The field of psychoneuroimmunology (PNI) addresses how psychological factors influence the immune system and physical health through neural and endocrinological pathways. These relationships are especially relevant to immunologically mediated health problems, including infectious disease, cancer, autoimmunity, allergy, and wound healing. In this chapter, we briefly introduce two major physiological systems that modulate immune function and then provide evidence for stress-immune relationships. Next, we explore the psychosocial factors that may be important in moderating and mediating these relationships, including negative affect, social support, and interpersonal relationships. Finally, we review intervention strategies that may be beneficial in reducing the negative effects of stress on the immune system. For more detailed explanations of immunological terms or processes, we recommend the text by Rabin (1999).

**STRESS-IMMUNE PATHWAYS**

**HPA Axis**

Activation of the hypothalamic-pituitary-adrenal (HPA) axis by stress results in a predictable cascade of events (see Figure 4.1). Neurons in the hypothalamus release corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH) into the general circulation. The adrenal cortex then responds to ACTH by releasing glucocorticoids, predominantly cortisol in humans.

Some of cortisol’s effects are anti-inflammatory and immunosuppressive. These immunological effects may be adaptive, as they can limit a potentially overactive immune response that could result in inflammatory or autoimmune disease (Munck & Guyre, 1991; Munck, Guyre, & Holbrook, 1984; Sternberg, 1997). Although glucocorticoids exert anti-inflammatory and immunosuppressive effects, they have a more complex role in immune modulation than originally thought. For example, glucocorticoids suppress cytokines that promote a cell-mediated TH-1 type immune response (e.g., interleukin-2 [IL-2]), but they enhance the production of cytokines that promote a humoral TH-2 type immune response (e.g., IL-4; Daynes & Araneo, 1989). Thus, there may be a shift in the type of immune defense toward an antibody-mediated response. This shift may or may not be adaptive depending on the types of pathogens that are present. Additionally, glucocorticoids induce a redistribution of immune cells from the blood to other organs or tissues (McEwen et al., 1997). Thus, a drop in peripheral blood lymphocyte counts may mistakenly be interpreted as immunosuppression when the cells may simply be migrating to other organs or tissues.
Sympathetic Nervous System (SNS)

As with the HPA axis, the hypothalamus is centrally involved in the regulation of autonomic nervous system activity. Neurons in the hypothalamic area project to autonomic centers in the lower brainstem and spinal cord, including preganglionic sympathetic neurons (Luiten, ter Horst, Karst, & Steffens, 1985). During a classical “fight or flight” response, sympathetic nerve terminals release norepinephrine into various effector organs including the adrenal medulla, which releases the catecholamines, epinephrine and norepinephrine, into the bloodstream; hence the term sympathetic renomedullary (SAM) axis (see Figure 4.1).

Additionally, sympathetic nerve terminals innervate primary and secondary lymphoid tissue and appose lymphocytes and macrophages in synaptic-like contacts (Felten, Ackerman, Wiegand, & Felten, 1987; Felten et al., 1985; Felten & Olschowka, 1987; Madden, Rajan, Bellinger, Felten, & Felten, 1997). Consequently, catecholamines released from either the adrenal medulla or local sympathetic nerves may influence immune function. Indeed, lymphocytes possess adrenergic receptors that induce a change in the pattern of cytokine production following stimulation. For example, adrenergic agonists decrease TH-1 cytokine production (e.g., IL-2 and IFN-γ), but have no effect on TH-2 cytokine production (e.g., IL-4; Ramer-Quinn, Baker, & Sanders, 1997; Sanders et al., 1997). In humans, catecholamine infusion increases the number of peripheral blood lymphocytes, likely due to actions at the β₂ adrenergic receptor (Schedlowski et al., 1996). Natural killer (NK) cells, thought to be important in the surveillance and elimination of tumor and virus-infected cells, appear to be especially sensitive to catecholamines, increasing in number (Crary et al., 1983) and cytotoxic ability (Nomoto, Karasawa, & Uehara, 1994).

Although the HPA axis and SNS are major pathways by which stress can influence immune function, other systems, such as the opioid system, are also involved (Rabin, 1999). Furthermore, brain-immune communication is bidirectional. A growing body of literature acknowledges that the immune system can modulate brain activity and subsequent behavior via the production of cytokines (Dantzer et al., 1998). The immune system acts as a diffuse sensory organ by providing information about antigenic challenges to the brain, which, in turn, regulates behaviors appropriate to deal with these challenges (Maier & Watkins, 1998).

ACUTE VERSUS CHRONIC STRESS

As stress-induced modulations of brain-immune relationships were discovered, multiple types of stressors that varied in duration, intensity, and controllability were studied. In comparing the effects of acute and chronic stress on immune function, different patterns have emerged depending on the model of stress being studied. Using an animal model of stress, Dhabhar and McEwen (1997) operationally defined acute stress as restraint for two hours, and chronic stress as daily restraint for three to five weeks. Exposure of humans to...
laboratory stressors generally falls within this definition of acute stress, while the chronic stress of long-term events such as caregiving may last for years (Heston, Mastri, Anderson, & White, 1981). The stress of major academic examinations is often preceded by a period of anxiety that varies (Bolger, 1990), and therefore, may fall somewhere along the continuum of acute and chronic stress (i.e., subacute stress). No definitive criterion has been established for classifying stressors as acute, subacute, or chronic, but the general categories of acute and chronic will be used to illustrate the complexity of the different patterns of immunological changes that occur in various models of stress.

Acute Stress

**Laboratory Stress**

Exposure to laboratory stressors, such as mental arithmetic and public speaking tasks that generally lasted no longer than 20 minutes, were associated with lower CD4+/CD8+ (T helper/T cytotoxic-suppressor) cell ratios, poorer blastogenic responses, and increased catecholamine release (Bachen et al., 1995; Bachen et al., 1992; Burleson et al., 1998; Cacioppo et al., 1995; Herbert et al., 1994). These same studies also revealed that peripheral NK cell number and cytotoxicity (NKCC) were consistently increased. Furthermore, these stress-induced immune changes were blocked by an adrenergic receptor blocker (Bachen et al., 1995), suggesting that these short-term immune changes were largely mediated by sympathetically activated catecholamine release.

Studies using laboratory stressors have also revealed important individual differences in physiological responses to stress. For example, subjects who showed the greatest change in sympathetic activity to laboratory mental stress also had the greatest change in HPA activity and immune function, despite reporting similar levels of stress (Cacioppo et al., 1995; Herbert et al., 1994; Matthews et al., 1995). This suggests additional psychological or genetic factors may be responsible for the observed differences in physiological reactivity to laboratory stressors, and possibly other types of stressors. These differences may be explained, in part, by psychosocial factors such as negative affect, social support, and interpersonal relationships.

