

# Stress, Immunity, and Susceptibility to Infectious Disease



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**P**sychoimmunology is the study of relations between behavioral 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 (S. Cohen & Herbert, 1996). Upper respiratory infections (URI) have served as the primary disease model in this literature and recent prospective studies support popular belief and provide compelling evidence that stressful life events and psychological distress predict biologically verified infectious illness (S. Cohen et al., 1998; S. Cohen, Tyrrell, & A. P. Smith, 1991, 1993; Stone et al., 1992). To date, however, the mechanism(s) of this effect remains unclear. Although there is substantial evidence that stress is associated with changes in immune function (Herbert & S. Cohen, 1993), the implications of stress-induced immune changes for susceptibility to disease have not been 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

There is consistent evidence that persons under stress report more symptoms of URI, and that stress results in greater health care utilization for URI (S. Cohen & Williamson, 1991). For example, Stone, Reed, and Neale (1987) found that for 79 couples followed over 3 months, daily life events rated as undesirable increased 3 to 4 days prior to the onset of self-reported symptoms of URI. However, whereas self-reported symptoms of URI may tap underlying pathology, it is also possible that they reflect a biased interpretation of physical sensations without underlying illness. This possibility is supported by studies in which effects of stress are observed on symptom reporting, but not verified disease (S. Cohen & Williamson, 1991).

In support of a relation between stress and increased susceptibility to URI, epidemiological studies in which the pres-

ence 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 (Grahami, Douglas, & Ryan, 1986; Meyer & Haggerty, 1962; Turner Cobb & Steptoe, 1996). For example, Meyer and Haggerty followed 100 members of sixteen 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. Similarly, Turner Cobb and Steptoe (1996) found that among 107 adults followed for 15 weeks, individuals who developed clinically verified URI ( $n = 29$ ) endorsed higher levels of life event stress than individuals who remained healthy. In another study, individuals who perceived their families as being more "chaotic" or "rigid" were found to be at greater risk of verified influenza B infection than individuals who described their families as more "balanced" (Clover, Abell, Becker, Crawford, & Ramsey, 1989). However, community studies like these do not control for the possible effects of stressful life 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 immunosuppression.

More recent studies provide control for exposure by experimentally inoculating healthy individuals with common cold or flu viruses (viral challenge studies). Here, volunteers are assessed for degree of stress and then experimentally exposed to a cold or influenza virus or placebo. They are then kept in quarantine and monitored for the development of infection and illness. Early viral inoculation studies were limited by a range of methodological weaknesses, including insufficient sample 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 health practices, such 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 (S. Cohen & Williamson, 1991). In contrast, recent viral challenge studies have included multiple controls for factors known to be independently associated with susceptibility to viral infection (S. Cohen et al., 1991, 1993, 1998; Stone et al., 1992). These studies consistently find an association between stress and susceptibility to URI. For example, among 394 healthy adults, stressful life events, perceptions of current stress, and negative affect all predicted the probability of developing a biologically verified cold, with greater stress related linearly to susceptibility (S. Cohen et al., 1991, 1993). This dose-response relation was found across five different URI viruses. In addition, recent research suggests that the longer the duration of stressful life events, the greater the risk of becoming infected (S. Cohen et al., 1998). A large number of control factors (including, age, sex, allergic status, body weight, season, and virus-specific antibody status before challenge) have not been able to explain the increased risk for

colds among persons reporting greater stress. Smoking, alcohol consumption, diet, exercise, and sleep quality have also failed to account for the relation between stress and illness in these studies (S. Cohen et al., 1991). Similar results have been independently replicated by Stone et al. (1992).

In addition to episode onset, severity of infectious disease appears to be influenced by stress. For example, S. Cohen et al. (1995) found that negative mood measured prior to viral exposure was related to colds and influenza of greater severity, as determined by the amount of mucus produced over the course of illness. In sum, recent well-controlled studies corroborate prospective studies of community samples in indicating that psychological stress is associated with increased susceptibility to upper respiratory disease. In addition, there is consistent evidence for increased symptom reporting under stress.

### MECHANISMS THAT MAY LINK STRESS TO DISEASE

A number of potential pathways exist through which an association between stress and infectious pathology might occur, 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 (Irwin, Lacher, & Caldwell, 1992; Kiecolt-Glaser & Glaser, 1988; Kronfol et al., 1989; Kusaka, Kondou, & Morimoto, 1992). However, as noted earlier, these behavioral factors do not account for much of the variability among individuals in infectious disease susceptibility. Hence, 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), corticosteroids, and opiates (e.g., Darko, Irwin, Risch, & Gillin, 1992; Herberman & Ortaldo, 1981; Irwin et al., 1992). 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 bloodstream, have receptors for a variety of hormones and neurotransmitters that are released during stress (see Plaut, 1987). Thus, there is extensive evidence for direct anatomical and functional links between the central nervous and immune systems, providing a biological pathway for the influences of stress on susceptibility to infectious disease.

