an individual to demonstrate a robust antibody response to vaccination that is maintained well over time. Parameters for a sufficient antibody response, referred to as seroconversion, depend on the vaccine in question. A fourfold increase in antibody titers is considered to be the standard for a sufficient response to influenza vaccine.

The cellular immune response is governed by T-cells. Cellular immune responses to vaccination are commonly

quantified in terms of production of certain cytokines (e.g., IL-2, IFN-ψ), that promote cell-mediated immune responses. In the context of vaccination, higher IL-2 and IFN-ψ cytokine production to in vitro virus exposure is desirable because these cytokines activate virus-specific cytotoxic T-cells as well as natural killer cells.

Effects of Psychological Factors on Vaccine Response

As described above, the chronic stress of caring for a relative with dementia promotes systemic inflammation and slows wound healing. In addition, exposure to this chronic stressor impairs immune responses to vaccination. Three studies to date have demonstrated that caregivers are less likely to seroconvert following influenza vaccination compared with well-matched control subjects (Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998; Kiecolt-Glaser et al., 1996; Vedhara et al., 1999). For example, in a study of 32 caregivers and 32 demographically matched controls, caregivers were significantly less likely to achieve a fourfold increase in influenza-specific antibody levels 1 month after vaccination; this effect was more pronounced among older subjects (Kiecolt-Glaser et al., 1996). In addition, caregivers' peripheral blood lymphocytes produced less IL-2 in response to in vitro influenza stimulation, evidencing a poorer cellular response to vaccination.

In a similar study, caregivers showed impaired maintenance of the response to pneumoccocal pneumonia vaccination. Although caregiver and control groups demonstrated equivalent responses to the vaccine initially (at 2 weeks and 1 month), current caregivers had lower levels of antibody at 3 months and 6 months postvaccination compared

with both former caregivers and controls (Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000). Notably, the immune response to influenza is largely mediated by T-lymphocytes while the immune response to pneummococcal pneumonia is not dependent on T-lymphocytes. Therefore, studies of caregivers indicate that chronic stress affects responses to both classes of vaccine.

Greater self-reported stress also predicts impaired vaccine responses among younger populations. For example, in a study of 31 college students who received influenza vaccination, those who reported less perceived stress and fewer stressful life events in the period following vaccination demonstrated significantly better maintenance of antibody levels compared with students reporting greater stress (Burns, Carroll, Drayson, Whitham, & Ring, 2003). Similarly, among 260 healthy college students, a greater number of negative life events in the previous year predicted lower hepatitis B antibody levels only among those who had been vaccinated more than 1 year prior; number of negative life events was not associated with antibody level among those who were vaccinated within the past year (Burns, Carroll, Ring, Harrison, & Drayson, 2002). These data indicate that stress affected long-term maintenance of immunological memory for the antigen.

Additional research has examined the effects of stress among college students on both T-cell dependent (influenza) and T-cell independent (meningococcal C) vaccinations. Those who reported a greater number of stressful life events in the year prior to vaccination had lower antibody responses to one strain of the influenza vaccine at both 5 weeks and 5 months. Moreover, although the final antibody response levels were similar at 5 months, students who reported greater stress mounted a slower antibody response to the meningococcal C vaccination (Phillips, Burns, Carroll, Ring, & Drayson, 2005).

It is important to consider perceived stress in the context of objectively stressful experiences. A sample of 48 medical students underwent a series of 3 hepatitus B inoculations scheduled to coincide with three major examination periods. Those who seroconverted after the first vaccination reported significantly less stress and anxiety across the three exam periods. Moreover, following the third exam period, students who reported lower anxiety and stress across exam periods demonstrated higher antibody responses to the vaccine and a stronger T-cell response to a hepatitis B challenge in vitro (Glaser et al., 1992).

A study addressed the question of which time points are most critical in terms of stress affecting immune responses to vaccination. A sample of 83 healthy young adults received influenza vaccination, and their subjective stress levels were measured for 2 days prior to vaccination, the day of vaccination, and the 10 days following vaccination. Although stress prior to or on the day of vaccination did not predict

antibody responses, greater stress levels in the 10 days following vaccination were associated with poorer antibody response (Miller et al., 2004).