**Academic Examination Stress**

Using academic examinations as a model of “subacute” stress, depression and loneliness in first-year medical students increased during final exams compared to the less stressful baseline period (Kiecolt-Glaser et al., 1984). In contrast to studies that used laboratory stressors, NKCC was decreased, and students who reported the highest levels of loneliness had the lowest NKCC (Kiecolt-Glaser et al., 1984). Compared to the less stressful baseline period, examination stress also impaired blastogenic responses to the mitogens PHA and concanavalin A (Con A; Glaser, Kiecolt-Glaser, Stout, et al., 1985). An inhibition of the memory immune (blastogenic) response to Epstein-Barr Virus (EBV) polypeptides was also observed (Glaser et al., 1993). Production of interferon-gamma (IFN-γ), an important antitumor and antiviral cytokine (Bloom, 1980), was decreased in leukocytes obtained at the time of exams (Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986). Additional studies confirmed examination stress-induced changes in leukocyte numbers (Maes et al., 1999), serum immunoglobulin levels (Maes et al., 1997), and cytokine production (Maes et al., 1998).

Comparison of the delayed type hypersensitivity (DTH) response to acute stress in animals and humans adds complexity to the domain of acute stress. For example, stress associated with an academic examination suppressed DTH responses in subjects who reported higher levels of stress (Vedhara & Nott, 1996), while acute restraint stress in rodents during the sensitization or challenge phase enhanced DTH responses (Dhabhar & McEwen, 1997; Dhabhar, Satoskar, Bluethmann, David, & McEwen, 2000). In another study, socially inhibited individuals showed heightened DTH responses compared to controls following five weekly sessions of high-intensity social engagement (Cole, Kemeny, Weitzman, Schoen, & Anton, 1999). Further research will be required to understand these complex interactions.

The clinical importance of the immunological changes associated with examination stress is underscored by several findings. First, students who reported greater distress during exams took longer to seroconvert after inoculation with a hepatitis B vaccine (Glaser, Kiecolt-Glaser, Bonneau, Malarkey, Kennedy, et al., 1992). They also had lower antibody titers to the vaccine six months postinoculation and a less vigorous virus-specific T cell response. Furthermore, examination stress was associated with reactivation of two latent herpesviruses, EBV and herpes simplex virus type-1 (HSV-1; Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985; Glaser, Pearl, Kiecolt-Glaser, & Malarkey, 1994). Finally, examination stress prolonged the time to heal a standardized oral wound compared to a low stress period (three days or 40% longer to heal); in fact, none of the students healed as fast during exams as they did during vacation (Marucha, Kiecolt-Glaser, & Fava-gehi, 1998). This delay in wound healing was accompanied by a reduction in the production of the proinflammatory cytokine IL-1β, which, in addition to IL-1α, is important in the early stages of wound healing (Barbul, 1990; Lowry, 1993).
Importantly, glucocorticoids modulate processes involved in wound healing. For example, exogenously administered glucocorticoids suppressed the production of several proinflammatory cytokines, delaying wound healing (Hubner et al., 1996). Furthermore, restraint stress in mice increased corticosterone levels and prolonged wound healing, which was normalized when a glucocorticoid receptor antagonist was administered (Padgett, Marucha, & Sheridan, 1998). In a related human study, perceived stress was associated with increased salivary cortisol production and decreased mRNA levels of the cytokine IL-1α in peripheral blood leukocytes (Glaser, Kiecolt-Glaser, et al., 1999). Thus, the HPA axis appears to be an important factor in the stress-induced delay of wound healing, likely via regulation of cytokine production.

**Chronic Stress**

To explore the question of whether stress-induced immunological changes adapt over time and perhaps eventually return to prestress values, we studied a sample of chronically stressed caregivers of family members with progressive dementia disorders, primarily Alzheimer’s disease (AD). Following disease onset, modal survival time for patients with AD is about eight years (Heston et al., 1981). Caregivers report greater distress and depression and reduced social support compared to noncaregivers (Bodnar & Kiecolt-Glaser, 1994; D. Cohen & Eis dorfer, 1988; Dura, Stukenberg, & Kiecolt-Glaser, 1990; Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991; Redinbaugh, MacCallum, & Kiecolt-Glaser, 1995). Thus, caregiving has been conceptualized as a model of chronic stress.

As with short-term stress, chronic stress has significant effects on immune function. For example, caregiving was associated with lower percentages of T helper and total T cells and poorer cellular immunity against latent EBV (Kiecolt-Glaser, Glaser, et al., 1987). In a longitudinal study of spousal caregivers and community matched controls, caregivers showed greater decrements in cellular immunity over time as measured by decreased blastogenic responses to PHA and Con A (Kiecolt-Glaser et al., 1991). Additional studies have confirmed that caregiving is associated with reduced blastogenic responses (Castle, Wilkins, Heck, Tanzy, & Fahey, 1995; Glaser & Kiecolt-Glaser, 1997), decreased virus-specific-induced cytokine production (Kiecolt-Glaser, Glaser, Gravenstein, Malark ey, & Sheridan, 1996), inhibition of the NK cell response to recombinant IL-2 (rIL-2) and rIFN-γ (Esterling, Kiecolt-Glaser, & Glaser, 1996), and reduced sensitivity of lymphocytes to certain effects of glucocorticoids (Bauer et al., 2000).

Other studies have confirmed that chronic stress may have behavioral and immunological consequences. Following the nuclear reactor meltdown at Three Mile Island (TMI) in 1979, psychological assessments revealed that local TMI residents reported more symptoms of distress and intrusive thoughts and continued to have higher blood pressure, heart rate, norepinephrine, and cortisol levels than control subjects who lived 80 miles away, up to five years after the accident (Davidson & Baum, 1986). TMI residents also had fewer B lymphocytes, T-suppressor/cytotoxic lymphocytes and NK cells, as well as evidence for reactivation of latent HSV (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989). In the aftermath of the Northridge earthquake, local residents similarly showed a decrease in T cell numbers, blastogenic responses, and NKCC (Solomon, Segerstrom, Grohr, Kemeny, & Fahey, 1997).

