

7

Psychological Stress and Immune Competence

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I. INTRODUCTION

Psychoneuroimmunology (PNI) is an interdisciplinary science which attempts to elucidate the relations among behavioral factors; nervous, endocrine, and immune systems; and health. A major hypothesis in this discipline is that stressful life events influence risk for the onset or progression of immune-related illness. This chapter focuses on the human literature in PNI and explores evidence linking stressful events to immune-related disease, as well as potential mechanisms that may mediate this relationship. Particular attention is given to the hypothesis that altered immune functioning during stress is one plausible biological pathway through which stress influences health outcomes.

II. STRESSFUL LIFE EVENTS AND IMMUNE-RELATED DISEASE

A. Stressful Life Events

Stressful life events are commonly believed to suppress host resistance. These events include major stressful experiences such as the loss of a spouse or a job, but also include the accumulation of minor daily hassles such as misplacing keys, missing a bus, or having an argument with a spouse or coworker. When demands imposed by events exceed a person's ability to cope, a psychological stress response composed of negative cognitive and emotional states is elicited [1]. In turn, psychological stress is thought to influence immune function through autonomic innervation of lymphoid tissue or hormone-mediated alterations of immune cells. Stress may also alter immune response through coping behaviors such as increased smoking and alcohol consumption.

B. Evidence of Stress and Disease Associations

Stressful life events have been associated with a range of immune-related disorders, including autoimmune diseases, infectious illness, and cancer [2-4]. Some of the most compelling evidence involves susceptibility to upper respiratory infections. Here, prospective epidemiological studies have found that major stressful life events, chronic family conflict, and disruptive daily events predicted serologically verified infectious illness [5,6].

Converging evidence comes from viral challenge studies, which, importantly, control for exposure to infectious agents. In these studies, after stressful life events and negative mood are assessed, volunteers are exposed to a cold or influenza virus and then monitored in quarantine for the development of infection and illness. Three recent viral-challenge studies have suggested that psychological stress is a risk factor for susceptibility to upper respiratory infections [7-9]. In one prospective study involving 394 volunteers, reports of stressful life events, perceived stress (i.e., feeling stressed), and negative affect all predicted a greater probability of development of a cold. This association occurred for both those with and those without prechallenge antibody to the experimental virus and was independent of health practices (e.g., smoking and alcohol consumption) or numbers of various white blood cell populations or total (nonspecific) antibody levels measured before viral challenge [7,8]. The relationships among stress, mood, and health were observed across five different upper respiratory viruses. Finally, in a study examining predictors of disease severity, rather than episode onset, negative mood measured before viral exposure was related to more severe colds and influenza, as determined by the amount of mucus produced over the course of the illness [10].

In addition to disease outcomes, stressful life events may also delay the healing of wounds. Kiecolt-Glaser and colleagues [11] found that long-term care giving for a severely ill family member was associated with heightened emotional distress and slower healing of a 3.5-mm-punch biopsy wound, as determined by photographic evidence and wound response to hydrogen peroxide. Indeed, wound healing took an average of 9 days longer in care givers than in age- and income-matched controls. Health-related variables such as alcohol and caffeine use, physical activity, body mass, weight change, and smoking did not account for the group differences observed. As the authors note, such decrements in wound repair may have important clinical implications with respect to surgical recovery [11].

III. POTENTIAL MECHANISMS LINKING STRESS AND IMMUNE DISEASE

How stress influences health outcomes is not entirely clear. One possibility is that people cope with stress by initiating coping behaviors, such as smoking or drinking alcohol, and that these behaviors compromise health and the immune system [12]. Alternatively, stress may influence health by directly altering immune function through the activation of neuroendocrine pathways and release of hormones and neurotransmitters, such as cortisol and catecholamines. It is now known that anatomical links exist between the nervous and immune systems, as indicated by the sympathetic innervation of lymphoid organs, such as the thymus and spleen [13]. In

addition, lymphocytes have receptors for a variety of hormones that are secreted during psychological stress, including catecholamines, glucocorticoids, dopamine, prostaglandins, serotonin, endorphins/enkephalins, substance P, and vasoactive intestinal peptide [14]. These findings, along with evidence indicating that such hormones can influence immune function *in vitro*, suggest that hormonal and neuroendocrine substances may play a role in altering cell function during stress.

