Stress, Immunity, and Susceptibility to Upper Respiratory Infectious Disease

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Psychoneuroimmunology is the study of relations between psychosocial factors, the central nervous system, the immune system, and health. To date, the human literature within this field has focused on a working model that stressful life events impact immune function, which in turn modifies host resistance to immune-related disease (Cohen & Herbert, 1996). Upper respiratory infections (URIs) have served as one of the primary disease models in this literature, and early prospective studies supported popular belief and provided compelling evidence that stressful life events and psychological distress predict biologically verified infectious illness (Cohen et al., 1998; Cohen, Tyrrell, & Smith, 1991, 1993; Stone et al., 1992). More recent attention has focused on possible mechanisms of this effect. In this regard, there is substantial evidence that stress is associated with changes in immune function (Segrestrom & Miller, 2004); however, the implications of stress-induced immune changes for susceptibility to disease largely remain to be established. This chapter provides an overview of the human literature in psychoneuroimmunology, exploring evidence linking stress to immune function and susceptibility to infectious disease. Particular attention is given to individual differences in the magnitude of stress-related changes in immunity as one plausible explanation for variability in susceptibility to infectious pathogens.

STRESS AND SUSCEPTIBILITY TO INFECTIOUS DISEASE

Stress is a generalized set of diverse host responses to external or internal stimuli (stressors) that are harmful or are perceived to be harmful (Lazarus & Folkman, 1984). There is consistent evidence that persons under stress report more symptoms of infectious disease and that stress results in greater health care utilization for these infections (Cohen & Williamson, 1991). Indeed, results from numerous prospective cohort studies document a direct relationship between negative life events and/or perceived stress and increased risk for symptoms of URI (Graham, Douglas, & Ryan, 1986; Stone, Reed, & Neale, 1987; Takkoche, Regueira, & Gestal-Otero, 2001; Turner Cobb & Steptoe, 1998). For example, Takkoche and colleagues (2001) found that among 1,149 adults followed for one year, greater stressful life events, trait negative affectivity, and perceived stress predicted...
greater self-reported symptoms of URI. Similarly, recent findings from a prospective epidemiologic study of 5,404 adults showed that psychological stress and trait negative mood predicted the onset of self-reported symptoms of influenza, with perceived stress and trait negative affect contributing independently to symptom report (Smoldersen, Vingerhoets, Croon, & Denollet, 2007). However, whereas self-reported symptoms of infectious disease may tap underlying pathology, it is also possible that they reflect a biased interpretation of physical sensations without underlying illness. The latter interpretation is supported by studies in which effects of stress on symptoms, but not verified disease, are observed, and by evidence that stress is associated with increased symptom reporting in general, not only with symptoms directly associated with infectious pathology (Cohen & Williamson, 1991).

In support of a relationship between stress and increased susceptibility to infectious disease, epidemiological studies in which the presence of pathology was verified by physician diagnosis or biological methods have found that major stressful life events, chronic family conflict, and disruptive daily events increase risk for upper respiratory disease (Graham et al., 1986; Meyer & Haggerty, 1962; Turner Cobb & Steptoe, 1996). For example, Meyer and Haggerty (1962) followed 100 members of 16 families for a 12-month period. Daily life events that disrupted family and personal life were four times more likely to precede than to follow new streptococcal and nonstreptococcal infections (as diagnosed by throat cultures and blood antibody levels) and associated symptomatology. Similar results were reported in a study of viral URIs in 235 members of 94 families (Graham et al., 1986). Here, number of major stressful and minor daily life events and ratings of psychological stress were positively associated with verified episodes and symptom days of respiratory illness. Turner Cobb and Steptoe (1996) also found that higher levels of life event stress were associated with increased clinically verified URI among 107 adults followed for 15 weeks. In sum, studies verifying infectious episodes suggest that stress increases risk for upper respiratory disease. However, community studies, such as these, do not control for the possible effects of stressful events on exposure to infectious agents. Indeed, increased incidence of infection in these studies may be attributable to stress-induced increases in exposure to infectious agents rather than to stress-induced immune modulation.

Several prospective studies have eliminated the possible role of psychological effects on exposure by experimentally inoculating healthy individuals with common cold viruses (viral challenge studies). Here, volunteers are assessed for degree of stress and then experimentally exposed to a cold virus or placebo. They are then kept in quarantine and monitored for the development of infection and illness. Early viral challenge studies were limited by a range of methodological weaknesses (Cohen & Williamson, 1991), including insufficient samples sizes and lack of control for factors known to influence susceptibility to viral infection (including preexisting antibodies to the infectious agent and age). Furthermore, the possible role of stress-elicited changes in such health practices as smoking and alcohol consumption was not considered. These limitations may account for initial failures to find consistent relations between stress and susceptibility to URI. In contrast, later viral challenge studies included multiple controls for factors known to be independently associated with susceptibility to viral infection (e.g., Cohen, Tyrell, & Smith, 1991, 1993; Cohen et al., 1998; Stone et al., 1992). These studies consistently found an association between stress and susceptibility to URI. For example, Cohen, Miller, and Rabin (1991) exposed 394 adult subjects to one of five upper respiratory viruses and assessed rates of infection and illness. Measures of negative life events in the past year, perceived stress, and negative affect were combined to form a stress index for each subject. After adjusting for control variables, the rates of verified infections and symptomatic illness increased with increasing values of the stress index for all five viruses. In a subsequent analysis of the data, Cohen, Tyrell, and Smith (1993) reported that perceived stress and negative affect were significant predictors of becoming infected (replicating virus), whereas negative life events increased the probability of infected people developing clinical symptoms. This pattern was independently reproduced in a smaller study of 17 subjects experimentally infected with rhinovirus that found a significant positive correlation of major negative life events, but not perceived stress.
or negative affect, with the development of clinical colds (Stone et al., 1992). Subsequent studies showed that severe chronic negative life events (primarily underemployment or unemployment and enduring interpersonal difficulties with family and/or friends), but not severe acute negative life events, predicted increased risk for the development of a clinical cold (Cohen et al., 1998) and that negative mood prior to viral exposure predicted colds and influenza of greater severity, as determined by the amount of mucus produced over the course of illness (Cohen et al. 1993). A large group of control factors have not been able to explain increased risk for colds among persons reporting greater stress in these studies, including age, sex, allergic status, body weight, season, and virus-specific antibody status before challenge. Smoking, alcohol consumption, diet, exercise, and sleep quality also have failed to account for the relationship between stress and illness.