Chronic stress can have significant clinical consequences. As previously mentioned, caregivers and TMI residents showed evidence for reactivation of latent herpes viruses (Glaser & Kiecolt-Glaser, 1997; McKinnon et al., 1989). Following influenza vaccination, caregivers were less likely to achieve a four-fold increase in antibody titers than controls (Kiecolt-Glaser, Glaser, et al., 1996; Vedhara et al., 1999), which suggests greater susceptibility or more serious illness in the event of exposure to influenza virus. Caregivers also took 24% longer to heal a standardized punch biopsy wound (Kiecolt-Glaser, Marucha, Malark ey, Mercado, & Glaser, 1995) and reported a greater number and duration of illness episodes, with more physician visits than control subjects (Kiecolt-Glaser & Glaser, 1991).

The immune dysregulation associated with caregiving may be especially relevant for older adults, as cellular immunity declines with age (Bender, Nagel, Adler, & Andres, 1986; Murasko, Weiner, & Kaye, 1987), and is associated with greater morbidity and mortality, especially due to infectious diseases (Murasko, Gold, Hessen, & Kaye, 1990; Wayne, Rhyne, Garry, & Goodwin, 1990). However, even in younger populations, longer term stress (greater than one month) has been associated with immune dysregulation and increased susceptibility to infection by a common cold virus (Cohen et al., 1998).

The studies mentioned support the argument that immunological dysregulation associated with chronic stress does not necessarily undergo habitation over time. Rather, these effects appear to be present for the duration of the stressor, and in some cases, persist even after the stressor is no longer present (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994).

**INDIVIDUAL PSYCHOLOGICAL DIFFERENCES**

Negative emotions are related to a range of diseases whose onset and course may be influenced by the immune system,
particularly by inflammation resulting from the production of proinflammatory cytokines (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Individual differences in emotional and coping responses may account for some of the variation in neuroendocrine and immunological changes associated with stress. Currently, research is aimed at identifying the relationships among these changes and emotional traits and states, daily subclinical fluctuations in mood, bereavement, clinical disorders of major depression and anxiety, and coping strategies.

**Negative and Positive Affect**

Negative affect is defined as general subjective distress and includes a range of negative mood states, such as depression, anxiety, and hostility (Watson & Pennebaker, 1989). Cohen and colleagues demonstrated an association between negative affect and rates of respiratory infection and clinical colds following intentional exposure to five different respiratory viruses (S. Cohen, Tyrrell, & Smith, 1991). A dose-response relationship was found between rates of respiratory infection and clinical colds and increased levels of a composite measure of psychological stress that included negative affect, major stressful life events, and perceived ability to cope with current stressors. In further analyses of these data, negative affect predicted the probability of developing a cold across the five different upper respiratory infection viruses independent of negative life events (S. Cohen, Tyrrell, & Smith, 1993). Furthermore, the higher illness complaints in individuals high in state negative affect were associated with increased severity of colds and influenza as seen in the amount of mucus produced (S. Cohen et al., 1995). However, negative affect was not related to the development of clinical colds among already infected individuals but rather was associated with individuals’ susceptibility to infection (S. Cohen et al., 1993; Stone et al., 1992).

In another study, baseline personality variables that are thought to be characteristic of negative affect (high internalizing, neuroticism, and low self-esteem) predicted lower titers of rubella antibodies 10 weeks postvaccination in subjects who were seronegative prior to vaccination (Morag, Morag, Reichenberg, Lerer, & Yirmiya, 1999). This relationship was found in subjects who were seropositive prior to vaccination.

Dispositional positive affect and the expectation of positive outcomes, termed optimism, have been less well studied in relation to immune variables. Davidson and colleagues (Davidson, Coe, Dolski, & Donzella, 1999) demonstrated positive relationships between NKCC and greater positive dispositional mood, defined by relative left-sided anterior brain activation. Greater relative left-sided activation was associated with higher levels of basal NKCC and with smaller declines in NKCC from a nonstress baseline to a final exam period that occurred six weeks later.

Although optimism has been related to positive physical health outcomes in surgery patients (Scheier et al., 1999), its association with immune function has been inconsistent among prospective studies of naturalistic stressors. These inconsistencies might be due to different methodology in defining optimism, different periods of follow-up for immune measures, and differences in the presence and definition of acute and chronic stress. Segerstrom, Taylor, Kemeny, and Fahey (1998) examined optimism and immune function in first-year law students before entry into the law school program and again at midsemester, two months before students’ first examination period. Dispositional optimism was not related to immune measures but to higher situational optimism (defined as positive expectations specific to academic performance) and was associated with higher NKCC. This association was partially mediated by lower levels of perceived stress. In another study, healthy women were followed for three months, using daily self-reports of stressful events. In this case, dispositional optimism was associated with a greater reduction in NKCC following high stress that lasted longer than one week compared to less optimistic individuals (F. Cohen et al., 1999). Thus, optimism may have differential effects on NKCC, depending on whether situational or dispositional optimism is measured.

**Daily Negative and Positive Mood**

The relationships between normal daily mood fluctuations and immune variables have been evaluated by tracking subjects’ naturalistic mood changes and by inducing positive and negative mood states in the laboratory. In the first case, negative mood over the course of two days was associated with reduced NKCC, but there was evidence that positive mood moderated this association (Valdimarsdottir & Bovbjerg, 1997). In the second case, studies of induced mood in the laboratory have shown transient increases in NKCC (Futterman, Kemeny, Shapiro, & Fahey, 1994; Knapp et al., 1992), but conflicting outcomes related to the lymphocyte proliferative response to PHA. Both positive and negative induced mood conditions were associated with a decreased response to PHA (Knapp et al., 1992), whereas positive induced mood was associated with an increased response to PHA and negative induced mood was associated with a decreased response to PHA (Futterman et al., 1994). The differences in immune outcomes in these two laboratory-induced mood studies may be, in part, due to different levels of arousal and physical activity during the mood induction procedure and the use of
trained actors in one study (Futterman et al., 1994). Nevertheless, the different NKCC responses to mood in the naturalistic and laboratory studies parallel the different NKCC responses to stress in the acute and laboratory studies described earlier.

**Bereavement**

Early studies of bereavement and immune function showed reduced lymphocyte proliferation to the mitogens Con A and PHA relative to controls in bereaved spouses two months after the death of their spouse (Bartrop, Luckhurst, Lazarus, Kiloh, & Penny, 1977). In a within-subjects design, lymphocyte proliferation to Con A, PHA, and pokeweed mitogen (PWM) was decreased for two months, relative to the bereavement response (Schleifer, Keller, Camerino, Thorton, & Stein, 1983). The severity of depressive symptoms in women experiencing bereavement or anticipating bereavement due to their husbands’ diagnosis of metastatic lung cancer was negatively related to NKCC (Irwin, Daniels, Smith, Bloom, & Weiner, 1987). Conflicting immunological consequences of bereavement in HIV seropositive gay males have been reported (Kemeny et al., 1995; Kessler et al., 1991) but may be, in part, due to individuals’ different coping strategies in response to bereavement (Bower, Kemeny, Taylor, & Fahey, 1998).