The remainder of this chapter focuses on existing evidence that changes in immune function are associated with mood alterations evoked by life events and, therefore, represent a plausible pathway by which stress influences susceptibility to immune-related disease. It is important to keep in mind, however, that while substantial changes in immune function have been shown to index health status (e.g., major declines in T helper lymphocyte counts in human immunodeficiency virus [HIV] infection), it is not clear whether less pronounced alterations associated with psychological stress are sufficient to influence health. As will be discussed further, it is possible that the most pronounced health consequences will occur in individuals who have already weakened immune systems (e.g., the elderly or individuals with HIV infection) [15].

IV. MEASUREMENTS OF IMMUNOCOMPETENCE

Human studies in PNI are limited to quantitative and functional assessments of immune parameters sampled from peripheral blood and mucus. Quantitative assessments in blood include the absolute numbers or percentages of specific populations of immune cells in circulation, including T helper, T suppressor, T cytotoxic, and B lymphocytes; natural killer (NK) cells; and phagocytes.

With respect to functional assessments, lymphocyte proliferation assays are commonly used in PNI research. These typically include the T cell mitogens phytohemagglutinin (PHA) and concavalin A (Con A), as well as the T and B cell stimulant pokeweed mitogen (PWM). Natural killer cell cytotoxicity is also frequently measured. In some cases, NK cells may be initially incubated with stimulatory cytokines, such as interleukin 2 (IL-2) or gamma-interferon (IFN- γ). The effectiveness of these cytokines in enhancing NK cell activity is then compared to cytotoxicity levels found in unstimulated samples.

Finally, *in vitro* functional assays are also used to measure cytokines that are produced and secreted by lymphocytes and monocytes after stimulation by mitogens. Frequently levels of IFN- γ and various interleukins, such as IL-2, are measured.

Other functional assays measure antibody responses to novel antigens in saliva or serum, such as vaccination with an influenza virus, recombinant hepatitis B, or keyhole limpet hemocyanin (KLH). In addition to measuring *in vivo* production of antibodies to a primary challenge, investigators have measured the level of proliferative response of blood lymphocytes to a specific challenge virus *in vitro*.

Although greater antibody response is usually interpreted as better immunocompetence, elevated antibody levels to latent herpesviruses may reflect a weakened ability of the immune system to prevent such viruses from becoming active. Therefore, higher antibody levels to herpesviruses are often interpreted as indicating poorer immunocompetence [15]. Studies frequently measure antibody titer to Ep-

stein-Barr virus (EBV) because EBV is widespread, with seropositivity rates at approximately 90% in the adult population [16,17].

Finally, levels of the pteridine compound neopterin, which is released from activated macrophages, can also be obtained from blood or urine and are considered an index of cell-mediated immune activation.

V. NATURALISTIC STRESSORS AND IMMUNITY

A. Overview

A growing literature in both humans and animals indicates that immunological changes are associated with psychological and physical forms of stress (for extensive reviews involving humans, see Refs. 18–19). Changes in the immune system have been found to accompany major and minor life events, such as exams, bereavement, divorce, work-related stress, and the ongoing uncertainty associated with living near Three Mile Island (TMI) several years after the nuclear accident.

1. Minor Stressful Daily Events

Minor stressful events (i.e., daily hassles, such as losing one's keys) have been associated with changes in salivary immunoglobulin A (sIgA) and serum antibody response to a novel antigen. In a study by Stone et al. [20], participants ingested a novel protein capsule daily for 12 weeks to stimulate an sIgA antibody response. Saliva samples were collected each day to assess sIgA levels to the protein, and participants recorded the occurrence of both desirable (e.g., accomplishing a goal) and undesirable (e.g., arguing with a spouse) daily events. Desirable events were related to greater sIgA antibody production, whereas undesirable events were related to lower levels. These findings were recently replicated by Stone et al. [21], who also demonstrated that undesirable events were associated with lowered antibody levels primarily when accompanied by increased negative mood. In contrast, desirable events were linked to increased antibody production when accompanied by decreases in negative mood.

Jabaaij et al. [22] also found that serum antibody responses to three recombinant hepatitis B vaccines covaried with the frequency and intensity of daily hassles and concurrent distress. In this prospective study, an index of combined hassles and distress scores measured early in the immunization series predicted less production of antibody in response to the vaccine. With respect to daily events and health outcomes, it is interesting that Stone, Reed, and Neale [23] found that *before* the onset of an infectious illness, individuals reported a peak number of undesirable events (e.g., difficulties with their boss or coworkers) and a diminished number of desirable events. This suggests that people may become more susceptible to infection when negatively perceived events appreciably exceed good ones.