More recent attention has turned to an examination of psychosocial factors that may decrease susceptibility to URI by regulating emotion-sensitive biological systems and/or encouraging health-enhancing behaviors. These factors include dispositional positive affect and social dispositions and networks. Initial findings from viral challenge studies suggest that susceptibility to URI decreases in a dose-response manner with increased diversity of social network and with trait sociability (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997; Cohen, Doyle, Turner, Alper, & Skoner, 2003b). Furthermore, higher positive affect has been associated with decreased incidence of objective symptoms of upper respiratory disease among infected people (Cohen, Alper, Doyle, Treanor, & Turner, 2006; Cohen, Doyle, Turner, Alper, & Skoner, 2003a). These relationships appear to be independent of negative emotional styles, baseline immunity, demographics, and health practices.

In sum, well-controlled studies corroborate prospective studies of community samples in indicating that psychological stress is associated with increased susceptibility to infectious disease. In addition, there is consistent evidence for increased symptom reporting under stress. More recent evidence also shows that positive emotional styles, sociability, and more diverse social networks are protective, being related to greater resistance to infection and the expression of fewer objective clinical symptoms.

MECHANISMS THAT MAY LINK STRESS TO DISEASE

A number of potential pathways exist through which stress may contribute to infectious pathology, including behavioral and immune mechanisms. In the first case, psychosocial factors could directly or indirectly influence health through changes in health-related behaviors. For example, poor nutritional status, smoking, drug and alcohol intake, lack of exercise, and poor sleep have all been shown to compromise immune status and health (e.g., Brolinson & Elliott, 2007; Diaz et al., 2002; Gleeson, 2007; Irwin et al., 1996; Kiecolt-Glaser & Glaser, 1988; McAllister-Sistilli et al., 1998; Romeo et al., 2007), with smoking (Cohen, Tyrrell, & Smith, 1993; Cohen et al., 1997), lack of regular exercise (Cohen et al., 1997), poorer diet and poorer sleep efficiency (Cohen et al., 2003b; Cohen, Doyle, Alper, Janicki-Deverts, & Turner, 2009) being associated with increased susceptibility to infectious disease. However, as noted earlier, these behavioral factors do not account for much of the stress-related variability among individuals in URI risk. Thus, other mechanisms must also be operating.

The influence of stress on the immune system is considered the primary biological pathway through which stress can influence infectious pathology. Numerous neurochemicals released during stress are associated with modulation of immune function, including catecholamines (epinephrine and norepinephrine) and corticosteroids (Rabin, 1999). In addition, direct anatomical links exist between the central nervous and immune systems, as evidenced by sympathetic and parasympathetic innervation of lymphoid organs (Felten & Olschowka, 1987; Livnat, Felten, Carlson, Bellinger, & Felten, 1985). Moreover, immune cells, which migrate between lymphoid organs and the peripheral blood stream, have receptors for a variety of hormones and neurotransmitters that are released during stress, including catecholamines, corticosteroids, and various neuropeptides (Stevens-Felten & Bellinger, 1997). Activation of these receptors has immunomodulatory effects,
altering leukocyte function and providing a biological pathway for the influences of stress on susceptibility to infectious disease. Pathways connecting the central nervous and immune systems are bidirectional, with peripheral immune activation signaling the brain to effect behavioral, affective, and cognitive changes that typically accompany infectious disease (Maier & Watkins, 1998). Indeed, it is now understood that alterations in cytokine secretion that result from innate immune responses to infection mediate many of these effects (Blalock & Smith, 2007; Maier & Watkins, 1998), penetrating the blood–brain barrier directly through active transport mechanisms (Banks & Kastin, 1991) or indirectly through activation of the afferent vagus nerve (Tracey, 2002) to stimulate the production of central proinflammatory cytokines that modulate brain function. Thus, empirical evidence supports a communication network linking the nervous, endocrine, and immune systems. It is likely that psychological stress modulates immune function through direct activation of this network, by means of neural pathways that innervate lymphoid tissue and the activation of neuroendocrine systems that result in the release of hormones (e.g., cortisol) that bind to receptors on immune cells.

Conversely, activation of the immune system in response to infection results in the secretion of cytokines that affect the central nervous system, resulting in symptoms of sickness, central activation of the hypothalamic-pituitary-adrenal axis, and peripheral release of corticosteroids, which function to shut off the immune response (Blalock & Smith, 2007). Thus, these pathways create a systemic feedback loop that fine-tunes the magnitude of the immune response.

A few studies have begun to examine whether the immune system mediates the association of chronic stressors with susceptibility to URI. However, this literature is in its infancy. Cohen and colleagues (1997) reported that higher urinary levels of epinephrine, but not norepinephrine or cortisol, measured prior to viral challenge predicted risk for developing a clinical cold; however, this effect was independent of the positive association of chronic negative life events with URI risk. In another study by the same group (Cohen et al., 2002), negative life events and physiologic responses to an acute stressor were assessed among 115 adults who were then followed for 12 weeks for the development of a URI. The results showed that individuals who produced high levels of cortisol to the acute stressor (cortisol reactors) and had high levels of negative life events were at greater risk for URI than were low reactors or those with low levels of negative life events. Immune responses to acute stress also interacted with weekly perceived stress levels to predict self-reported colds. Here, low immune reactors were more likely to report cold symptoms during weeks of high perceived stress when compared to low-stress weeks, whereas high immune reactors did not exhibit differences in colds as a function of weekly stress level (Cohen et al., 2002). Thus, initial evidence suggests that physiologic responses to acute stress may contribute to susceptibility to infectious disease in the face of life event stress; however, further research is necessary to fully understand the nature of these associations.

Other studies suggest that the magnitude of the local inflammatory response to infection may mediate positive associations of stress with symptom severity. For example, Cohen, Doyle, and Skoner (1999) showed that nasal levels of the proinflammatory cytokine interleukin (IL)-6 contributed to the relationship between perceived stress and greater symptoms of URI among 55 adults experimentally infected with influenza A virus. Similarly, nasal levels of IL-6 have been shown to partially account for the inverse association of objective and subjective symptoms of illness with positive emotional style following exposure to a rhinovirus (Doyle, Gentile, & Cohen, 2006). Together, these results are consistent with the hypothesis that IL-6 acts as a biological mediator linking psychological stress to the expression of infectious illness.

Other studies have failed to provide support for neuroendocrine or immune mediators of the association between psychosocial factors and susceptibility to infectious disease (Cohen et al., 1998). In this regard, it should be noted that the immune response to viral pathogens involves a complex cascade of events. Researchers measuring immune function in humans are limited to a few basic markers that provide a poor overall estimate of the body's ability to resist disease. Hence, it remains likely that multiple immune components operate as pathways in the link between stress...
and susceptibility to disease. The remainder of this chapter focuses on evidence that stress is accompanied by changes in immune function, which may in turn render individuals more susceptible to infectious disease. First, however, a brief overview of measures of immune function is offered.