To date, the only study to examine whether the immune system mediates the association of chronic stressors and colds found little evidence for the role of either numbers of circulating white blood cell populations or NK cell activity (S. Cohen et al., 1998). However, 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 other 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 the individual 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 (Cunnick, Lysle, Armfield, & Rabin, 1988). Human studies are limited to quantitative and functional assessments of immune parameters sampled from peripheral blood 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 specific 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.

With respect to functional assessments, 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. Natural killer cell cytotoxicity is also frequently measured. NK cells are a subset of lymphoid cells with the ability to spontaneously kill some human tumor and virally infected cells. The ability of NK cells to destroy tumor cells (NK cell activity) is most commonly assessed by a chromium release assay. Enhanced NK cell activity may also be measured by incubating NK cells with stimulatory cytokines, such as interleukin-2 (IL-2) or gamma-interferon (IFN- $\gamma$ ). 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 the circulation or the production of cytokines by lymphocytes and monocytes following stimulation with mitogens.

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 (e.g., vaccination with recombinant hepatitis B vaccine or keyhole limpet hemocyanin). Here, individuals ingest or are inoculated with an antigen 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 weakened ability of the immune system to keep such viruses in check. Therefore, higher antibody levels to herpes viruses (e.g., Epstein-Barr virus) are often interpreted as indicating poorer immunocompetence (Kiecolt-Glaser & Glaser, 1987).

### CHRONIC STRESSORS AND IMMUNITY

Several reviews (Bachen, Marsland, Manuck, & S. Cohen, 1998; Kiecolt-Glaser & Glaser, 1991; O'Leary, 1990) and a meta-analysis of the literature on stress and immunity in humans (Herbert & S. Cohen, 1993) conclude that naturalistic stress (as measured by both self-report and objective life events) is reliably associated with modulation of functional and enumerative aspects of the immune system. The most consistent functional alterations include reduced NK cell activity and lymphocyte proliferation to PHA and Con A, and increased antibody levels to latent herpes viruses, suggesting decreases in the competence of the immune system to control latent virus activity. In terms of enumerative parameters, chronic stress is associated with decreases in percentages or absolute numbers of circulating B cells, T cells, T-helper cells, T suppressor/cytotoxic cells and NK cells. Stress has also been associated with decreases in total serum IgM (Herbert & S. Cohen, 1993) and in the concentration of total salivary IgA (Evans, Bristow, Hucklebridge, Clow, & Walters, 1993).

To date, the majority of studies in this literature has examined the influence of naturally occurring stressors on immune function. Numerous life event stressors and environmental demands have been associated with immune changes, including job stress (Arnetz et al., 1987), long-term unemployment (Arnetz et al., 1987; Dorian et al., 1985), loss of an intimate relationship due to death (Kemeny et al., 1995; Schleifer, Keller, Camerino, Thornton, & Stein, 1983) or separation/divorce (Kennedy, Kiecolt-Glaser, & Glaser, 1988), caring for a relative with Alzheimer's disease (Kiecolt-Glaser, Glaser, Shuttleworth, Dyer, Ogrocki, & Speicher, 1987), marital conflict (Kiecolt-Glaser et al., 1997), and natural disasters, such as earthquakes (Soloman, Segerstrom, Grohr, Kemeny, & Fahey, 1997) and hurricanes (Ironson et al., 1997), missile attacks during the 1991 Persian Gulf War (Weiss et al., 1996) and residing near a damaged nuclear power plant (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989). Interestingly, there is also evidence that alterations in immunity may persist (i.e., fail to habituate) with prolonged stressor exposure (e.g., Baum, 1990; Kiecolt-Glaser & Glaser, 1991; Kiecolt-Glaser, Glaser, et al., 1987).