Studies of the immunological impact of bereavement have generally included small sample sizes and short follow-up periods. The mechanisms underlying the association between bereavement and immune changes and the time line of such changes have not been identified, but changes in mood, health behaviors, and neuroendocrine function have been proposed.

**Depression**

Clinical depression has been associated with reduced NKCC (Irwin, Patterson, & Smith, 1990; Irwin, Smith, & Gillin, 1987), decreased lymphocyte proliferation to mitogens (Schleifer et al., 1984), poorer specific proliferative response (memory) to varicella-zoster virus (Irwin et al., 1998), and decreased delayed-type hypersensitivity (Hickie, Hickie, Lloyd, Silove, & Wakefield, 1993). Nonmeta-analytic review studies have drawn different conclusions about the existence of an association between depression and immune function (Stein, Miller, & Trestman, 1991; Weisse, 1992); however, a meta-analytic review concluded that clinically depressed individuals, especially older and hospitalized individuals, have lower lymphocyte proliferative responses to PHA, Con A, and PWM and have lower NKCC compared to nondepressed, healthy controls (Herbert & Cohen, 1993). A classic study by Schleifer, Keller, Bond, Cohen, and Stein (1989) most clearly showed the interactions of age, depression, and immune function; older depressed individuals had the lowest lymphocyte proliferation to mitogen compared to controls.

Mild to moderate levels of clinical depression in nonhospitalized individuals were associated with reduced lymphocyte proliferation and decreased NKCC (Miller, Cohen, & Herbert, 1999). Nonclinical depressed mood also has been reliably associated with decreased NKCC and decreased lymphocyte proliferative response to PHA, although the effect sizes of these relationships are smaller than for clinically depressed mood (Herbert & Cohen, 1993). The time course of immunological correlates in depression is not known, but individuals that recovered from depression no longer showed decreased NKCC (Irwin, Lacher, & Caldwell, 1992).

One potential pathway for the association of depression and immune function includes alterations in health behaviors, such as sleep, exercise, smoking, diet, and alcohol and drug use (Kiecolt-Glaser & Glaser, 1988). Patients with depression or alcoholism showed reduced NKCC relative to controls, and dually diagnosed patients showed even greater NKCC reductions (Irwin, Caldwell, et al., 1990). Physical activity mediated the association between mild to moderate depression and reduced proliferation to Con A and PHA in ambulatory female outpatients (Miller, Cohen, et al., 1999). Depressed men who smoked light to moderate amounts had the lowest NKCC, whereas nonsmoking depressed subjects, control smokers, and control nonsmokers did not differ from one another (Jung & Irwin, 1999). Other potential pathways include SNS and endocrine dysregulation. Although such physiological dysregulation has been shown in depression (Chrousos, Torpy, & Gold, 1998; Gold, Goodwin, & Chrousos, 1988), these pathways have not been consistently linked to alterations in immune function in depressed individuals (Miller, Cohen, et al., 1999; Schleifer, Keller, Bartlett, Eckholdt, & Delaney, 1996; Schleifer et al., 1989).

**Anxiety**

Higher levels of anxious mood have been related to a poorer immune response to a hepatitis B vaccination series (Glaser, Kiecolt-Glaser, Bonneau, Malarkey, & Hughes, 1992), lower proliferative responses to Con A and lower plasma levels of IL-1β (Zorrilla, Rede, & DeRubeis, 1994), decreased NKCC (Locke et al., 1984), and higher antibody titers to latent EBV (Esterling, Antoni, Kumar, & Schneiderman, 1993). Anxiety related to the anticipation of HIV serostatus notification has been associated with higher plasma cortisol levels, which were associated with lower lymphocyte proliferation to PHA.
Individual Psychological Differences

(Antoni et al., 1990) and decreased NKCC in the postacute notification period in gay males (Ironson et al., 1990). High levels of trait worry, a central feature of generalized anxiety disorder (GAD), interfered with the increase in NK cells in peripheral blood seen in individuals with a normal level of trait worry during exposure to an acute stressor (Segerstrom, Glover, Craske, & Fahey, 1999), and was associated with 25% fewer NK cells throughout a four-month follow-up period following the natural disaster of an earthquake (Segerstrom et al., 1998b).

The association between clinical diagnoses of anxiety disorders and immune function is a recent focus of investigation. Significant associations have not been found with obsessive-compulsive disorder (Maes, Meltzer, & Bosmans, 1994), and discrepant outcomes have been reported with panic disorder (Andreoli et al., 1992; Brambilla et al., 1992; Rapaport, 1998; Weizman, Laor, Wiener, Wolmer, & Bessler, 1999). More consistent immune relationships have been reported for GAD and posttraumatic stress disorder (PTSD). Patients with GAD showed changes in monocyte function and structure, reduced NKCC, reduced lymphocyte proliferation to PHA, and a poorer response to two DTH tests compared to controls (Castilla-Cortazar, Castilla, & Gurpegui, 1998), reduced IL-2 production (Koh & Lee, 1998), and lower expression of IL-2 receptors on stimulated T cells compared to controls (La Via et al., 1996). Chronic PTSD has been associated with elevated lymphocyte, total T cell, and CD4+ T cell counts in Vietnam combat veterans (Boscarino & Chang, 1999) and a higher index of lymphocyte activation in patients with a history of childhood sexual abuse (Wilson, van der Kolk, Burbridge, Fisler, & Kradin, 1999).

The outcomes of the studies that have evaluated the association of clinical anxiety disorders and immune function should be considered preliminary. The sample sizes are small and there is wide variability in the methodology and rigor of the studies. It is not yet known what aspects of clinical anxiety disorders, such as classes of symptoms, severity and time course of symptoms, arousal, or hypervigilance, are most important for immunity. The consequences of comorbid disorders, especially depression, and mixed groups of anxiety disorder patients require further evaluation.

Coping

Individual differences in appraisal and response to stressful situations have been evaluated through assessment of coping strategies. The positive or negative association of coping strategies with immune function appears to depend, to some extent, on stress levels, with active coping being significantly related to more vigorous proliferative responses to PHA and Con A in individuals who report high stress levels, but not in those who report low stress levels (Stowell, Kiecolt-Glaser, & Glaser, 2001).