2. Examinations

Perhaps the most commonly studied stressful events in relation to immunological status are examinations. Academic examinations have long been known to elicit stressful reactions in students, including heightened anxiety and depression and elevated concentrations of cortisol and catecholamines [24,25]. Most studies of examination stress and immune function compare blood samples collected on an

exam day to those taken during a relatively stress-free period of the semester (e.g., just after a vacation). Overall, several indices of immunosuppression have been observed in medical students during important examinations. These include decrements in lymphocyte response to mitogenic stimulation, reduced NK cell activity, alterations in T cell populations, decreased antibody responses to vaccinations, and diminished production of cytokines and neopterin [15,26–32]. Increased levels of circulating antibodies to Epstein-Barr virus and other herpesviruses have also been found during examination periods, indicating reactivation of latent virus by either direct neuroendocrine influences or weakened immunocompetence [15,29].

Several studies have found that certain people are more susceptible to immune alterations during exams than others. For example, the largest exam-related immunological changes were found in students who reported higher levels of overall life stress or loneliness [29,30]. Similar findings were reported by Glaser et al. [31], who found an association between anxiety levels during exams and antibody response to a series of three hepatitis B vaccinations. Although there was no effect of anxiety on the antibody levels achieved after the third dose of antigen, heightened anxiety was related to a delay in seroconversion to hepatitis B. In a similar study, Bovbjerg et al. [32] vaccinated students with trivalent influenza vaccine immediately after an examination period. Here, greater reported distress was related to lower proliferative response of blood lymphocytes to the influenza virus *in vitro*.

How long do immunological changes persist after exams? While immune alterations are thought to return to baseline shortly after exam periods, some individuals may show a delayed recovery lasting up to 4 weeks after examinations end [33]. This corresponds to periods of persistent stress hormone elevations in some students [24] and is interesting in light of anecdotal reports that students often become ill after, but not during, exams [27].

3. Bereavement

The loss of an intimate relationship through either death or divorce has also been associated with altered immunity, including suppression of lymphocyte responses to mitogenic stimulation, reduced NK cell activity, and changes in T cell subpopulations. Early investigations found lowered lymphocyte proliferation among bereaved subjects after the loss of their spouse, as compared to that of both nonbereaved controls [34] and the prebereavement period [35]. In these studies, immunological alterations persisted from 2 to 14 months after the loss.

Recent studies indicate that the degree of immune change among bereaved persons varies greatly and may be related to the severity of depressed mood. Thus, Linn, Linn, and Jensen [36] reported reduced lymphocyte proliferation to PHA only among bereaved spouses with concomitant depressive symptoms. This is consistent with findings by Irwin, Daniels, Smith, Bloom, and Weiner [37] that greater depression during bereavement is associated with lower NK cell activity ($r = -.89$).

In addition to depressed mood, the availability of a supportive social network may influence immunological responses to the anticipated or actual loss of a loved one. In a sample of 23 spouses of patients with cancer, Baron et al. [38] found that individuals reporting greater support from their social ties had higher NK cytotoxicity and proliferative responses to PHA than those reporting less support. The presence of depression and other life events did not account for these associations.

Because individuals in the gay community are often subjected to multiple

losses attributable to acquired immunodeficiency syndrome (AIDS), investigators have begun to examine the immunological correlates of bereavement in human immunodeficiency virus- (HIV)-seropositive and HIV-seronegative gay men. Recently, Kemeny et al. [39] found that HIV-seropositive men who had lost an intimate partner to AIDS in the previous year showed decreases in proliferative responses to PHA and increases in serum neopterin levels after the loss. Life-style and medication factors (recreational drug use, smoking, level of exercise, sleep loss, and use of azidothymidine (zidovudine) [AZT]) did not account for the findings. While stress has been linked to *decreased* neopterin levels in healthy individuals [27], infection from HIV is known to increase neopterin production, and heightened levels have been shown to be a strong predictor of the development of AIDS [40]. However, in the case of HIV-negative men, no immunological changes were found after the death of an intimate partner.

Immunological alterations were also observed in HIV-seropositive gay men by Goodkin et al. [41], who assessed immune function after the death of a lover or close friend. When the subjects were compared to nonbereaved controls, loss was associated with diminished NK cell cytotoxicity within 6 months after the death and again 6 months later. Decreased mitogenesis to PHA was also found at the later time point and, interestingly, was related to elevations in plasma cortisol level in the bereaved group. However, there were no differences in the number of T helper lymphocytes between bereaved and nonbereaved groups in either study [39,41].