#### Naturalistic Stressors

One stressor that has been associated consistently with altered immunity is the loss of a close personal relationship from either death or divorce. Early studies demonstrated that lymphocyte proliferative responses among bereaved subjects were lower after the death of a loved one than during the

pre-bereavement period (Schleifer et al., 1983), and were also lower than in nonbereaved controls (Bartrop, Lazarus, Luckhurst, Kiloh, & Penny, 1977). In these studies, immunologic alterations persisted from 2 to 14 months after the loss. Recent studies support these findings (e.g., Goodkin et al., 1996; Kemeny et al., 1995) and also demonstrate that the degree of immune change associated with bereavement may be related to the severity of concomitant depressed mood. For example, Irwin, Daniels, T. L. Smith, Bloom, and Weiner (1987) found that levels of depression among a group of bereaved women correlated inversely with NK cell activity ( $r = .89$ ). Similarly, M. W. Linn, B. S. Linn, and Jensen (1984) found reduced lymphocyte proliferation to PHA in bereaved spouses, but only among those who also had depressive symptomatology.

Loss of a relationship from separation or divorce has also been associated reliably with immune alterations. In this regard, Kiecolt-Glaser, Fisher, et al. (1987) found decreased proliferative responses to PHA, higher antibodies to Epstein-Barr virus, 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. Similarly, in a study of 32 men, individuals who had been separated or divorced for up to 3 years had higher antibody levels to latent viruses than matched, married controls (Kiecolt-Glaser et al., 1988). Other studies have demonstrated that poorer marital quality among married couples is related to greater distress, loneliness, and latent virus antibody response. For example, in a study of newlyweds, couples who expressed greater hostility during a discussion of marital problems showed the most pronounced suppression of immune function, as measured by natural killer cell activity and proliferative responses to PHA and Con A over a 24-hour period, and by higher antibody titers to latent Epstein-Barr virus. Similar findings were reported recently 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 latent Epstein-Barr virus displayed more negative behavior during conflict, and described their usual marital disagreements as more negative, than individuals who showed better immune responses (Kiecolt-Glaser et al., 1997).

Several studies have also examined immune responses to the stress associated with caring for a family member with Alzheimer's disease (AD). Here, it has been demonstrated that caregivers frequently suffer higher levels of depression, more frequent health complaints, and decreased life satisfaction, due to the stressfulness of the caregiving experience (Light & Lebowitz, 1989; S. H. Zarit, Orr, & J. M. Zarit, 1985). Kiecolt-Glaser and colleagues published a series of studies examining immunologic alterations associated with caregiving for a family member with AD. To date, results indicate changes in several cellular immune components supportive of immunosuppression, including lower percentages of total lymphocytes and T-helper subsets, lower *in vitro* interleukin-1B responses to lipopolysaccharide stimulation, poorer NK cell response to stimulatory cytokines (IFN- $\gamma$  and IL-2), and higher antibody titers to Epstein-Barr virus (Esterling,

Kiecolt-Glaser, Bodnar, & Glaser, 1994). Interestingly, caregivers also showed slower healing of a 3.5 mm punch biopsy wound (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995), making it possible that the decreases in immune function observed among caregivers leads to an impairment in wound healing. Taken together, then, there is a large body of evidence demonstrating that chronic naturalistic stressors, such as loss due to death or divorce, marital conflict, or caring for a relative with AD, modulate immune function.

### 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 are the series of studies by Kiecolt-Glaser, Glaser and colleagues (e.g., Kiecolt-Glaser et al., 1986; Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984) examining immune responses of medical students to examination stress. Compared to measures taken at less stressful times (e.g., just following a vacation), students demonstrate modulation of a number of immune components during examinations, including decreases in the total number of circulating T lymphocytes and NK cells, and in lymphocyte response to mitogen stimulation, lowered gamma interferon production and reduced NK cell activity (Dobbin, Harth, McCain, Martin, & Cousin, 1991; Glaser, Kiecolt-Glaser, Stout, Tarr, Speicher, Holliday, 1985; Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986; Kiecolt-Glaser, & Glaser, 1987). During exams, students have also shown increased levels of circulating antibodies to Epstein Barr and other herpes viruses (Glaser et al., 1993; Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985) and slower healing of a punch biopsy wound (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998).

### Vaccination Responses

Other investigations have explored the impact of perceived stress on the ability to produce antibodies (develop immunity) to novel antigens. These *in vivo* immune measures may provide a more proximate mechanism of stress-infectious disease associations because they are directly related to host resistance. Results of early retrospective studies examining relations between life event stressors and antibody response to influenza viruses are inconclusive, possibly due to the memory distortion and bias inherent in recalling stressful events. For example, Green, Betts, and Ochitill (1978) found that higher perceived life change stress, during the 12 months preceding inoculation with an influenza virus, was associated with a lower antibody response; however, others reported no significant relations (Locke & Heisel, 1977; Locke, Hurst, & Heisel, 1979). Results of prospective studies are more consistent, indicating that higher levels of perceived stress around the time of influenza vaccination are associated with lower antibody responses (Bovbjerg, Manne, & Gross, 1990; Locke et al., 1979).