Reactivation of latent EBV in healthy college students was associated with a repressive personality style and a tendency to not disclose emotion on a laboratory task (Esterling, Antoni, Kumar, & Schneiderman, 1990) and to higher levels of defensiveness (Esterling et al., 1993). Repressive personality or coping style were not related to immune measures following an earthquake, but an appropriate psychological reactivity to the realistic degree of life stress caused by the earthquake was described as least disruptive to immune measures (Solomon et al., 1997). In partners of bone marrow transplant patients, escape-avoidance coping was the strongest and most consistent variable associated with changes indicative of poorer immune function, especially during the anticipatory period prior to the initiation of the transplant (Futterman, Wellisch, Zigelboim, Luna-Raines, & Weiner, 1996). Greater denial in gay men awaiting notification of HIV seronegative status was associated with less impairment in PHA response at baseline, perhaps through a reduction in intrusive thoughts related to notification (Antoni et al., 1990).

Disease Progression

Evidence of greater risk of physical morbidity and mortality in individuals with depression (Herrmann et al., 1998; Penninx et al., 1999) suggests an important association between psychosocial factors and disease onset and progression. The association of psychosocial factors and cancer remains controversial due to conflicting study outcomes. Some prospective studies have found greater cancer-related mortality in depressed individuals (Persky, Kemphorne-Rawson, & Shekelle, 1987; Shekelle et al., 1981), while other studies have not found this relationship (Kaplan & Reynolds, 1988; Zonderman, Costa, & McCrae, 1989). The most promising psychological factors related to tumor progression include a low level of social support, hopelessness, and repression of negative emotions (see for review Garssen & Goodkin, 1999; Kiecolt-Glaser & Glaser, 1999).

Significant psychosocial associations have been found in the progression of HIV. Depression has been associated with an increased rate of CD4+ T-cell decline in HIV-seropositive men, but the relationship appears to depend on the presence of higher levels of CD4+ cells in the early stage of disease (Burack et al., 1993; Lyketsos et al., 1993). More rapid disease progression has been associated with greater concealment of homosexual identity (Cole, Kemeny, Taylor, Visscher, & Fahey, 1996), high realistic acceptance and negative
expectations about future health (Reed, Kemeny, Taylor, Wang, & Visscher, 1994), attribution of negative events to the self (Segerstrom, Taylor, Kemeny, Reed, & Visscher, 1996), a passive coping style (Goodkin, Fuchs, Feaster, Leeka, & Rishel, 1992), and denial of diagnosis in seropositive gay men (Ironson et al., 1994). Alternatively, more deliberate cognitive processing about the death of a close friend or partner was associated with greater likelihood of finding positive meaning in the loss, and greater positive meaning was associated with a less rapid decline in levels of CD4+ cells over three years and lower rates of AIDS-related mortality nine years later in HIV-seropositive men (Bower et al., 1998).

From the studies reviewed, it appears that the immunological effects of stressors are influenced by affective, cognitive, behavioral, and psychosocial individual differences in appraisal and response to stressors. Through better understanding and assessment of the role of individual differences in physiological responses, we may more accurately predict immune changes in the context of stress. The physiological mechanisms that underlie the psychosocial and immune function associations are not yet fully known, but the HPA, SAM, SNS, and opioid systems are likely involved (Rabin, 1999).

SOCIAL RELATIONSHIPS AND PSYCHONEUROIMMUNOLOGY

Psychoneuroimmunology research focusing on social relationships originated from a larger literature on the relationships between social support and health. Cassel (1976) and Cobb (1976) provided important theoretical and empirical integration of social support and health research, concluding that social support was positively associated with health outcomes. Following the publication of these reviews, research on social support and health experienced “geometric growth” (House, Landis, & Umberson, 1988). In particular, epidemiological studies showed that lower social integration (lower number of social relationships and activities) was consistently associated with higher risk of mortality, independent of age, physical health, and a number of other health behavior risk factors (Berkman & Syme, 1979; House, Robbins, & Metzner, 1982; Schoenbach, Kaplan, Fredman, & Kleinbaum, 1986). In their seminal review of this work, House et al. (1988) concluded that “social relationships, or the relative lack thereof, constitute a major risk factor for health—rivaling the effects of well-established health risk factors such as cigarette smoking, blood pressure, blood lipids, obesity, and physical activity” (p. 541). The underlying theme of psychoneuroimmunology and social support research is that positive support provided by social relationships protects against susceptibility to disease by promoting immune competence. At the same time, negative qualities of social relationships may act as stressors, resulting in compromised immune function.

Social Relationships

Cross-Sectional Studies

In the first published cross-sectional study of social support and immune function, a greater number of frank and confiding relationships was associated with higher total lymphocyte counts and a greater blastogenic response to PHA in women, with smaller effects found for men (Thomas, Goodwin, & Goodwin, 1985). Subsequent studies examined these relationships in the context of stressful life events. In the context of job strain, greater social support was associated with lower levels of serum IgG, but only for persons under high job strain (Theorell, Orth-Gomer, & Eneroth, 1990). As previously discussed, in a series of studies of spousal caregivers for AD patients, lower levels of helpful emotional and tangible support in caregivers were associated with an inhibition of NK cell responses (Esterling, Kiecolt-Glaser, et al., 1994; Esterling et al., 1996). Similarly, in spouses of cancer patients, lymphocyte proliferation to PHA and NK cell activity were positively associated with perceived provision of various types of social support (Baron, Cutrona, Hicklin, Russell, & Lubaroff, 1990).

Prospective Studies

Prospective studies of social support and immune function have focused on samples undergoing both chronic and acute life events. Caregivers of AD patients reported less social support than controls, and caregivers with low social support showed a greater negative change in immune function from intake to follow-up (Kiecolt-Glaser et al., 1991). In patients undergoing an acute stress, hernia surgery, perceived social support was positively correlated with lymphocyte proliferation to mitogens both pre- and post-operation (Linn, Linn, & Klimas, 1988). Finally, in a sample of both healthy and asthmatic adolescents, social support was positively associated with CD4+/CD8+ ratios and neutrophil superoxide production at higher levels of perceived stress (Kang, Coe, Karszewski, & McCarthy, 1998).

Clinical Disease Studies

Studies of clinical disease and social support are important in psychoneuroimmunology research because they are directly relevant to clinical health outcomes. This research is
especially informative to current approaches to clinical treatment of infectious disease and cancer, by suggesting that psychosocial interventions can promote lower susceptibility and increased resistance (Andersen, Kiecolt-Glaser, & Glaser, 1994; Glaser, Rabin, Chesney, Cohen, & Natelson, 1999). One of the first studies used an academic examination paradigm to investigate acute stress, social support, and immune response to hepatitis B vaccination (Glaser, Kiecolt-Glaser, Bonneau, Malarkey, & Hughes, 1992). Although no differences in seroconversion rates were found when comparing subjects on social support, social support was positively associated with the immune response to the vaccine as measured by total antibody titers and T cell responses to the vaccine antigen. Similarly, subjects with low social integration (less diverse social roles) were three times more likely to develop clinical symptoms of cold when infected with a cold virus compared to subjects with high social integration (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997).