MEASUREMENTS OF IMMUNOCOMPETENCE

The immune system is a highly complex, interactive network, and there is no single, adequate measure of its status (Cuninck, Lysle, Armfield, & Rabin, 1988). Human studies are limited to quantitative and functional assessments of immune parameters sampled from peripheral blood, nasal lavage, and saliva. These tests include assessment of the numbers and functional abilities of various subgroups of immune cells. In enumerative assays, the various populations of leukocytes are identified and counted by staining the unique surface molecules of each cell type with fluorescent reagents. Using this technique, the percentages or absolute numbers of circulating T-lymphocytes (and their subsets), B lymphocytes, macrophages, and NK cells can be determined. It should be noted that the normal range for circulating numbers of these cell subtypes is quite large, so that small changes in circulating levels are unlikely to have any clinical significance in healthy individuals.

In addition to quantitative measures are a number of functional assessments that provide an in vitro measure of the ability of immune cells to perform specific activities. For example, lymphocyte proliferation assays are commonly used in human research. In this assay, leukocytes are incubated with experimental antigens called mitogens that nonspecifically stimulate T or B lymphocytes to divide. The rate of resultant proliferation is taken as a measure of immunocompetence, with greater cell division reflecting a more effective immune response. Commonly used mitogens include phytohemagglutinin (PHA) and concanavalin A (Con A), which stimulate the proliferation of T lymphocytes, and pokeweed mitogen (PWM), which activates T and B lymphocytes. NK cell cytotoxicity is another frequently assessed measure of immune function. NK cells are a subset of lymphoid cells with the ability to spontaneously kill some human tumor and virally infected cells. NK cell cytotoxicity is a measure of the ability of NK cells to destroy tumor cells in vitro. Enhanced NK cell activity may also be measured by incubating NK cells with such stimulatory cytokines as IL-2 or interferon-gamma. The ability of these cytokines to increase NK cell activity is then compared to cytotoxicity levels found in unstimulated samples. Finally, in vitro assays are also used to measure cytokine concentrations in peripheral circulation, a measure of current immune activation, or the production of cytokines by lymphocytes and monocytes following stimulation with endotoxin (e.g., lipopolysaccharide) or mitogens, a measure of immune competence.

In contrast to these laboratory measures, other indices of immunocompetence are performed in vivo, assessing immune function in the living organism. One such measure is antibody production in response to inoculation with an antigen. Here, individuals ingest or are inoculated with an antigen, for example, influenza vaccine or rabbit albumin, and the amount of antibody produced in response to that specific antigen is quantified in serum. Certain antibody responses (e.g., salivary immunoglobulin A) can also be measured in saliva. In general, greater antibody response is thought to reflect better immunocompetence; however, elevated antibody levels to latent herpes virus may reflect a reactivation of virus resulting from the weakened ability of the immune system to keep such viruses in check. Therefore, high antibody levels to herpes viruses (e.g., Epstein-Barr virus, or EBV) are often interpreted as indicating poorer immunocompetence (Kiecolt-Glaser & Glaser, 1987).

CHRONIC STRESSORS AND IMMUNITY

It is now widely accepted that chronic naturalistic stress (as measured by both self-report and objective life events) is reliably associated with modulation of functional aspects of the immune system. Indeed, a comprehensive meta-analysis of more than 300 empirical articles examining associations of stress with the immune system revealed 23 studies that examined the impact of chronic
stress (Segerstrom & Miller, 2004).Although there were no consistent associations between chronic stress and enumerative measures of immunity, stress was inversely related to functional measures of the immune system, including NK cell activity, lymphocyte proliferation to PHA and Con A, IL-2 cytokine production, and antibody response to influenza vaccination. Many studies also show that chronic stress is associated with increased antibody levels to latent herpes viruses, suggesting decreases in the competence of the immune system to control latent virus activity (for a review, see Herbert & Cohen, 1993a; Pierson, Mehta, & Stowe, 2007). Stress has also been associated with decreases in total serum immunoglobulin (Ig)-M (Herbert & Cohen, 1993a) and in the concentration of total salivary IgA (Evans, Bristow, Hucklebridge, Clow, & Walters, 1993). Finally, more recent evidence shows a positive association of chronic stress with circulating levels of markers of inflammation, such as C-reactive protein (CRP) and IL-6 (Kiecolt-Glaser et al., 2003; Miller, Rohleder, & Cole, 2008; von Kanel et al., 2006).

To date, the majority of studies in this literature have examined the influence of naturally occurring stressors on immune function. Numerous life event stressors and environmental demands have been associated with a down-regulation of immune function, including job stress (Arnot et al., 1987), long-term unemployment (Arnot et al., 1987; Dorian et al., 1985), loss of an intimate relationship because of death (Kemeny et al., 1995; Schleifer, Keller, Camerino, Thornton, & Stein, 1983) or separation and divorce (Kennedy, Kiecolt-Glaser & Glaser, 1988), caring for a relative with dementia (Kiecolt-Glaser, Glaser, et al., 1987), marital discord (Kiecolt-Glaser et al., 1997), forced displacement from home by war (Sabioncello et al., 2000), space flight (Pierson et al., 2007), natural disasters such as earthquakes (Soloman, Segerstrom, Grohr, Kemeny, & Fahey, 1997) and hurricanes (Ironson et al., 1997), missile attacks in the 1991 Persian Gulf War (Weiss et al., 1996), and residing near a damaged nuclear power plant (McKinnon, Weiss, Reynolds, Bowles, & Baum, 1989). Of interest, there is also evidence that alterations in immunity may persist (i.e., fail to habituate) for months or years with prolonged stressor exposure (e.g., Baum, 1990; Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998; Kiecolt-Glaser, Glaser, et al., 1987).

**Naturalistic Stressors**

Considerable research indicates that chronic interpersonal difficulties are particularly provocative stressors, being associated reliably with the down-regulation of immune function. For example, studies show that loss of a close relationship from death or divorce is associated with a reduction in lymphocyte proliferation responses and NK cell activity when compared with bereavement levels (Schleifer et al., 1983) or nonbereaved controls (Bartrop, Lazarus, Luckhurst, Kiloh, & Penny, 1977; Gerra et al., 2003; Goodkin et al., 1996; Kemeny et al., 1995). In these studies, immunologic alterations persisted from 2 to 14 months after the loss, with evidence showing that the degree of immune changes associated with bereavement may be related to the severity of concomitant depressed mood (Irwin, Daniells, Smith, Bloom, & Weiner, 1987; Linn, Linn, & Jenson, 1984).