One limitation of using a common live virus, such as influenza vaccine, to examine development of immunity is the

likelihood that individuals have already been exposed to the virus. Consequently, antibody response is influenced by factors such as preexisting antibody levels, the amount of time since prior sensitization, and ongoing environmental exposure. In order to avoid these potential confounds, more recent prospective studies have examined antibody responses to novel antigens, to which the individual has not had prior exposure. Once again, results suggest that an individual's psychological "state" around the time of antigen challenge and antibody formation may influence their level of antibody response. For example, Snyder, Roghmann, and Sigal (1993) demonstrated that 3 weeks after inoculation with keyhole limpet hemocyanin (KLH), individuals reporting more psychological distress and "bad" life events mounted a lower lymphocyte proliferation response to KLH than individuals who reported "good" life events and social support. Similarly, Stone et al. (1994) had volunteers ingest a capsule containing an innocuous novel antigen daily for 12 weeks. During this period, volunteers also completed daily diaries, recording positive and negative daily events, and gave daily saliva samples to assess secretory immunoglobulin A (sIgA), an antibody to the novel antigen. Once again, more desirable daily events were associated with greater, and more undesirable events with less, antibody to the novel antigen.

Other research has explored the impact of perceived stress on antibody response to hepatitis B vaccination. To date, these studies have yielded inconsistent findings. Glaser et al. (1992) followed medical students who received each of three hepatitis B inoculations during an examination period. Those individuals who mounted an adequate immune response to the first dose of vaccine (25% of sample) reported less stress and anxiety to subsequent examinations than those who did not seroconvert until later. However, there was no prospective relation between perceived stress and antibody response to the first vaccination in the series. In another study, Jabaajj et al. (1993) demonstrated that greater perceived stress around the time of the initial vaccination was associated with lower final antibody levels, as assessed after a series of three vaccinations. In contrast, Petry, Weems, and Livingstone (1991) found a positive relation between negatively perceived stress, irascibility, depression, and anxiety and peak antibody titers.

Reasons for contradictory findings across studies are unclear. Comparisons are made difficult by variability in study design, including psychological constructs measured, and timing of psychological and immune measurements. In regard to the latter, it is possible that psychological stress influences antibody response to hepatitis B vaccination in a time-dependent fashion, with stress having a greater impact in the earlier phases of the immune response around the time of initial antibody formation. In support of this possibility, Jabaajj et al. (1993) demonstrated that whereas psychological distress at the time of the initial vaccination was associated with lower peak antibody responses following a complete vaccination series, levels of distress around the time of the final booster vaccination were unrelated to the final immune response. Other studies measuring stress later in the antibody response also failed to find an association or found opposite effects (Marsland et al., in press; Petry et al., 1991). In sum,

there is consistent evidence that high levels of perceived stress around the time of antigen challenge are associated with a decreased *in vivo* immune response. It remains to be determined whether a reduction in the magnitude of antibody response to vaccinations translates into increased susceptibility to infection; however, it has been demonstrated that individuals who mount lower antibody responses lose their protective status more quickly (Hollinger, 1989).

#### 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 only have an impact on immune function 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, a recent meta-analysis of the literature concluded 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 lymphocytes, NK and B cells, and T-cell subpopulations (Herbert & S. Cohen, 1993). Furthermore, a number of studies have demonstrated that level of perceived distress moderates the impact of life event stress on immune function. For example, Locke and colleagues (1984) found that among students who reported high levels of life-change stress, those with many psychological symptoms of distress, including anxiety and depression, had lower NK cell activity than similarly stressed peers with few symptoms. Thus, there is some consensus that psychosocial adaptation to stress modulates immune function, with poor coping and emotional distress being associated with greater changes in immune components.

Interindividual variability in the magnitude of immune responses to stress may also be attributable to psychosocial buffers (e.g., interpersonal resources) that modulate the negative impact of adverse life events. 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), caregivers of relatives with AD (Kiecolt-Glaser, Glaser et al., 1987), and psychiatric inpatients on the day of admission (Kiecolt-Glaser et al., 1984). There is also evidence that supportive interpersonal relationships buffer the adverse impact of negative life events on immune function (Kennedy et al., 1988). 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, there is some evidence that psychosocial adaptation modulates immune function, with distress (as measured by symptoms of anxiety or depression) being associated with greater immunosuppression.