The studies reviewed thus far focus on chronic stress, perceived stress, and brief naturalistic stressors (e.g., exam stress). Some evidence suggests that acute stress (e.g., 2-hour restraint stress in mice; mental arithmetic or exercise stress in people) can enhance immune responses to vaccination (Edwards et al., 2006; Silberman, Wald, & Genaro, 2003). Additional research is needed to describe in better detail the processes involved in brief acute stress relative to longer lasting stress experiences.

As reviewed, evidence for effects of stress on vaccine response is seen across a variety of vaccines and types of stressors. Variability between specific outcomes across studies may be explained in part by the different vaccines and measurement time frames used. Moreover, prior vaccination or naturalistic exposure to an antigen will affect responses to vaccination. This can cause a range restriction problem that impedes the ability to detect effects of psychosocial factors (Vedhara et al., 1999). These methodological factors should be carefully considered in research using vaccination.

Studies to date demonstrate that stressors ranging from relatively brief (e.g., academic exams) to chronic (e.g., caregiving) can significantly affect the rapidity and magnitude of antibody response as well as long-term maintenance of immunological memory conferred by vaccination. Such stress is also predictive of decreased cellular immune responses to vaccination. Although beyond the scope of this chapter, animal models demonstrate multiple effects of glucocorticoid hormones on cell-trafficking, and production of proinflammatory cytokines and chemokines that contribute to these effects (for review, see Glaser & Kiecolt-Glaser, 2005; Godbout & Glaser, 2006; Padgett & Glaser, 2003). Notably, effects of stress on responses to vaccination are seen in both older and younger adults, although effects tend to be stronger among older adults because of age-related decreases in immune responses to vaccination. In addition, deficits in immune response to vaccination have particular importance for older adults who are more vulnerable than younger adults to serious complications and death in the face of illness such as influenza (Yoshikawa, 1983).

Infectious Illness

Measuring Infectious Illness

Consistent with findings that stress affects immune responses to vaccination, stress also affects susceptibility, severity, and duration of infectious illnesses including influenza and rhinovirus (the common cold). In studies of infectious illness, the rates of both respiratory infection and clinical illness are of interest. Respiratory infection is defined by the

presence of the virus in circulation or significant increases in virus-specific antibody titers following experimental exposure to the infectious agent. In contrast, clinical illness is typically defined by physician-judged severity of illness symptoms. Assessing both respiratory infection and clinical illness is important because among those exposed to a virus, only a portion will become infected. In turn, among those infected, only a portion will develop clinical symptoms.

Effects of Psychosocial Factors on Infectious Illness

Naturalistic studies have reported associations between stress and frequency of infectious illness. In a sample of 117 adults, the experience of stressful life events in the previous 12 months and during a 15-week observation period was assessed. During the observation period, 29 participants experienced at least one clinically verified upper respiratory illness. Risk of illness was greater among those who reported a greater number of stressful life events (Turner-Cobb & Steptoe, 1996). Although naturalistic studies provide good evidence of effects of stress on susceptibility to infectious illness, such methodology allows for limited control of important confounding variables including rates of exposure to infectious agents.

The strongest evidence of effects of stress on infectious illness comes from studies in which participants have been purposefully exposed to infectious agents that can cause upper respiratory infections (URIs) and then tracked over time in a well-controlled environment. In a key study using experimental exposure methodology, Cohen and colleagues demonstrated that self-reported stress predicted susceptibility to respiratory viruses in a dose-response manner. Specifically, 394 healthy subjects were exposed to 1 of 5 respiratory viruses, while 26 control subjects were given saline nasal drops. Participants were then quarantined and their respiratory symptoms as well as their virus-specific antibody titer levels were assessed (Cohen, Tyrrell, & Smith, 1991). Individuals reporting greater stress (as determined by 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. This effect was found across each of the 5 types of virus, and the effect remained after controlling for potential confounding factors including age, sex, education, season, and personality factors.