Separation, divorce, and marital conflict have similarly been associated with immune alterations. For example, Kiecolt-Glaser, Fisher, et al (1987) found decreased proliferative responses to PHA, higher antibodies to EBV, and lower percentages of circulating NK and T-helper cells among 16 recently separated or divorced women than among a matched group of married women. Higher antibody levels to two latent herpes viruses—EBV and herpes simplex Type 1—were also found among separated or divorced men when compared to matched, married controls (Kiecolt-Glaser et al., 1988). In a study of newlyweds, couples who expressed greater hostility during a discussion of marital problems showed the most pronounced down-regulation of immune function, as measured by lower NK cell activity and proliferative responses to PHA and Con A over a 24-hour period and by higher antibody titers to EBV (Kiecolt-Glaser et al., 1993). Similar findings were reported in a study of 31 older couples who had been married an average of 42 years. Here, men and women who showed greater suppression of lymphocyte proliferative response and higher antibodies to EBV displayed more negative behavior during conflict and described their usual marital disagreements as
more negative than did individuals who showed more protective immune responses (Kiecolt-Glaser et al., 1997).

Other studies have examined the chronic stress of caring for a sick child or a spouse with Alzheimer’s disease. Here, it has been demonstrated that caregivers suffer higher levels of mortality, depression, more frequent health complaints, and decreased life satisfaction as a result of the stressfulness of the caregiving experience (Bodnar & Kiecolt-Glaser, 1994; Light & Lebowitz, 1989; Schulz & Beach, 1999). Consistent evidence also shows that caregiving is associated with immune dysregulation. When compared to well-matched controls, caregivers show poorer antibody responses to vaccinations (Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000; Vedhara et al., 1999), lower percentages of circulating lymphocytes and T-helper cells (Kiecolt-Glaser, Glaser, et al., 1987), poorer NK cell response to stimulatory cytokines (IL-2 and interferon-gamma; Esterling, Kiecolt-Glaser, & Glaser, 1996), higher antibody titers to EBV (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994), and greater increases in IL-6 over a six-year period (Kiecolt-Glaser et al., 2003). It is of interest that caregivers also show slower healing of a 3.5-mm punch biopsy wound (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995), making it possible that decreases in immune function observed among caregivers lead to an impairment of wound healing. In summary, there is a large body of evidence demonstrating that such chronic naturalistic stressors as loss through death or divorce, marital conflict, or caring for a sick relative modulate immune function, with immune changes occurring in a direction that is consistent with increased susceptibility to immune-related disease.

EXAMINATION STRESS

Numerous studies in the PNI literature have employed a quasi-experimental design, examining immune changes from before to after a naturally occurring event. Probably best known in this literature is the series of studies by Kiecolt-Glaser, Glaser, and colleagues (e.g., Glaser et al., 1999; Kiecolt-Glaser et al., 1986; Kiecolt-Glaser et al., 1984) examining immune responses of students to examination stress. In their meta-analytic review of the literature, Segerstrom and Miller (2004) identified 63 studies examining the impact of brief naturalistic stress (95% examination stress) on immune parameters. Results of the meta-analysis provided no evidence that examination stress affected the number of cells in peripheral circulation. However, compared to measures taken at less stressful times (e.g., summer vacation), studies consistently show modulation of immune function during examinations. These stress effects include (a) a decrease in production of the cytokine interferon-gamma, which stimulates natural and cellular immune functions; (b) an increase in the production of IL-6, which stimulates inflammation, and IL-10, which inhibits T-helper 1 cytokine production; (c) a decrease in lymphocyte proliferation in response to mitogen stimulation; (d) a decrease in NK cell cytotoxicity; and (e) an increase in antibody production to latent virus, particularly EBV (Segerstrom & Miller, 2004). Taken together, these changes suggest that acute naturalistic stress is associated with a suppression of cellular immunity and an enhancement of humoral immunity, including inflammation. These immune changes may contribute to the slower healing of wounds that is observed at examination time. For example, in dental students, punch biopsy wounds placed three days before examinations healed an average of 40% slower than did wounds made in the same students during the summer vacation (Marucha, Kiecolt-Glaser, & Favageh, 1998).

VACCINATION RESPONSES

Other investigators have explored the impact of stress on ability to produce antibodies (develop immunity) to novel antigens. This in vivo immune measure is directly related to host resistance and may provide a more proximate mechanism of stress–infectious disease associations than in vitro markers of immune competence, which provide limited information about the status of the highly integrated and complex immune system. Although not all findings are consistent, reviews of the
literature examining the impact of stress on antibody response to immunization generally support
an association of chronic psychological stress with suppression of secondary antibody response
(Burns, Carroll, Ring, & Drayson, 2003; Cohen et al., 2001; Wetherell & Vedhara, 2007). These
conclusions are consistent with a large animal literature indicating that chronic stress is associated
with reduced ability to mount an antibody response on exposure to novel antigens (Moynihan,
Cohen, & Ader, 1994).

The most consistent findings in the human literature come from studies that measure
severe enduring stress (e.g., caring for a spouse with Alzheimer’s disease) or a traitlike stress characteristic,
such as trait negative affect. These enduring measures of stress have been associated with poorer
antibody responses to a number of vaccinations, including influenza (e.g., Kiecolt-Glaser, Glaser,
Gravenstein, Malarkey, & Sheridan, 1996; Phillips, Carroll, Burns, & Drayson, 2005; Vedhara et al.,
1999), rubella (Morag, Morag, Reichenbaum, Lerner, & Yirmiya, 1999); pneumococcal polysaccha-
ride (Glaser et al., 2000), and hepatitis B (Burns, Ring, Drayson, & Carroll, 2002; Marsland, Cohen,
Rabin, & Manuck, 2001), with older adults being at particular risk for stress-related reductions in
antibody response (Glaser et al., 1998). Higher levels of perceived stress around the time of vaccina-
tion have also been associated with poorer antibody responses to meningitis C (Burns et al., 2003)
and influenza (Miller et al., 2004; Moynihan et al., 2004) vaccines. For example, Miller and
colleagues (2004) recorded perceived stress four times a day for the 10 days following administration
of the influenza vaccine among 83 healthy, young adults. Results showed that higher mean levels of
stress across this 10-day period predicted lower antibody response to one of three influenza viral
strains at one- and four-month follow-up. Taken together, these results suggest that an individual’s
psychological “state” following the antigen challenge and antibody formation may negatively influence
their levels of antibody response.

A similar pattern of findings is observed when individuals are exposed to nonpathogenic antigens, to which the individual has not had prior exposure. For example, Snyder, Roghmann, and Sigal (1993) demonstrated that three weeks after inoculation with an innocuous novel antigen (keyhole limpet hemocyanin, or KLH), individuals reporting more psychological distress and “bad” life events mounted a lower lymphocyte proliferation response to KLH than did individuals who reported “good” life events and social support. Similarly, Stone, Neale, Cox, and Napoli (1994) had volunteers ingest a capsule containing an innocuous novel antigen daily for 12 weeks. During this period, volunteers also completed daily dairies, recording positive and negative daily events, and gave saliva samples to assess secretory immunoglobulin A (sIgA), an antibody to the novel antigen. Here, more undesirable daily events were associated with lower, and more desirable with higher, antibody to the novel antigen. Thus, immune dysregulation associated with psychological stress can down-regulate both virus-specific antibody responses and T-cell-proliferative responses to specific antigens.