### Intervention Studies

Related to the stress-buffering hypothesis, studies have also examined whether interventions designed to lower emotional distress also reduce or prevent stress-related changes in immunity. These studies have used a diverse array of psychological interventions, including stress management training, relaxation, hypnosis, cognitive-behavioral strategies, exercise, and coping skills training. In general, results are consistent with improved immune function, or an amelioration of stress-related changes (Kiecolt-Glaser & Glaser, 1992). For example, Kiecolt-Glaser et al. (1985) demonstrated increases in NK cell activity and decreases in HSV antibody titers following progressive relaxation training in a group of older adults. One of the most widely cited studies in this literature evaluated the effects of a six-session group intervention for patients with malignant melanoma (R. I. Fawzy et al., 1993). 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 the percentage of NK cells and NK cell activity, and a decrease in the percentage of T-helper cells. Other studies suggest that the down regulation of immune components known to accompany notification of positive HIV antibody status can be attenuated by aerobic exercise training (La Perriere et al., 1990, 1991) or by cognitive-behavioral stress management intervention (Antoni et al., 1991). However, not all findings are consistent. An 8-week stress reduction intervention was not associated with changes in immunological measures in HIV-seropositive men when compared with waiting list controls (Coates, McKusick, Kuno, & Sities, 1989). Similarly, Kiecolt-Glaser et al. (1986) found that a hypnotic/relaxation intervention did not attenuate the decline in NK cell activity associated with examination stress in medical students. Despite these negative findings, the majority of studies in this literature 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, however, the health significance of these positive, but relatively small, immunologic changes remains unknown.

### Persistence of Immunological Changes

Many studies suggest that chronic naturalistic stressors are capable of evoking psychological and immunological changes that continue long after a stressful event has ended. For example, extended stress responses were found in former

caregivers of AD relatives who had died at least 2 years earlier (Esterling et al., 1994). Similar ongoing responses were observed among residents of Three-Mile Island (TMI) more than 6 years after the nuclear plant accident occurred. In comparison to a group of demographically similar controls, many TMI-area residents continued to exhibit heightened levels of distress, elevated 24-hour urinary catecholamine excretion, increased latent herpes virus antibodies, and diminished numbers of B lymphocytes, T-suppressor/cytotoxic lymphocytes, and NK cells (Baum, 1990; McKinnon et al., 1989). These differences were not attributable to health behavior, because the two groups did not differ on diet, smoking, health, medications, or substance abuse.

It is unclear why stress-elicited changes in immune function persist over prolonged periods of time. As previously discussed (see Bachen et al., 1998), one possibility is that stressful life events may initiate a series of other related stressors, such as financial difficulties or social isolation, as well as behavioral or mood changes that could perpetuate immune alterations (Kasl, 1984; Kiecolt-Glaser & Glaser, 1988; Stone, Marco, Cruise, Cox, & Neal, 1996). In addition, cognitions, such as intrusive thoughts or images, may be important in sustaining stress reactions even when the initiating event no longer exists (Baum, 1990; Baum, L. Cohen, & Hall, 1993). For example, McKinnon et al. (1989) found that intrusive thoughts or imagery about the TMI accident and its health effects were related to elevated anxiety and immunologic changes in TMI-area residents. Similarly, intrusive thoughts about upcoming stressful events, such as a medical school examination (Workman & LaVia, 1987) or waiting for HIV test results (Antoni et al., 1990), have been shown to be related to poorer proliferative responses to PHA.

## SUMMARY OF NATURALISTIC STRESS

In sum, it is well established that naturalistic stress modulates both functional and enumerative aspects of immunity. The most consistent alterations suggest that stress may suppress immune function over protracted intervals 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 stress. This interindividual variability has been attributed to a number of psychosocial buffers, including interpersonal resources and coping skills, which are thought 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., changes in diet, exercise or sleep) and/or the stress-induced activation of more physiological pathways (e.g., neuroendocrine parameters). Few naturalistic investigations have examined relations between health practices, neuroendocrine factors, and immune measures during stress (Herbert & S. Cohen, 1993). However, recent studies indicate that sleep disturbances may play an important role in the modulation of immune function during naturalistic stress. For example, Ironson et al. (1997) found evidence that the onset of

sleep problems following Hurricane Andrew partially mediated the relation between posttraumatic stress symptoms and lowered NK cell activity in a community sample affected by this disaster. Such findings are consistent with earlier reports that partial sleep deprivation is associated with reduced NK cell activity in humans (Irwin et al., 1992, 1994).