A large number of studies on social support have involved HIV-positive individuals who had not yet progressed to AIDS (asymptomatic). Given the positive benefits of social support on immune function, perhaps HIV-positive individuals with high social support would show a slower decline in immune competence associated with progression to AIDS. Although initial studies indicated negative findings (Goodkin, Blaney, et al., 1992; Perry, Fishman, Jacobsberg, & Frances, 1992), later studies found increased social participation and decreased loneliness to be associated with higher CD4+ counts (Persson, Gullberg, Hanson, Moestrup, & Ostergren, 1994; Straits-Troester et al., 1994). Moreover, low perceived emotional support was associated with a more rapid decline in CD4+ cells (Theorell et al., 1995).

Social Support-Immune Pathways

Considerable evidence suggests that social support contributes positively to immune function. The pathways through which social relationships can influence immune competence appear to be through primarily stress-buffering effects (Esterling, Kiecolt-Glaser, et al., 1994; Esterling et al., 1996; Goodkin, Blaney, et al., 1992; Kang et al., 1998; Kiecolt-Glaser et al., 1991; Theorell et al., 1990), although ample evidence suggests that immunological regulation is promoted by the mere presence of supportive others (S. Cohen et al., 1997; Levy et al., 1990; Linn et al., 1988; Persson et al., 1994; Theorell et al., 1995; Thomas et al., 1985). The magnitude of these effects appears to be small (r = .21), as shown in a meta-analysis of the literature up to 1995 (Uchino, Cacioppo, & Kiecolt-Glaser, 1996). However, these effects may have clinical relevance because social relationships can be associated with both disease susceptibility (common cold, hepatitis B studies) and progression (breast cancer, HIV/AIDS). Moreover, this effect is impressive given the diverse conceptualizations and assessments of both social support and immune function.

Close Personal Relationships

While the previously reviewed studies explored the support relationships provided by one’s social network (friends, family, coworkers, etc.), certain social relationships have greater psychological and physiological importance than others. Close personal relationships provide a unique source of social support, often encompassing all of the four general components of social support (e.g., emotional support, instrumental support, informational support, and appraisal support). Arguably, the most important close personal relationship is the marital relationship. Married persons have lower rates of morbidity and mortality compared to nonmarried persons across a variety of conditions, including cancer, myocardial infarction, and surgery (Chandra, Szklo, Goldberg, & Tonascia, 1983; Goodwin, Hunt, Key, & Samet, 1987; Gordon & Rosenthal, 1995; House et al., 1988).

Although healthy marital relationships afford health benefits, disruptions in the marital relationship are associated with health risks. Separated or divorced adults have higher rates of acute illness and physician visits compared to married persons and higher rates of mortality from infectious diseases, including pneumonia (Somers, 1979; Verbrugge, 1979, 1982). As such, PNI studies in this domain have focused on disruptive aspects of the marital relationship and their consequences for immune competence.

Marital Disruption

Initial studies of marital relationships and immune function focused on the immune consequences of separation and/or divorce (Kiecolt-Glaser, Fisher, et al., 1987; Kiecolt-Glaser et al., 1988). In these studies, married adults were compared to separated and/or divorced adults on enumerative and functional measures of immune function. Separated/divorced males and females showed higher IgG antibody titers to latent EBV, indicative of poorer immune competence in controlling the latent virus. Separated/divorced males also showed higher antibody titers to latent HSV, and separated/divorced females showed poorer blastogenic response to PHA compared to married counterparts. Poorer psychological adjustment to separation, particularly stronger feelings of attachment and shorter separation periods, were associated with increased distress, lower helper to suppressor T-cell
ratios, and poorer blastogenic responses to mitogen. Subjective ratings of low marital quality, as measured by the Dyadic Adjustment Scale (Spanier, 1976), were associated with higher antibody titers to latent EBV for males and females. These findings suggest separation and divorce result in dysregulation of cell-mediated immunity, particularly for persons who have difficulty adapting.

*Marital Interaction*

Further studies of marital disruption focused on how behaviors exhibited during a couple's interaction were related to immune function. In the first study, we assessed autonomic, endocrine, and immune function over a 24-hour period in 90 newlywed couples who met stringent mental and physical criteria (Kiecolt-Glaser et al., 1993). Couples engaged in a 30-minute conflict resolution task in which they discussed current marital problems. Individuals who exhibited more hostile or negative behaviors during conflict showed greater decrements in functional immune measures, including decreased NK cell lysis, blastogenic response to PHA and Con A, and proliferative response to a monoclonal antibody against the T cell receptor. Notably, these declines in immune function were more likely to occur in women than men. In addition, similar to the previous findings, individuals who exhibited more negative or hostile behaviors during conflict had higher antibody titers to latent EBV. Thus, not only were negative behaviors during conflict a significant predictor of declines in marital satisfaction (Markman, 1991), but these same behaviors significantly predicted declines in immune function during a 24-hour period and in immune competence in controlling latent herpes viruses.

Older couples display less negative behavior and more affectionate behavior than younger couples during conflict (Carstensen, Levenson, & Gottman, 1995), and therefore may display a different pattern of immune changes. To explore this possibility, older couples (mean age = 67) who had been married an average of 42 years, were studied using the same paradigm as our newlywed study (Kiecolt-Glaser et al., 1997). Subjects who showed poorer responses on functional immune measures, including blastogenic responses to PHA and Con A, and antibody titers to latent EBV, engaged in more negative behavior during conflict. Moreover, these subjects characterized their typical marital disagreements as more negative than subjects with relatively better immune function. Overall, these results are particularly striking given that these couples, both young and old, had happy marriages and were mentally and physically fit. Thus, it is likely that these findings actually underestimate the physiological impact of marital strife (Kiecolt-Glaser, 1999).

Other studies of marital interaction also show that behavior during conflict is associated with immune modulation. A decrease in the blastogenic response to PHA was found in females, but not in males, in response to marital conflict, and this negative change was associated with increased hostility (Mayne, O'Leary, McCrady, Contrada, & Labouvie, 1997). Consistent with immunological changes during acute laboratory stress, marital conflict was associated with increased NK cell cytotoxicity, specific to male subjects high in hostility (Miller, Dopp, Myers, Felten, & Fahey, 1999). This is likely due to altered trafficking of specific NK cell subtypes into peripheral blood (Dopp, Miller, Myers, & Fahey, 2000).