The impact of chronic stress on vaccination response appears to influence not only the magnitude of peak antibody levels but also their maintenance over time. In this regard, several studies suggest that chronic stress has a detrimental impact on the maintenance of antibody response (Burns et al., 2003; Glaser et al., 2000). For example, among older adults administered the pneumococcal pneumonia vaccine, dementia caregivers and matched controls mounted similar antibody responses at two weeks, one month, and three months postvaccination, but caregivers had significantly lower titers at six-month follow-up (Glaser et al., 2000). These results suggest that stress may impact the rate of deterioration of protection following vaccination.

It remains to be determined at what point during the process of antibody production and mainten-
ance stress impacts antibody levels. As noted, studies that employ stable (enduring) measures of
chronic stress that likely reflect elevated distress over the entire process show an inverse association
of stress with magnitude of immune response. However, findings from studies employing more
acute measures of stress—for example, perceived stress, recent life events, or level of daily hassles
that are annoying or unpleasant—are less consistent. If it is assumed that physiological or behav-
ioral responses to stress are the mechanisms of stress-related changes in immune function, then the
timing of the event is a critical factor in predicting immune response. Consistent with such specula-
tion, Snyder et al. (1993) found that daily minor stressors were correlated more strongly (negatively)
with antibody response to immunization with KLH than were major negative life events. Similarly,
Miller et al. (2004) showed that daily stress across the 10 days following influenza vaccine predicted
lower antibody levels at one- and four-month follow-up. However, other studies find no significant
associations of psychological distress and daily hassles around the time of exposure to a novel anti-
gen with magnitude of antibody response (Glaser et al., 1992; Petrie, Booth, Pennebaker, Davison, &
Thomas, 1995). Furthermore, findings from two recent experimental studies show that exposure to
acute laboratory stress (mental arithmetic or physical exercise) immediately prior to influenza and
meningococcal A vaccination resulted in higher peak antibody responses when compared with the
responses of individuals randomly assigned to a no-stress control condition (Edwards et al., 2008,
2006). Thus, it is possible that acute and chronic stress have differential and time-dependent effects
on vaccination response. This is consistent with evidence that acute stress is associated with activation
of innate inflammatory processes that likely potentiate the initial antibody response, whereas
chronic stress is associated with the down-regulation of cellular immune processes involved in
antibody production and maintenance (Segerstrom & Miller, 2004).

**INDIVIDUAL DIFFERENCES IN IMMUNE RESPONSES TO NATURALISTIC STRESS**

Not all individuals demonstrate immune changes following stressful life events. Indeed, there is
marked variability among individuals in the magnitude of their immune responses to stress. In this
regard, it is suggested that negative events have an impact on immune function only when they lead
to negative affect or psychological distress. It is proposed that such distress is elicited when persons
perceive that demands imposed by life events exceed their ability to cope (Lazarus & Folkman,
1984). In support of this model, meta-analytic reviews of the literature conclude that depressed
mood states in clinical and nonclinical samples modulate various immune components, as evidenced
by a down-regulation of NK cell activity, lowered proliferative response of lymphocytes to
the mitogens PHA, Con A, and PWM, and decreases in the total numbers of circulating lympho-
cytes, NK, B, and T-cells (Herbert & Cohen, 1993b; Zorilla et al., 2001). These depression-related
effects suggest a down-regulation of components of natural and cellular immune function. More
recent evidence also supports depression-related activation of innate inflammatory pathways, as
marked by higher levels of proinflammatory cytokines (IL-6, IL-1, tumor necrosis factor [TNF]-α)
and such acute-phase proteins as CRP (Irwin & Miller, 2007).

A number of studies provide further evidence that emotional reactions and personality character-
istics associated with affect regulation contribute to interindividual variability in the magnitude of
immune responses to life circumstances (e.g., Locke et al., 1984; Segerstrom, 2001). For example,
decreased positive mood partially mediated associations of the stress of relocating with reduced
NK cell cytotoxicity among healthy older adults (Lutgendorf, Vitaliano, Tripp-Reimer, Hervey, &
Lubaroff, 1999). In regard to personality characteristics, dispositional optimism—that is, general-
ized positive expectations for the future—often buffers the immune system from the effects of life
event stress (Segerstrom, 2005). However, at times when stressors are more difficult, persistent,
and uncontrollable, optimists can show greater down-regulation of cellular immune function than
can pessimists (Segerstrom, 2005). In support of popular belief, recent findings suggest that indi-
viduals who characterize themselves by such moods as happy, pleased, relaxed, and lively show
higher NK cell number and activity (Valdimarsdottir & Bovbjerg, 1997), better control of latent
EBV (Lutgendorf et al., 2001), increased T-helper Type 1 (TH1) cytokine (IL-2 and interferon-
gamma) responses to in vitro stimulation with live influenza virus (Costanzo et al., 2004), higher
antibody responses to hepatitis B vaccination, as measured following the first two doses of the
vaccine (Marsland, Cohen, Rabin, & Manuck, 2006), and decreased incidence of experimentally
induced URIs (Cohen et al., 2003b, 2006) than do their less positive counterparts. Indeed, recent
evidence suggests that previously reported associations of negative affective styles with decreased
antibody response to vaccination and increased susceptibility to viral infection may reflect diminished positive affect, rather than the presence of negative mood traits (Cohen et al., 2006; Marsland et al., 2006). Taken together, these findings suggest that individual differences in affective style may contribute to variability in immune response, either as a main effect or by buffering the negative impact of adverse life events.

Interindividual variability in the magnitude of immune responses to stress may also be attributable to social buffers (i.e., interpersonal resources). In this regard, literature reviews document abundant evidence that higher levels of social support and more positive social relationships improve immunoregulation and are associated with decreased morbidity and mortality (House, Landis, & Umberson, 1988; Uchino, Cacioppo, & Kiecolt-Glaser, 1996). For example, perceived inadequacy of interpersonal relationships, as measured by self-report, is related to distress and diminished immune function among medical students taking examinations (e.g., Kiecolt-Glaser & Glaser, 1991) and caregivers of relatives with dementia (Kiecolt-Glaser, Glaser, et al., 1987). There is also evidence that supportive interpersonal relationships buffer the adverse impact of negative life events on immune function. For example, Baron, Cutrona, Hicklin, Russell, and Lubaroff (1990) found that social support was associated with higher NK cell activity and greater proliferative responses to PHA (but not Con A) among 23 women whose husbands were being treated for urological cancer. Similarly, Glaser et al. (1992) showed that when compared with individuals reporting low levels of social support, medical students with more support mounted greater antibody responses to hepatitis B vaccination. In sum, although few studies examine individual differences in immune response to naturalistic stressors, it is clear that dispositional factors and interpersonal resources moderate emotional responses to life circumstances, with distress (as measured by symptoms of anxiety or depression) or reductions in positive moods being associated with immune changes that are consistent with increased risk for infectious disease.