### LABORATORY STRESSORS AND IMMUNITY

In order to examine whether psychological stress, independent of concomitant changes in health behaviors, alters immune components, investigators have recently begun to examine 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 Kiecolt-Glaser, Cacioppo, Malarkey, & Glaser, 1992). In contrast to some of the less common naturalistic stressors (e.g., bereavement or caring for a relative with AD), 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 immediate effects of short-term laboratory challenge on immune function are not entirely consistent with longer term changes seen following chronic forms of naturalistic stress. In contrast to the chronic stress literature, acute stressors are usually associated with a transient increase in the number of circulating T-suppressor/cytotoxic lymphocytes and NK cells (Bachen et al., 1992; Brosschot, Benschop, Godaert, Heijen, & Ballieux, 1992; Herbert et al., 1994; Manuck, S. Cohen, Rabin, Muldoon, & Bachen, 1991; Marsland et al., 1995; Naliboff et al., 1991; Zakowski, McCallister, Deal, & Baum, 1992). Decreases in the ratio of T-helper to T-suppressor lymphocytes (CD4:CD8 ratio) have also been reported (Bachen et al., 1992; Brosschot et al., 1992; Landmann et al., 1984). Less consistent findings include alterations in the number of T-helper and B-cell populations (Bachen et al., 1992; Caggiula et al., 1995; Gerritsen, Heijnen, Wiegant, Bermond, & Frijda, 1996; Marsland et al., 1995).

With regard to functional measures, both chronic naturalistic and acute laboratory stress have been associated with reduced lymphocyte mitogenesis on exposure to PHA, Con A, and PWM (Bachen et al., 1992; Caggiula et al., 1995; Gerritsen et al., 1996; Manuck et al., 1991; Marsland et al., 1995; Weisse et al., 1990; Zakowski, L. Cohen, Hall, Wollman, & Baum, 1994); however, not all results are consistent (Brosschot et al., 1992; Zakowski et al., 1994). In contrast to the decreases associated with chronic stress, a growing number of studies suggest that NK cell activity is increased following acute challenge (Cacioppo, 1994;

Naliboff et al., 1991; but not Sieber, Rodin, Larson, Ortega, & Cummings, 1992). Indeed, recent evidence suggests that the NK cell response to stress is biphasic, with an immediate increase in activity, followed by a later decrease to below baseline levels (Delahanty et al., 1996; Schedlowski et al., 1993).

Immune responses to acute stress appear to be rapid and short lasting, occurring as early as 5 minutes after stressor onset (Herbert et al., 1994) and returning to baseline levels within 15 minutes, in the case of cell subset redistribution (Brosschot et al., 1992). Changes in functional measures have been shown to last longer, with reductions in lymphocyte proliferation remaining for at least 90 minutes after challenge (Weisse et al., 1990; Zakowski et al., 1992); elevations in NK cell activity may persist for at least 1 hour (Gerritsen et al., 1996). Studies that include both sexes demonstrate that immune responses to acute stress are similar among men and women (Herbert et al., 1994).

How the transient immune responses seen following discrete acute stress relate to those associated with chronic naturalistic stress is unknown. However, it is hypothesized that alternative physiological mechanisms may account for these differential effects (Herbert & S. Cohen, 1993). In the case of acute psychological stress, research findings suggest that immune responses are largely mediated by activation of the sympathetic nervous system. 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 (Landmann et al., 1984; Manuck et al., 1991; Zakowski et al., 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 mental stress (Crary et al., 1983; van Tits et al., 1990). Finally, the speed of the immune reactions to acute stress makes it unlikely that other, slower responding hormones (e.g., cortisol) mediate these effects. Indeed, two studies have demonstrated immune changes in the absence of concomitant changes in cortisol levels (Manuck et al., 1991; Zakowski et al., 1992).

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-suppressor/cytotoxic cells (Bachen et al., 1995; Benschop et al., 1995).

The exact mechanism of sympathetic-immune mediation remains unclear. Recent 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 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 lymphocytes (C. Jern, Wadenvik, Mark, Hallgren, & S. Jern, 1989). It is

possible to mathematically correct changes in lymphocyte subtype numbers to determine the degree to which the passive concentration of blood constituents accounts for changes in circulating cell numbers. By using this arithmetic correction, it has been shown that increases in the concentration of circulating T-suppressor/cytotoxic and NK cells following acute stress are partly, but not wholly, attributable to hemoconcentration (Marsland et al., 1997). Interestingly, an active decrease in the circulating numbers of T-helper and B lymphocytes during stress was also revealed, but only when hemoconcentration was taken into account. This raises the possibility that there is a stress-induced decrease in these cell subtypes, which is frequently masked by a simultaneous reduction in plasma volume.