4. Separation, Divorce, and Marital Discord

Like bereavement, separations and divorce have been associated with immune alterations. Kiecolt-Glaser, Glaser, and colleagues found that 16 recently separated or divorced women had lower percentages of circulating NK and T helper cells, decreased proliferative responses to PHA, and higher antibodies to Epstein-Barr virus than a comparison group of married women [42]. Similar findings were reported in a subsequent investigation of 32 men who had been separated or divorced for up to 3 years [43]. As in the previous study, separated or divorced men had higher antibody levels to latent viruses (here, both Epstein-Barr and herpes simplex viruses) than matched married controls. T lymphocyte populations, however, did not differ between the two groups. Both studies showed that for married couples, poorer marital quality was related to higher levels of distress, loneliness, and latent virus antibody response. Finally, in a recent investigation of newly married couples, decrements in immune functioning were similarly related to marital discord [44]. Newlyweds who demonstrated more negative or hostile interactions during a brief discussion of marital problems showed greater decreases in natural killer activity and proliferative responses to PHA and Con A over a 24-hour period. These individuals also had higher antibody titers to latent Epstein-Barr virus than their less hostile counterparts.

5. Other Prolonged Stressful Events

Immunological changes accompany other prolonged stressful events, such as care giving for a terminally ill patient, long-term unemployment, job stress, and residence near a damaged nuclear power plant. Several studies have investigated psychosocial consequences of caring for a family member with Alzheimer's disease (AD). In general, such care givers are found to be at higher risk for depression,

health complaints, and decreased life satisfaction [45,46]. Examining the immunological sequelae of care giving for a family member with AD, Kiecolt-Glaser and colleagues [47] found that care givers exhibited lower percentages of total lymphocytes and T helper cell subsets and higher antibody titers to Epstein-Barr virus. Care givers also showed lower in vitro interleukin-1B responses to lipopolysaccharide stimulation and, as indicated earlier, slower healing of a 3.5-mm punch biopsy wound [11]. Finally, in a study comparing AD care givers with former care givers (i.e., those whose relative with AD had died at least 2 years earlier), Esterling et al. [48] found that former and current care givers did not differ from each other and had poorer NK cell response to two stimulatory cytokines (IFN- γ and IL-2) than a group of matched controls.

The findings reported by Esterling et al. [48] suggest that the psychological and immunological consequences of exposure to chronic stressors may persist well beyond the cessation of the actual event. Protracted stress responses were also found among residents of Three-Mile Island, where more than 6 years after the nuclear accident, many community members continued to exhibit heightened levels of distress, 24-hour urinary catecholamine excretion, and latent herpesvirus antibodies when compared with a group of demographically similar controls [49,50]. Residence near TMI was also associated with enumerative changes in immune activity, including a larger population of circulating neutrophils and diminished numbers of B lymphocytes, T suppressor/cytotoxic lymphocytes, and NK cells [50]. Importantly, the two community samples did not differ in reported diet, smoking, health, medications, or substance use.

Both job stress and long-term unemployment have also been linked to lowered lymphocyte reactivity to PHA [51,52]. In one study, immunological function was depressed in a group of women after 9 months of unemployment [51].

6. *Potential Reasons for the Persistence of Immunological Changes*

How is it that stress-elicited immunological changes persist over prolonged periods? One possibility is that ongoing behavioral and mood changes resulting from the stressful event may perpetuate immune alterations [12; see also Refs. 21, 53, and 54 for data suggesting mood and immune associations]. In addition, many stressful events, such as the death of a loved one, may unfold a number of other stressful situations relating to finances, social relations, and other long-term concerns [55]. Finally, cognitive influences, such as intrusive thoughts and imagery, may sustain stress reactions even when the objective event no longer exists [49]. For example, McKinnon et al. [50] observed elevated anxiety and immunological changes in TMI-area residents who continued to experience intrusive thoughts or imagery about the damaged nuclear plant and its potential health effects.

B. Summary of Naturalistic Stressors and Immunity

Taken together, most studies involving stress and immunity indicate that psychological stressors are associated with changes in immune cell numbers and functions [18]. The most consistent alterations include reduced NK cell activity and lymphocyte proliferation to PHA and Con A; diminished antibody response to viral antigens, such as hepatitis B; and increased antibody levels to latent herpesviruses.