**Intervention Studies**

A number of studies have investigated whether psychological interventions designed to lower emotional distress also reduce or prevent stress-related changes in immunity. These studies use a diverse array of psychological interventions. Findings are inconsistent, with some studies showing intervention-related improvements in immune function and others not. Indeed, a meta-analytic review of this literature concluded that there is only modest evidence that interventions can reliably alter immune parameters (Miller & Cohen, 2001). Miller and Cohen (2001) attributed the many null findings to theoretical and methodological limitations of existing studies, including a general failure to (a) focus on individuals with high levels of stress, (b) use interventions demonstrated to be effective at reducing stress, or (c) measure immune parameters that are typically dysregulated by stress. When limited to studies that recruited populations experiencing heightened levels of stress, results are more consistent and document intervention-related improvements in immune function (e.g., Andersen et al., 2004; Antoni et al., 1991; Antoni et al., 2009; Carlson, Speca, Faris, & Patel, 2007; Fawzy et al., 1990; Hewson-Bower & Drummond, 2001; Witek-Janusek et al., 2008). To date, the majority of effective interventions have employed stress-management techniques, including coping skills training, cognitive restructuring, relaxation training, mindfulness-based stress reduction (MBSR), and social support.

One of the most widely cited early studies in this literature evaluated the effects of a six-session group intervention for patients with malignant melanoma (Fawzy et al., 1990). When compared with patients who received routine medical care, the intervention, comprised of psychological support and training in relaxation, stress management, problem-solving and coping skills, effectively enhanced coping and reduced psychological distress and was associated with an increase in NK cell percentage and activity. Another study suggests the down-regulation of immune components known to accompany notification of positive-HIV-antibody status can be attenuated by a 10-week group cognitive-behavioral stress-management (CBSM) intervention (Antoni et al., 1991). More
recent attention has focused on the psychological and immune benefit of stress-management training for women with breast cancer. For example, both CBM and MBSR interventions have been shown to facilitate psychological adaptation and improve cellular immune function in this population (Andersen et al., 2004; Antoni et al., 2009; Carlson et al., 2007; McGregor et al., 2004; Wittek-Janusek et al., 2008), with positive associations of intervention-related improvements in psychological and immune function (McGregor et al., 2004). In sum, recent findings from studies that focus on populations with chronic diseases or heightened levels of stress suggest that interventions designed to manage or reduce stress are associated with improved immune function or an amelioration of stress-related changes in immunity. Again, the health significance of these positive, but relatively small, immunologic changes remains unclear.

SUMMARY OF NATURALISTIC STRESS

It is well established that naturalistic stress modulates functional aspects of immunity. The most consistent alterations suggest that stress suppresses immune function over protracted periods during particularly intense or prolonged stressors. Despite these central tendencies, not all individuals demonstrate immune changes following stressful life events. Indeed, there is marked variability among individuals in the magnitude of immune responses to naturalistic stress. This interindividual variability has been attributed to a number of psychosocial buffers, including trait characteristics and interpersonal resources that are proposed to modulate the negative impact of adverse life events. To date, it remains unclear how stress may contribute to changes in the immune system. Potential pathways include the impact of stress on health practices (e.g., diet, exercise, or sleep) and/or stress-induced activation of physiological pathways (e.g., neuroendocrine parameters). Few naturalistic investigations have examined relations between health practices, neuroendocrine factors, and immune measures during stress. However, growing evidence suggests that sleep disturbances may play an important role in the modulation of immune function during naturalistic stress. For example, Ironson et al. (1997) showed that the onset of sleep problems following Hurricane Andrew partially mediated the relationship between posttraumatic stress symptoms and lowered NK cell activity in a community sample affected by this disaster. Furthermore, psychological stress is reliably linked to disrupted sleep (e.g., Mezick et al., 2009), and poorer sleep efficiency and shorter sleep duration predict a greater likelihood of developing a cold following experimental exposure to a rhinovirus (Cohen et al., 2009).

LABORATORY STRESSORS AND IMMUNITY

In order to examine whether psychological stress, independent of concomitant changes in health behaviors, alters immune components, investigators have examined the effects of acute laboratory stress on immune functioning in healthy individuals. These controlled, experimental studies also provide a means to explore neuroendocrine pathways associated with stress and immunity. Findings from these studies reveal significant immunologic alterations following exposure to a range of standardized, short-term laboratory stressors that are generally perceived by subjects as aversive, demanding, or interpersonally challenging. Stressors employed in these studies include mental arithmetic, unsolvable puzzles, evaluative speech tasks, electric shocks and/or loud noise, marital discussions involving conflict, and disturbing films depicting combat surgery (for a review, see Segerstrom & Miller, 2004). In contrast to some of the less common naturalistic stressors (e.g., bereavement or caring for a relative with Alzheimer’s disease), some of these challenges may more accurately characterize everyday hassles and thus account for more observed interindividual variability in immune response to stress and susceptibility to disease.

The effects of short-term laboratory challenge on immune function are not consistent with longer term changes seen following chronic forms of naturalistic stress. In their meta-analytic review, Segerstrom and Miller (2004) identified 85 studies that examined the impact of acute psychological
stressors on immune parameters. Consistent findings support reliable changes in immune measures from pre- to post-task. In contrast to the chronic-stress literature, these changes include a transient increase in the number of NK cells, and cytotoxic T and large granular lymphocytes (neutrophils) in peripheral circulation, and in secretory IgA in saliva (Segerstrom & Miller, 2004). As a result of increased peripheral numbers of cytotoxic T-cells, acute stressors are also associated with a reliable decline in the ratio of helper-T to cytotoxic-T lymphocytes.