Later research from the same laboratory focused on better delineating the importance of different types of stressful life events. In this study, 276 participants completed in-depth interviews assessing occurrence, severity, and emotional significance of life stressors in the past year (Cohen et al., 1998). Participants were exposed to 1 of 2 rhinoviruses and kept in quarantine for the following 5 days during which their experience of infectious illness was assessed. Results indicated that acute stressors did not predict increased risk of infection or clinical colds. However, the experience of chronic stress lasting 1 month or longer was associated with significantly increased risk of developing a cold. These effects were not accounted for by differences in social network characteristics, personality, or health behaviors.

The same study explored potential endocrine mediators linking stress and virus susceptibility. In this sample, elevations in epinephrine and norepinephrine were associated with increased risk of developing colds. However, unexpectedly, the experience of chronic stress was not associated with higher levels of these stress hormones. This could be due in part to the stress and novelty of the experimental situation, which may have caused acute stress in all participants and masked effects of chronic stressors on these endocrine markers (Cohen et al., 1998).

Other research indicates that variability in physiological responses to stress affects stress-induced susceptibility to infection. In a sample of 115 healthy individuals, those who showed larger cortisol responses to laboratory stressors experienced greater risk of developing clinically verified colds under conditions of higher stress (Cohen et al., 2002). Stress level was unrelated to URI risk among those showing smaller cortisol responses to acute stress. Thus, individuals who experience greater physiological reactivity to stress may be more vulnerable to infectious illness in conditions of stress.

Subsequent research, also from the same laboratory, explored the role of inflammation in explaining the link between stress and symptom severity. In a study of 55 subjects who were exposed to an influenza virus, those reporting higher stress experienced greater symptoms of illness and greater mucus weight, as well as greater inflammatory responses to the infection, as indicated by higher IL-6 levels in nasal secretions (Cohen, Doyle, & Skoner, 1999). These data suggest that stress may contribute to an exaggerated local inflammatory response to infection, contributing to illness severity. However, in the context of infectious illness, effects of stress may differ for the production of other cytokines and at other sites (e.g., lungs). In mice exposed to influenza virus, restraint stress reduced the production of the proinflammatory cytokine IL-1α, but did not affect the production of IL-6 in the lungs (Konstantinos & Sheridan, 2001). In another animal study, restraint stress resulted in reduced production of IL-6 from splenocytes, but enhanced production of IL-6 from regional lymph nodes (Dobbs, Feng, Beck, & Sheridan, 1996). Thus, the effects of stress on inflammatory mediators during viral infection are complex and may best be understood as dysregulated,

rather than enhanced or suppressed. Moreover, the clinical relevance of noted alterations may differ for susceptibility versus severity of illness.

In sum, several well-controlled laboratory studies have demonstrated a relationship between stress and susceptibility, severity, and duration of infectious illness (see Figure 64.7). Naturalistic studies report parallel findings. Human models implicate glucocorticoids and local cytokine production in the link between stress and illness susceptibility and severity. Animal models support and extend these findings, providing evidence for effects of glucocorticoids, dysregulated cytokine production, alterations in cell trafficking, and dysregulated antibody responses (Bonneau, Padgett, & Sheridan, 2001; Konstantinos & Sheridan, 2001). A continued focus on physiological pathways will help to better delineate the role of specific immune alterations in affecting the susceptibility, duration, and severity of infectious illness.

Latent Viruses

Measuring Immune Control of Latent Viruses

Normally, viruses are eliminated from the host when infection is resolved. However, some viruses are maintained in the body in a latent state in asymptomatic individuals after primary infection. Such viruses include those from the herpesviruses family, such as herpes simplex virus (HSV) I and II, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). After primary infection, latent viruses are maintained within certain cells (e.g.,

B-lymphocytes for EBV). Although the immune system is typically quite effective in controlling latent viruses, reactivation of the opportunistic virus can occur when cellular immunity wanes. During reactivation, the virus produces greater quantities of viral proteins. This elicits cellular and humoral immune responses and results in the production of virus-specific antibody. Thus, higher levels of antigen-specific antibody can be used as an indicator of impaired cell-mediated control of a latent virus.

One strength of examining immune control of latent viruses is that some forms are ubiquitous and can therefore be studied in a variety of populations. More than 95% of the adult population is infected with EBV (Wolf & Morag, 1998). Therefore, the study of such latent viruses does not require experimental exposure to an antigen, a clear benefit for human studies.