The observation that hemoconcentration only partly accounts for acute rises in T-suppressor/cytotoxic and NK cell numbers suggests that more active mechanisms of immune response must also be implicated (see Bachen et al., 1995, 1998, for further discussion). In this regard, it is thought that alterations in adhesion molecules on cell surfaces may enable these cell populations to be mobilized into circulation from the endothelium of blood vessels. Recent studies indicate that catecholamines prevent the adherence of human NK cells to endothelial tissue *in vitro* (Benshop, Oostveen, Heijen, & Ballieux, 1993). It has also been demonstrated that acute psychological stress alters the expression of surface adhesion molecules on lymphocytes (Mills & Dimsdale, 1996). Finally, changes in mitogen-stimulated lymphocyte proliferation may, in part, reflect sympathetically mediated impairments of IL-2 production by T-helper lymphocytes (Heilig, Irwin, Grewal, & Sercarz, 1993) and decreased antigen-presentation by macrophages (Heilig et al., 1993).

In contrast to the rapid, short-lived immune responses associated with acute stress, exposure to more chronic stressors leads to relatively stable shifts in the baseline levels of immune measures (Herbert & S. Cohen, 1993). Here, it is likely that more prolonged secretion of stress hormones induces more stable changes in neuroendocrine pathways, such as modification of receptor density and sensitivity (Chrousos & Gold, 1992; Herbert & S. Cohen, 1993). Alternatively, the more delayed release of other hormones (e.g., cortisol, ACTH, and B-endorphin) may account for differential effects. In this regard, Goodkin et al. (1996) reported that plasma cortisol levels correlated inversely with proliferative response to PHA. Similarly, Antoni and colleagues (1990) found that anxiety levels and intrusive thoughts were associated with higher plasma cortisol levels and lower proliferative responses to PHA among individuals who were awaiting the results of HIV testing. Mechanisms aside, there is recent evidence that immune responses to acute and chronic stress may be related, with individuals who report higher levels of life event stress and daily hassles mounting greater immunologic responses to acute stress (Brosschot et al., 1994; Pike et al., 1997).

Although it is now well established that acute and chronic stress are associated with both 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 et al., 1992; Manuck et al., 1991; Naliboff et al., 1991), with many individuals exhibiting little or no response (Glaser, Kiecolt-Glaser, Stout et al., 1985; Manuck et al., 1991; Schleifer et al., 1983). It is suggested that these differences reflect variability among individuals in the magnitude of their sympathetic responsivity to stress, an aspect of individual difference that has been demonstrated to be relatively stable over time (Dimsdale, Young, Moore, & Struss, 1987). Recent findings provide initial evidence that interindividual variability of behaviorally evoked immune reactivity is also reproducible on retesting, and may therefore denote a stable dimension of individual differences (Marsland et al., 1995; Mills, Haeri, & Dimsdale, 1995). In these studies, the stability of cellular immune reactions to a laboratory stressor was assessed on two occasions, separated by a 2- or 6-week interval. Significant test-retest correlations were observed for the magnitude of change in proliferative response to PHA (but not Con A), numbers of T-suppressor/cytotoxic and NK cells, and the ratio of T-helper to T-suppressor/cytotoxic cells ( $r$ s ranged from .40-.60; Marsland et al., 1995; Mills et al., 1995). Similarly, another study has demonstrated that individuals who mount greater heart rate responses (an index of sympathetic arousal) to a speech task show greater increases in NK cell activity when exposed to a mental arithmetic task on a different day than do persons exhibiting low heart rate responses under the same stimulus conditions (Sgoutas-Emch et al., 1994). Taken together, these findings suggest that individuals vary consistently in the magnitude of their cellular immune reactivity to acute stress.

The existence of such dispositional characteristics makes it conceivable that exaggerated immune responsivity to behavioral challenge may be implicated in the pathogenesis of immune-related disease, such as host resistance to infection (S. 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 immunocompromised and hence more susceptible to infectious disease. To date, one published study has explored whether individual differences in immune reactivity moderate associations between psychological stress and infectious illness (Boyce et al., 1995). Boyce and colleagues found that children (age 3-5) showing the largest stress-induced increases in circulating numbers of B cells and in lymphocyte proliferation to PWM were at greatest risk for developing upper respiratory infections in response to a naturalistic stressor. However, interpretation of these effects is unclear because 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 (S. Cohen & Manuck, 1995). Moreover, previous studies involving adults have not found reliable increases in circulating B cell numbers or proliferative response to PWM following stress. Although intriguing, further replications of these findings are needed, not only with children, but using adult samples as well.