With regard to functional measures, acute laboratory stress has been associated with an increase in NK cell cytotoxicity, largely resulting from the increase in circulating numbers of NK cells (Segerstrom & Miller, 2004). Recent evidence also shows that circulating levels of the proinflammatory cytokines IL-6 and IL-1 beta are increased following acute challenge (Steptoe, Hamer, & Chida, 2007), with an increase in the rate of stimulated production of both IL-6 and interferon-gamma, cytokines that stimulate activation of macrophages and NK cells, respectively (Segerstrom & Miller, 2004). Taken together, the aforementioned changes suggest an up-regulation of natural immune function in response to acute stress. It has been suggested that this response may be adaptive and a component of the fight-or-flight response, preparing the organism for possible infection or injury (Dhabhar & McEwan, 1997, 2001; Segerstrom & Miller, 2004). In contrast, evidence suggests a down-regulation of acquired immune function under conditions of acute challenge. Here, findings are more consistent with the effects of chronic naturalistic stress, with acute laboratory stress resulting in a reduction in lymphocyte proliferation on exposure to PHA, Con A, and PWM. In this regard, it is suggested that it is not adaptive to invest energy in immune responses that take longer to develop (Dhabhar & McEwan, 1997, 2001; Segerstrom & Miller, 2004).

How the transient immune responses seen following discrete acute stress relate to those responses associated with chronic naturalistic stress is unknown. However, it is hypothesized that alternative physiological mechanisms may account for these differential effects (Herbert & Cohen, 1993a; Segerstrom & Miller, 2004). In the case of acute psychological stress, research findings suggest that immune responses are largely mediated by the autonomic nervous system (ANS). For example, it has been demonstrated that immune outcomes assessed after a laboratory stressor covary with the magnitude of sympathetic activation elicited under the same stimulus conditions (e.g., Manuck, Cohen, Rabin, Muldoon, & Bachen, 1991; Zakowski, McAllister, Deal, & Baum, 1992). Pharmacological studies also indicate that the administration of physiological doses of sympathetic stimulants (e.g., exogenous catecholamines or isoproterenol) invokes functional modulations of cellular immunity that are similar to those seen during acute challenge (e.g., Crarry et al., 1983). More direct evidence for sympathetic mediation derives from the observation that stress-related immune responses are blocked by adrenergic receptor inhibition (Bachen et al., 1995; Benschop et al., 1994). Indeed, it has been demonstrated that administration of an adrenergic inhibitor prevents stress-induced alterations in a variety of immune parameters, including proliferative responses to PHA and Con A, NK cell number and activity, and the ratio of T-helper to T-cytotoxic cells (Bachen et al., 1995; Benschop et al., 1994).

More recent evidence has examined the role of the parasympathetic branch of the ANS, which generally acts in opposition to the sympathetic branch of the system. Here, findings suggest that activation of efferent parasympathetic (vagal) neurons leads to the suppression of proinflammatory cytokine release through activation of nicotinic acetylcholine receptors expressed on macrophages and other immune cells involved in the inflammatory response, thus decreasing local and systemic inflammation (Czura & Tracey, 2005). Indeed, low levels of cardiac vagal activity, as measured by noninvasive indicators of heart rate variability, are associated with decreased stimulated production of the proinflammatory cytokines IL-6 and TNF-alpha (Marsland et al., 2007). This raises the possibility that increases in circulating levels of IL-6 observed one to two hours following acute psychological stress result from the decreases in parasympathetic activation that accompany acute challenge.

The exact mechanism of autonomic-immune mediation remains unclear. Evidence suggests that activation of the sympathetic nervous system may influence the immune system by both active and
passive processes (Marsland et al., 1997). Under conditions of acute stress, an increase in arterial blood pressure driven by activation of the sympathetic nervous system causes fluid to filter out of circulation into extravascular spaces, leading to a passive increase in the concentration of all nondiffusible constituents of blood, including blood cells and cytokines (Jern, Wadenvik, Mark, Hallgren, & Jern, 1989). It has been shown that stress-induced increases in the concentration of circulating T-lymphocyte and NK cells are partly, but not wholly, attributable to this hemoconcentration effect (Marsland et al., 1997). The observation that this passive effect only partly accounts for acute increases in cytotoxic-T and NK cell numbers suggests that more active mechanisms are also operating (Bachen, Marsland, Manuck, & Cohen, 1998). In this regard, it has been demonstrated that sympathetically mediated alterations in adhesion molecules on cell surfaces enable cytotoxic-T and NK cells to be mobilized into circulation from the peripheral margins of blood vessels (Mills & Dimsdale, 1996). Evidence also shows that acute stress results in rapid activation of the transcription factor nuclear factor kB (NF-kB) in peripheral blood mononuclear cells, by means of norepinephrine-dependent pathways (Bierhaus et al., 2003), and that activation of NF-kB results in the expression of genes for the production of proinflammatory cytokines. Parasympathetic activation has the opposite effect, inhibiting NF-kB activation (Pavlov & Tracey, 2005). Evidence also suggests that activation of the hypothalamic-pituitary-adrenocortical (HPA) system may also modulate immune function that accompanies acute challenge (Kunz-Ebrecht, Mohamed-Ali, Feldman, Kirschbaum, & Steptoe, 2003). Indeed, individuals who exhibited high sympathetic responses to acute stress also showed a stress-induced increase in plasma cortisol levels, when compared with low sympathetic responders, who showed no change in cortisol following stress (Cacioppo et al., 1998; Cohen et al., 2000). This finding is noteworthy, given extensive evidence that cortisol is associated with longer term down-regulation of cellular immune function (Cacioppo et al., 1995).

In contrast to the rapid immune responses associated with acute stress, exposure to more chronic stress leads to relatively stable shifts in the baseline levels of immune measures (Herbert & Cohen, 1993a; Segerstrom & Miller, 2004). Here, it is widely accepted that chronic stress can regulate immune function by direct activation of the HPA and sympathetic-adrenal-medullary axes, leading to an increase in the release of glucocorticoids (cortisol in humans). In contrast to activation of the sympathetic nervous system, which stimulates inflammatory pathways (Søndergaard, Ostrowski, Ullum, Pedersen, 2000), the HPA axis generally down-regulates immune function. Glucocorticoid receptors are expressed on a variety of immune cells, including lymphocytes and monocytes; and ligand binding to these receptors has a number of inhibitory effects, including reduced production of proinflammatory cytokines, decreased expression of cell adhesion molecules necessary for the inflammatory response, and decreased mitogen-stimulated lymphocyte proliferation (e.g., Almawi, Beyhun, Rahme, & Rieder, 1996; Cato & Wade, 1996). Based on knowledge that glucocorticoids suppress the inflammatory response, one would predict that stress would be associated with suppression of inflammatory processes. However, evidence supports the opposite, with chronic stress being associated with increased systemic inflammation and greater risk for inflammatory conditions. It has been suggested that this apparent paradox is the result of a reduction in the sensitivity of glucocorticoid receptors on immune cells, likely a result of prolonged exposure to cortisol, rendering the immune system less responsive to signals that turn off the inflammatory cascade (Miller, Cohen, & Ritchey, 2002). Animal studies support this model and show that glucocorticoid resistance is restricted to macrophages and is the result of impaired nuclear translocation of glucocorticoid receptors and a decrease in transcriptional suppression of NF-kB (Quan et al., 2003; Stark, Avitsur, Hunzeker, Padgett, & Sheridan, 2002; Stark et al., 2001).