Ineffective control of latent viruses can have important clinical implications among immunosuppressed individuals. Reactivation of latent viruses predicts increased mortality and morbidity among organ transplant recipients (Gray et al., 1995) and individuals infected with HIV (Cruess et al., 2000). Although reactivation of EBV typically causes no symptoms in healthy individuals (Hess, 2004), reactivation of HSV I or II can cause cold sores (Bystricka & Russ, 2005) and VZV reactivation can cause shingles (Quinlivan & Breuer, 2006). Even in the absence of clinical disease, reactivation of a latent virus provides a sensitive marker of impairment in cell-mediated immunity. Thus, studies of viral latency provide clinically relevant information even among asymptomatic individuals.
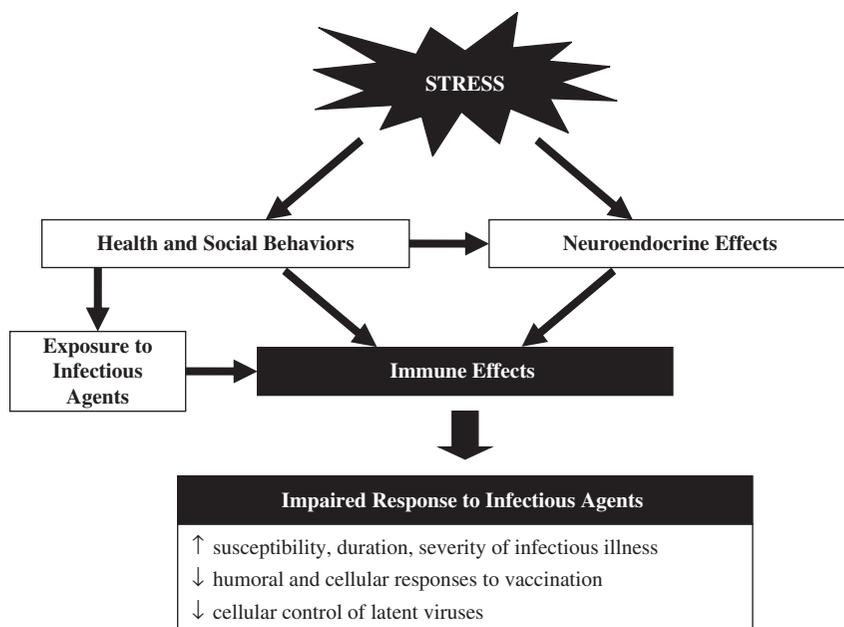
Figure 64.7 Behavioral and neuroendocrine pathways linking stress and response to infectious agents.

Note: By affecting health behaviors, social behaviors, and neuroendocrine function, stress can impair both humoral and cellular immune responses to infectious agents. This has important clinical implications for immune responses to exposure to infectious illnesses, vaccination, and control of latent viruses. (Although social support can buffer negative effects of stress, contact with a diverse social network can result in greater exposure to infectious agents.)

Effects of Psychosocial Factors on Immune Control of Latent Viruses

Given the effects of chronic stress on other aspects of immune function, it is not surprising that chronic stress impairs immune control of latent viruses. Individuals who are caregivers for a family member with dementia exhibited higher EBV (Kiecolt-Glaser et al., 1991) and HSV-1 (Glaser & Kiecolt-Glaser, 1997) antibody levels compared with well-matched controls. In addition, individuals experiencing the enduring stress of living near the Three Mile Island damaged nuclear plant showed higher HSV-1 antibody levels, compared with matched community controls living 80 miles away from the nuclear plant (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989).

Stress from disrupted significant relationships also affects immune function (Graham, Christian, & Kiecolt-Glaser, 2006a), including immune control of latent viruses. Women who had been divorced or separated for 1 year or less showed higher levels of EBV antibody compared with demographically matched women who were currently married (Kiecolt-Glaser et al., 1987). Similarly, men who were unsatisfied in their marriage had higher levels of EBV antibody than their happily married counterparts (Kiecolt-Glaser et al., 1988).