In the context of the marital relationship, negative behaviors during an interaction are also reliably associated with endocrine changes. Newlywed couples exhibiting higher levels of hostile and negative behavior during conflict showed elevated levels of epinephrine, norepinephrine, ACTH, and growth hormone, and lower levels of prolactin (Malarkey, Kiecolt-Glaser, Pearl, & Glaser, 1994). Moreover, the association between high negative behavior and endocrine changes were stronger and more consistent for women compared to men. Higher probabilities of a husband's withdrawal in response to their wife's negative behavior were associated with higher norepinephrine and cortisol in wives. Behavior during marital conflict accounted for a significant proportion of variance in various endocrine measures, accounting for 24% to 37% of the variance over a 24-hour period (Kiecolt-Glaser, Newton, et al., 1996). Similar effects were found in older couples, with negative behaviors accounting for 16% to 21% of the variance in changes in cortisol, ACTH, and epinephrine (Kiecolt-Glaser et al., 1997). These endocrine changes may mediate the immune function changes observed during conflict.

Overall, these findings suggest that marital disruption can influence health outcomes through immunological pathways. In particular, high levels of hostile and negative behavior during marital conflict may be particularly harmful. Moreover, the endocrine and immunological changes in response to negative behavior are more readily observed in women compared to men. This suggests that the negative physiological impacts of marital discord are greater for women compared to men, though the gender discrepancy in health outcomes is less clear (Kiecolt-Glaser & Newton, 2001).

**PSYCHOLOGICAL INTERVENTIONS**

Evidence that psychosocial characteristics are associated with alterations in immune function suggests that psychological interventions targeting psychosocial vulnerability factors...
may have beneficial immune outcomes. In both healthy and ill (e.g., cancer, HIV) populations, psychological interventions, such as classical conditioning, relaxation and hypnosis, emotional disclosure, and cognitive-behavioral strategies, have been used to improve mood, coping ability, and social support in attempts to modulate immune function.

Classical Conditioning

Classical conditioning studies in rodents have demonstrated modulation of humoral, cell mediated, and nonspecific immunity with potential biological significance related to the onset and course of autoimmune diseases, morbidity, and mortality (see for review, Ader & Cohen, 1993; Ader, Felten, & Cohen, 1991). Although there have been few human studies of classical conditioning, their findings are encouraging. In one study, tuberculin DTH responses were conditioned by administering tuberculin once a month for six months. Tuberculin was drawn from a red vial and administered to one arm, while saline was drawn from a green vial and administered to the other arm. On the double blind test trial, the contents of the vials were switched. Saline did not produce a skin reaction on the arm that had previously received tuberculin, but the reaction to tuberculin was diminished on the arm that normally received saline (Smith & McDaniel, 1983).

In a second study, conditioning in a naturalistic setting was observed in women undergoing chemotherapy for ovarian cancer. Following repeated pairing of immunosuppressive chemotherapy with hospital stimuli, the hospital stimuli alone produced a suppression of lymphocyte proliferation to PHA and Con A (Bovbjerg et al., 1990). In a case study of pediatric lupus, neutral stimuli (a taste and a smell) were paired with a toxic immunosuppressive medication (cyclophosphamide). Following monthly conditioning trials, the patient showed significant increases in NKCC and better control of latent HSV following one month, three times weekly, of progressive muscle relaxation training with guided imagery, compared to social contact and no intervention (Kiecolt-Glaser et al., 1985). These benefits were maintained at one-month follow-up. In a subsequent study, relaxation intervention with medical students prior to exams did not significantly alter stress-induced changes in immune function in the group as a whole. However, students who practiced relaxation more frequently had higher helper T-lymphocyte percentages during examinations, after controlling for baseline levels (Kiecolt-Glaser et al., 1986). Varied methods of relaxation and guided imagery intervention have been associated with increased lymphocyte proliferation to mitogens (McGrady et al., 1992), increased NKCC (Zachariae et al., 1990), increased plasma IL-1 (Keppel, Regun, Heffemeider, & McCoy, 1993), and enhanced neutrophil phagocytic activity (Peavey, Lawlis, & Goven, 1986).

Hypnosis studies using the “double arm” technique have evaluated whether individuals can intentionally modify their immunological response, such as immediate and delayed hypersensitivity. In these studies, the same allergic substance is injected into both arms of a subject and hypnotic suggestions are made about inflammatory response changes (e.g., itching, wheal, erythema) in one arm and no changes in the other arm. Differences in the responses of both arms have been found in several studies (Black, 1963; Black & Friedman, 1965; Black, Humphrey, & Niven, 1963; Zachariae & Bjerring, 1990; Zachariae, Bjerring, & Arendt-Nielsen, 1989), but not in others (Bearns, Harris, & Hilgard, 1970; Locke et al., 1987).

Whether the hypersensitivity changes found in some studies are due to immune function changes or only skin surface changes remains to be determined. However, high hypnotizable individuals do produce greater immune changes than low hypnotizable subjects (Gregerson, Roberts, & Amiri, 1996; Ruzyla-Smith, Barabasz, Barabasz, & Warner, 1995; Zachariae, Jorgensen, Christensen, & Bjerring, 1997; Zachariae, Oster, & Bjerring, 1994).

Emotional Disclosure

Negative life events can have psychological impact for many years (Tait & Silver, 1989) and can result in persistent elevation of stress hormones (Baum, Cohen, & Hall, 1993). There is evidence that social constraints to emotional expression and discussion of negative events are associated with negative emotional (Lepore & Helgeson, 1998) and physiological (Helgeson, 1991) outcomes, including increased intrusive thoughts, more avoidant coping, and greater depression and anxiety. Emotional disclosure interventions, to the extent that they increase cognitive processing, alter appraisals, reduce intrusive thoughts, and reduce negative mental health consequences of negative events, have been related to positive alterations in immune function. These immune changes are found typically weeks to months postintervention. For
example, healthy college students who wrote about personal, traumatic experiences showed increased lymphocyte proliferation to PHA and fewer health center visits at the six-week follow-up, and this effect was strongest for those who wrote about experiences they had not previously shared (Pennebaker, Kiecolt-Glaser, & Glaser, 1988). In another study, medical students who wrote about a highly traumatic personal event generated higher antibody titers to a hepatitis vaccination given on the last day of writing by four- and six-month follow-up than did control subjects who wrote about trivial topics (Petrie, Booth, Pennebaker, Davison, & Thomas, 1995). Four months following a written emotional disclosure intervention, asthma patients experienced improved lung function and rheumatoid arthritis patients had clinically significant improvements in overall disease activity, compared to controls (Smyth, Stone, Hurewitz, & Kaell, 1999). Finally, the extent to which individuals became emotionally and cognitively involved in the disclosure process, reorganized the meaning of the traumatic event, and reduced avoidance of the topic was correlated with the degree of change in antibody titers to latent EBV (Esterling, Antoni, Fletcher, Margulies, & Schneiderman, 1994; Lutgendorf, Antoni, Kumar, & Schneiderman, 1994).