Marsland, S. Cohen, Rabin, and Manuck (in press) further explored whether individual differences in immune reactivity are germane to susceptibility to infectious disease. This study examined whether immune reactivity predicted antibody response to recombinant hepatitis B vaccination, an *in vivo* measure of host resistance to viral infection. For this purpose, 84 healthy graduate students who tested negative for prior exposure to hepatitis B virus were administered the standard series of three hepatitis B vaccinations. The first two vaccinations were given 6 weeks apart, with a follow-up booster dose administered 6 months following the first shot. Five months after the first dose, each subject completed a battery of stress measures and a blood sample was drawn to assess hepatitis B surface antibody levels. Four to 6 weeks following completion of the vaccination series, subjects returned to the laboratory to perform an acute laboratory stress protocol, measuring immunologic responses to an evaluative speech task. Findings demonstrated that, when compared with high antibody responders, subjects who mounted lower antibody responses to hepatitis B vaccination following the first two doses displayed greater stress-induced suppression of immune function, as measured by proliferative response to PHA, but not Con A or PWM. As such, this study lends some support to the hypothesis that individual differences in the magnitude of stress-induced suppression of immune function may have clinical significance, being related to an *in vivo* immune response relevant for protection against infection. Consistent with other studies measuring the impact of stress later in the antibody response (Jabaajj et al., 1993; Snyder et al., 1993; Stone et al., 1994), no association was found between stress and antibody response.

At present, the clinical significance of the observed differences in magnitude of antibody response among the high and low responders is unknown. This study was conducted using young, healthy participants and a vaccination protocol designed to produce maximal immunity to hepatitis B in greater than 90% of individuals. Hence, the majority of subjects show an antibody titer that is considered to be protective against hepatitis B infection by the end of the vaccination series. However, it is known that individuals who mount lower antibody responses to hepatitis B vaccination lose their protective status more quickly (Horowitz, Ershler, McKinney, & Battiola, 1988). Hence, subjects who showed greater immune reactivity following acute stress might be expected to have a decreased duration of immunity to hepatitis B than individuals who are less immunoreactive. It is also possible that individual differences in reactivity would have a greater impact on vaccination response among less healthy populations (e.g., elderly or very young persons) or those who already have compromised immune function (e.g., individuals with HIV or cancer).

In sum, some initial evidence is provided that individual differences in the magnitude of immune responses to acute laboratory challenge are related to an *in vivo* measure of immune competence. However, prospective studies employing measures of individual difference as predictors of disease outcome are required in order to show that individuals who show greater suppression of immune function following stress are more vulnerable to infectious disease.

## CONCLUSIONS

In support of popular belief, there is now substantial evidence for the role of psychological stress in susceptibility to upper respiratory infectious disease (e.g., S. Cohen et al., 1991; Stone et al., 1992). One possible mediator of this relation 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, acute laboratory challenge) are associated with changes in immune function. However, it remains unclear whether associations between psychological factors and infectious disease are attributable to stress-induced changes in immunity. Indeed, the clinical significance of relatively small immunologic alterations has not been established. Many associations between stress and health or between stress and the immune system may be attributable to concomitant changes in health behaviors. Recent studies conducted in laboratory settings, however, provide evidence that the sympathetic nervous system mediates some immunologic changes during acute challenge stress. It has also been demonstrated that individuals differ substantially in the magnitude of their immunologic responsiveness to stress, with recent evidence suggesting that these response tendencies may reflect stable attributes of individuals. Hence, it is conceivable that there is a meaningful distribution of differences in immunologic reactivity that may form a physiological basis for differences in susceptibility to infection.

Future research in psychoneuroimmunology needs to focus on whether the type or magnitude of stress-related immune modulation influences host resistance to disease, especially in light of the fact that immune responses of stressed persons generally fall within normal ranges (Rabin, S. Cohen, Ganguli, Lysle, & Cunnick, 1989). Indeed, it has been suggested that substantial fluctuations in immune function can be tolerated without producing increased susceptibility to disease (S. Cohen, 1988). 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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*of*  
**Health Psychology**



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2001

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Mahwah, New Jersey London