More transient stressors also affect viral latency. In prospective studies of examination stress, medical students exhibited higher EBV, HSV-1, and CMV antibody titers on the day of an academic examination, compared with several weeks before or after the exam (Glaser, Friedman, et al., 1999; Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985; Sarid, Anson, Yaari, & Margalith, 2001). Other research has shown that the intense stress of space flight (Mehta, Stowe, Feiveson, Tyring, & Pierson, 2000, 2004; Payne, 1999; Pierson, Stowe, Phillips, Lugg, & Mehta, 2005) and Antarctic expeditions (Mehta, Pierson, Cooley, Dubow, & Lugg, 2000) resulted in higher EBV- and CMV-specific antibody titers and decreased EBV-specific T-cells responses. This is not surprising, given that effects of stress on viral latency are seen in response to much less significant stressors (e.g., examinations).

In addition to effects of objective stressors, other psychological factors have also been associated with poorer control of latent virus. Higher levels of EBV-specific antibodies have been found in students who reported a greater tendency to repress their emotions (Esterling, Antoni, Kumar, & Schneiderman, 1990), higher levels of anxiety (Esterling, Antoni, Kumar, & Schneiderman, 1993), and greater loneliness (Glaser et al., 1985). Similarly, patients 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; Irwin et al., 1998; Robertson et al., 1993) Conversely, older women reporting higher vigor during housing relocation had lower EBV-antibody titers compared with women who reported lower levels of vigor (Lutgendorf et al., 2001). Thus, in addition to objective stressors, certain psychological characteristics (e.g., mood, ways of coping) may be associated with impaired control of latent viruses.

Other research has addressed physiological mechanisms by which stress may impair control of latent viruses. In studies of examination stress, students exhibited poorer cytotoxic and proliferative T-cells responses to in vitro EBV exposure on examination days compared with non-examination days (Glaser et al., 1987, 1993). In addition, exam stress predicted suppression of leukocyte migration inhibition factor (MIF), a condition associated with HSV-2 lesions (Sheridan, Donnenberg, Aurelian, & Elpern, 1982). Glucocorticoids may also play a role in stress-induced reactivation of latent viruses; indeed, glucocorticoids can induce latent EBV and CMV replication in vitro (Tanaka et al., 1984). However, some human studies have failed to find an association between basal cortisol levels and control of latent viruses (Cruess et al., 2000; Glaser, Pearl, Kiecolt-Glaser, & Malarkey, 1994). Cacioppo et al. (2002) observed that increased tonic plasma concentration of synthetic glucocorticoid hormone did not lead to enhanced in vitro EBV replication. However, when the synthetic glucocorticoid hormone was administered in a pulsative manner with varying concentration, mimicking a dysregulation of its diurnal variation, increased EBV replication occurred. Thus, assessments of patterns of cortisol release may be key to understanding the role of glucocorticoids in stress-induced virus reactivation.

Interventions to Improve Response to Infectious Agents

A variety of factors have been demonstrated to reduce stress and benefit immune response to infectious agents. As emphasized throughout this chapter, social support can serve as an important stress buffer. College students who reported greater social support showed stronger antibody responses to influenza vaccination (Phillips et al., 2005) as well as better cellular and humoral immune responses to hepatitis B vaccination (Glaser et al., 1992). Similarly, when exposed to infectious agents in a controlled laboratory environment, participants reporting more social ties were less likely to develop colds than those reporting fewer social ties (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997). Although social support may buffer the effects of stress, having a diverse social network may also result in greater exposure to a broader diversity of viruses. In fact,

in a naturalistic study, greater social network diversity was associated with fewer URIs only under conditions of low stress (Hamrick, Cohen, & Rodriguez, 2002).

A key beneficial component of social support may be that it provides an outlet for emotional disclosure. Indeed, interventions designed to encourage disclosure benefit immune function. In a sample of 40 students, those who completed a writing task involving emotional disclosure prior to receiving hepatitis B vaccination had higher antibody titers at 6 months postvaccination than did control participants (Petrie, Booth, Pennebaker, Davison, & Thomas, 1995). Similarly, college students who were randomly assigned to write or talk about a traumatic event had lower EBV antibody titers at the end of the 4-week intervention while students in a control condition showed no such reduction (Esterling, Antoni, Fletcher, Margulies, & Schneiderman, 1994).