Cancer

A classic, well-controlled study of the impact of a psychological intervention on immune function and progression of cancer involved Stage I and II malignant melanoma patients. A six-week structured group intervention included stress management, relaxation, support, health education, and problem-solving skills related to participants' illness (Fawzy et al., 1990). The patients who received the intervention had reduced psychological distress, increased percentage of NK cells, increased IFN-α augmented NKCC, and a small reduction in the percentage of helper T cells by six-month follow-up. Decreased depression and anxiety symptoms and increased assertiveness and defiance were related to increased NKCC. At the six-year follow-up, there was a trend for fewer recurrences and significantly lower mortality in the intervention subjects, even after controlling for the size of the initial malignant melanoma (Fawzy et al., 1993). In a study of breast cancer patients, a six-month intervention, including relaxation, guided imagery, and biofeedback, was associated with greater NKCC, lymphocyte proliferative response to Con A, and mixed lymphocyte responsiveness in women post radical mastectomy for stage 1 breast cancer (Gruber et al., 1993).

Another relaxation intervention study was targeted at altering conditioned anticipatory immune suppression in women receiving chemotherapy for ovarian cancer. The intervention included progressive muscle, release-only, and cue-controlled relaxation techniques and was practiced daily for more than four weeks. Training began the day before the start of the first course of chemotherapy. In this case, the relaxation intervention was not associated with reliable changes in NKCC or lymphocyte proliferation to Con A measured prior to subsequent courses of chemotherapy (Lekander, Forst, Rotstein, Hurstli, & Fredrikson, 1997). Difficulties in interpreting the outcomes of cancer-related intervention studies stem from such methodological differences as method of assignment of subjects to control and intervention conditions, control for type and stage of disease, variable outcome measures, and different follow-up periods.

HIV

Several intervention studies involving HIV seropositive and seronegative gay men have found some positive effects of intervention on immune function. In the first of these studies, exercise interventions protected asymptomatic seropositive gay men from depression, anxiety, and a decrease in NK cell numbers that was observed in seropositive control subjects following notification of serostatus (LaPerriere et al., 1990). Similarly, a comprehensive 10-week cognitive-behavioral stress management intervention, which included relaxation training, cognitive restructuring, assertiveness training, anger management, and social support, was associated with significant increases in CD4+ and NK cell counts from 72 hours before to one week after HIV-positive serostatus notification in healthy, asymptomatic gay men (Antoni et al., 1991). Cognitive-behavioral and exercise interventions were also associated with better cellular immunity to the latent herpesviruses, EBV, and human herpes virus type-6 in asymptomatic seropositive gay men (Esterling et al., 1992), and HSV-2 in symptomatic gay men (Lutgendorf et al., 1997). Greater practice of relaxation (Antoni et al., 1991; Lutgendorf et al., 1997) and greater adherence to the intervention protocols (Ironson et al., 1994) were significant predictors of less distress and disease progression. In one other intervention study, progressive muscle relaxation and guided imagery were both associated with decreased depression in HIV seropositive individuals, but only progressive muscle relaxation was associated with a significant increase in CD4+ cell counts compared to controls (Eller, 1995).

Psychosocial factors may play a role in HIV progression because there is great variability among individuals in the length of time to develop clinical symptoms and in the severity of illness at different stages of AIDS. However, not all studies have shown significant relationships between psychosocial measures and immune variables in HIV-1
seropositive individuals (Perry et al., 1992; Rabkin et al., 1991) or between psychological intervention and immune changes (Coates, McKusick, Kuno, & Stites, 1989; Mulder et al., 1995). Such negative findings indicate the need for theoretically driven models of association between psychosocial and immune or health outcomes, controls for health behaviors, inclusion of a broad range of immune measures, and control for stage of disease (Goodkin et al., 1994).

Psychological interventions that show evidence of immune function modulation likely have their effects through alterations of appraisal, coping, or mood, which in turn affect health behaviors, endocrine activity, and immune function. The importance of intervention effects on negative emotions is demonstrated by studies showing covariation in immunological changes and reduced negative emotion (Antoni et al., 1991; Fawzy et al., 1990; Lutgendorf et al., 1997). The potential health outcomes of immunological changes that follow psychological interventions remain to be determined. Further studies are needed that more directly assess changes in disease incidence, severity, and duration, as well as studies that include immune measures in therapy outcome studies. Finally, in evaluating psychological intervention studies, it is important to remember that it may not be possible or desirable to enhance immune function (e.g., autoimmune disease) if the immune system is already functioning at normal levels. There is greater likelihood of positive intervention effects when participants show some degree of dysregulation in immune function relative to their demographically matched peers.

Health impact will likely depend on the type, intensity, and duration of intervention, the extent and duration of immune alteration, and prior immunological and health status (Kiecolt-Glaser & Glaser, 1992). Potential benefits of psychological interventions on immunity may be particularly relevant for wound healing and surgical recovery. In particular, interventions that target fear and distress before surgery and pain management following surgery may improve postoperative outcomes and recovery through modulation of endocrine and immune systems (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998).

CONCLUSIONS

Basic and applied PNI research studies have provided an encouraging foundation for characterizing the links between psychosocial and immunological factors. The current knowledge of PNI with respect to individual psychological differences, emotions, coping strategies, and interpersonal relationships has already had a significant impact on understanding the contribution that the psychosocial context has on immune function, health, and disease. Further understanding of the bidirectional relationships between brain, behavior, and immunity will be attained with theoretical and methodological refinements. In addition to these refinements, the next wave of PNI research will expand our knowledge of psychosocial factors and their role in the progression of immunologically mediated conditions, including HIV/AIDS, rheumatoid arthritis, certain cancers, and surgical recovery. From this knowledge, we can devise and implement effective interventions to enhance quality of life and improve health. Indeed, PNI embodies the biopsychosocial approach (Engel, 1977) that has come to define health psychology.

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