**Individual Differences in Immune Responses to Acute Laboratory Stress**

Although it is well established that acute and chronic stress are associated with functional and enumerative aspects of immunity, an examination of response variability reveals that individuals differ substantially in the magnitude of their immunologic reactivity to stress (Kiecolt-Glaser, Cacioppo,
Malarkey, & Glaser, 1992; Marsland, Henderson, Chambers, & Baum, 2002), with many individuals exhibiting little or no response. It is suggested that these differences reflect variability among individuals in the magnitude of their autonomic and HPA hormone responsivity to stress, aspects of individual difference that have been demonstrated to be relatively stable over time (Cohen & Hamrick, 2003;Dimsdale, Young, Moore, & Strauss, 1987). Evidence suggests that interindividual variability of behaviorally evoked immune reactivity is also reproducible over time and across stressor tasks and may therefore denote a relatively stable dimension of individual differences (Cohen & Hamrick, 2003; Marsland et al., 2002; Marsland, Manuck, Fazzari, Stewart, & Rabin, 1995). The existence of such dispositional characteristics makes it conceivable that exaggerated immune responsivity to behavioral challenge may be implicated in the pathogenesis of immunemediated disease, such as host resistance to infection (Cohen & Manuck, 1995). One possibility is that individuals who show exaggerated immune responses to laboratory stressors exhibit similarly exaggerated reactions to everyday hassles (e.g., work demands and time pressures), rendering them more susceptible to infectious disease.

More recent attention has focused on the possibility that individual differences in physiologic reactivity moderate associations of psychological stress with susceptibility to infectious illness (Cohen et al., 2002). As mentioned previously, Cohen and colleagues found that individuals who showed the largest increases in cortisol following acute stress (cortisol reactors) and had high negative life event scores were more likely to develop verified URIIs over the course of a three-month follow-up period. In contrast, low immune responders (T-cytotoxic cell number, NK cell number, and cytotoxicity) were more likely to experience a URI during high-stress weeks than high immune responders. Boyce and colleagues (1993, 1995) also found that cardiovascular and immune response to acute stress were associated with increased URI risk under conditions of heightened naturalistic stress in a study of young children (ages 3–5 years). However, here, it was the children who showed larger stress-induced immune reactions (increases in B-cell numbers and in lymphocyte proliferation to PWM) who were at greatest URI risk. Interpretation of these effects is unclear because these immune changes are not typically observed following acute stress in adults. Furthermore, the interaction between immune reactivity and stress, as a predictor of infection, was attributable in large part to an unexpectedly lower incidence of disease for high-reactive children not exposed to naturalistic stress (Cohen & Manuck, 1995).

Other studies have examined whether individual differences in sympathetic and immune reactions to acute stress predict antibody responses to vaccination, an in vivo measure of host resistance to infection. Marsland et al. (2001) found that graduate students who mounted lower antibody responses to hepatitis B vaccination, as measured following the first two doses of vaccine, showed greater suppression of lymphocyte proliferation to PHA following laboratory stress than did higher antibody responders. Similarly, Burns et al. (2002) found that individuals who responded to acute stress with larger cardiac sympathetic activation exhibited lower antibody titers to hepatitis B vaccination than did their less reactive counterparts. Cacioppo (1994) also found that sympathetic activation predicted response to an influenza vaccine, with larger cardiac sympathetic activation to acute challenge being associated with poorer vaccine-specific T-cell responses. Taken together, initial evidence suggests that individual differences in the magnitude of stress-induced activation of sympathetic and HPA pathways, as well as suppression of immune function, may have clinical significance, being related to an in vivo immune response relevant for protection against infection and, in the case of cortisol, increased URI risk. Further prospective studies employing measures of individual difference as predictors of susceptibility to disease are warranted.

CONCLUSION

In support of popular belief, there is now substantial evidence for the role of psychological stress in susceptibility to URI disease (e.g., Cohen et al., 1991, 1993; Cohen et al., 1998, Stone et al. 1992). One possible mediator of this relationship is the modulation of immune function, thereby
influencing host susceptibility to infectious pathogens. In this regard, it is well established that both major stressful experiences (e.g., bereavement or natural disasters) and more minor stressors (e.g., arguing with a spouse or facing an acute laboratory challenge) are associated with changes in immune function. Although the clinical significance of stress-related changes in many measures of immune function remains to be determined, recent evidence suggests that stress-related increases in the production of proinflammatory cytokines may result in greater susceptibility to URI. In this regard, chronic stress has been associated with a decrease in the sensitivity of immune cells to cortisol, a hormone that down-regulates the production of proinflammatory cytokines and thus terminates the inflammatory response. This decrease in glucocorticoid receptor sensitivity, which likely results from chronically elevated levels of cortisol, may account for the increased levels of proinflammatory cytokines, such as IL-6, that accompany chronic stress. Initial findings suggest that increases in nasal secretory levels of IL-6 mediate associations of perceived stress and lower positive emotional style with subjective and objective symptom severity following viral challenge (Cohen et al., 1999; Doyle et al., 2006). Thus, chronic stress may interfere with the immune system’s ability to respond to hormonal signals that turn off the inflammatory response, resulting in increased inflammation and susceptibility to symptoms of infection.

To date, it remains unclear whether associations between psychological factors and vulnerability to infection are attributable to stress-induced changes in immunity. Indeed, the clinical significance of relatively small immunologic alterations has not been established. Many associations of stress with immune function and health may be attributable to changes in health behaviors. Growing evidence shows, however, that the autonomic nervous system mediates some immunologic changes during acute stress. Furthermore, it is likely that naturalistic stress modulates immune function through activation of neuroendocrine systems that result in the release of hormones, such as cortisol, that bind to receptors on immune cells. It has been demonstrated that individuals differ substantially in the magnitude of their immunologic responsivity to stress, with evidence suggesting that these response tendencies may reflect stable attributes of individuals. Recent evidence suggests that individuals who respond to acute laboratory stressors with large increases in cortisol are at greater risk for URI when exposed to stressors in the natural environment (Cohen et al., 2002; Cohen et al., 2009). Hence, it is conceivable that there is a meaningful distribution of differences in physiologic reactivity that may form a basis for differences in susceptibility to infection.

Future research on PNI needs to continue to focus on whether the type, magnitude, or pattern of stress-related immune modulation influences host resistance, for it is likely that substantial fluctuations in immune function can be tolerated without influencing susceptibility to disease. The role of the immune system in susceptibility to infectious disease needs to be addressed with prospective studies, measuring psychosocial parameters and immune mediators relevant for the disease under study, controlling for health behavior, and documenting disease outcomes.

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