Other studies have examined stress management groups that involved elements of social support and emotional disclosure, as well as a focus on coping or problem solving. In a study of caregivers, those who participated in a stress management group for an hour per week for 8 weeks and subsequently received influenza vaccination were more likely to achieve a fourfold increase in antibody titer than caregivers who did not receive the intervention (Vedhara et al., 2003). A number of studies have examined effects of cognitive-behavioral stress management interventions among HIV-infected and at-risk gay men. Such interventions have resulted in decreases in HSV-2 and EBV antibody titers, indicating improved control of latent viruses (Carrico et al., 2005; Esterling et al., 1992; Lutgendorf et al., 1997).

Stress reduction through relaxation and meditation has also been examined. In a study of 45 older adults, those randomized to relaxation training (3 practices/week for 1 month) exhibited decreased HSV-1 antibody titers and less distress at the end of the intervention, whereas no such changes were seen among control participants (Kiecolt-Glaser et al., 1985). Reductions seen in HSV-1 were maintained at 1-month follow-up. A more recent study demonstrated that meditation is a promising intervention strategy. In a study of 48 healthy adults, those who completed an 8-week meditation intervention prior to receiving influenza vaccination exhibited better antibody responses to vaccination compared with a waiting-list control group. The meditation group also demonstrated decreased trait anxiety and increased left-sided brain activation, presumably reflecting more positive affect (Davidson et al., 2003).

In addition, a recent study examined effects of tai chi, which involves physical activity as well as meditation (Irwin, Olmstead, & Oxman, 2007). A group of 112 older adults completed either a 16-week tai chi intervention or a health education group. At the end of the intervention, participants in both groups received a varicella-zoster virus (VZV) vaccine. VZV antibody levels were measured at the conclusion of the intervention, and following vaccination. Remarkably, tai chi alone resulted in increases in VZV-specific immunity equivalent to that conferred by vaccination. Moreover, tai chi in combination with vaccination had an additive effect. Thus, participants in the tai chi intervention group exhibited greater VZV-specific cell-mediated immunity than the health education group both at the end of the 16-week intervention and 9 weeks after the vaccination. Participants in the tai chi intervention group also showed significant improvements in mental health as measured by the SF-36, a quality-of-life index.

SUMMARY

Stressors ranging in magnitude and duration affect clinically meaningful health outcomes including inflammation, wound healing, and responses to viruses. Effects of stress on neuroendocrine parameters via the SAM and HPA axes play a primary mechanistic role in the link between stress and immune variables. In addition, mediators that are beyond the scope of this chapter are also implicated in this complex system (e.g., opioids, growth hormones, neuropeptides). Future studies should aim to more clearly delineate the multiple and complex neuroendocrine pathways linking stress to immune outcomes.

We have focused on physiological mediators in the link between psychological factors and immune outcomes. However, behavior change resulting from stress also plays an important role. The appropriate measurement and control of health behaviors will continue to be important for studies seeking to elucidate physiological pathways linking psychological factors with neuroendocrine and immune function. This is especially true for research with patients experiencing chronic illness as they may show considerable variability in terms of health behaviors including medication adherence, sleep, and diet.

Research to date indicates that age and stress interact to produce more significant immunological and neuroendocrine changes among older adults. An important area of future research is the examination of how early developmental experiences may set the stage for vulnerability in later life; psychosocial stressors during fetal development and early life can have lasting effects on physiology (Graham, Christian, & Kiecolt-Glaser, 2006b). A continued emphasis on understanding the interactive effects of stress and age throughout the life span will contribute to our understanding of the clinical significance of stress-related immune dysregulation.

There have been successful attempts to intervene in stress processes to benefit immune-related health outcomes. Such interventions include stress management, meditation, yoga, tai chi, exercise, dietary changes, psychotherapy, and antidepressant medications. In addition, social support can provide an important buffer from the effects of stress on health. In future research, an increased emphasis on the identification of physiological mechanisms underlying successful interventions would be of great value.

Over the past 25 years, research examining effects of stress on immune outcomes has grown dramatically. A continued emphasis on appropriately controlling for behavioral variables, delineating physiological mechanisms, and demonstrating the clinical significance of noted physiological alterations will contribute to future advances.

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