Decreases in percentage or absolute number of circulating B cells, T cells, T helper cells, T suppressor/cytotoxic cells, and NK cells are also frequently reported immune responses to stress. Evidence suggests that such alterations may persist over protracted intervals during particularly intense or prolonged stress.

Despite the general consistency of findings, there are some limitations associated with naturalistic studies of psychosocial influences on immune function. By design, naturalistic studies are able to demonstrate *correlational*, but not causal relations between stress and immunity. Furthermore, the potential mechanisms linking stress to immunity are difficult to delineate in such investigations. Relatively few naturalistic studies have examined health practices or neuroendocrine factors as mediators of changes in immunity, and at this point, it is not clear whether more modest changes in health practices during stress result in altered immune function [18].

VI. SHORT-TERM LABORATORY STRESSORS AND IMMUNITY

A. Overview

While most of the literature on stress and immune relationships involves naturally occurring stressors, there are now a number of controlled experimental investigations examining the impact of acute psychological stress on immune function. Experimental manipulation, in which subjects are assigned randomly either to a stress-exposed condition or to an unstressed, control condition is required to evaluate whether stress causes alterations in immune function. Experimental studies also serve as a useful model for transient daily life stressors and provide a means to investigate potential endocrine mechanisms underlying associated immunological changes.

Short-term laboratory studies have examined immunological responses to a range of behavioral stimuli perceived by subjects as aversive, demanding, or interpersonally challenging. Such stimuli are typically presented to participants for brief intervals (e.g., 10 to 20 minutes) and include either computer tasks, mental arithmetic, electrical shocks, loud noise, unsolvable puzzles, graphic films depicting combat surgery, evaluative speeches, marital discussions involving conflict, or interviews eliciting the recollection of positive and negative experiences and mood states (for a review, see Ref. 56). Immunological measurements are obtained either during or at the termination of the stressor and are compared to resting values obtained during a prestress period of adaptation and baseline measurement; occasionally, recovery measurements taken several minutes or hours after the task are also obtained.

Exposure to such challenging tasks has been shown to evoke a variety of enumerative immune changes; the most consistent findings include an increase in the numbers of circulating NK cells and T suppressor/cytotoxic lymphocytes and a decrease in the ratio of T helper to T suppressor cells. Some (but not all) studies have shown alterations in the number of T helper and B lymphocytes as well [57-61].

With respect to functional measures of immunity, stress-induced decreases in T cell proliferative responses to PHA and Con A are frequently reported [53,54,57-

60,62-69]. Diminished mitogenic responses to PWM have also been shown, suggesting similar reductions in B lymphocyte function [58,68]. Finally, there are numerous reports of altered NK cell activity after exposure to brief psychological stress, and here studies have demonstrated increases as well as decreases in this parameter [53,58,59,62,65,70-74].

The onset and duration of immunological reactions to acute mental stress are not entirely known, but preliminary data suggest that such changes are rapid and transient, occurring as early as 5 minutes from stressor onset [63]. In the case of cell subset redistribution, these changes return to baseline within 15 minutes of stressor termination [75]. In contrast to quantitative alterations, reductions in lymphocyte proliferation have been found to persist for at least 90 minutes after challenge [67,69]. Elevations in NK cell activity may last at least 1 hour [59]; however, the decreases reported in one experiment persisted as long as 72 hours after exposure to laboratory stress [73].

B. Evidence for Sympathetic Mediation of Stress-Immune Reactions

There is a growing body of evidence that acute immune responses to psychological stress are mediated by activation of the sympathetic nervous system. First, the rapid appearance of such changes makes it unlikely that other, slower-responding hormones (e.g., cortisol) are contributing to the effects. Indeed, two studies found immune alterations in the absence of concomitant cortisol responses [64,69]. Second, infusion of catecholamines leads to functional and enumerative immune alterations that are similar to those seen during acute mental stress (e.g., elevated T suppressor/cytotoxic and NK cells, decreased ratio of T helper to T suppressor/cytotoxic cells, and diminished proliferative response to mitogens) [76,77]. Finally, only those subjects with the most pronounced sympathetic responses to laboratory stressors display suppression of mitogen-stimulated lymphocyte proliferation [63,64,69].

Additional and more direct evidence for sympathetic mediation derives from the observation that changes in cellular immune function under stress are ameliorated by the administration of an adrenoceptor antagonist. In particular, the administration of labetalol (a nonselective alpha- and beta-adrenergic antagonist) was shown to prevent stress-induced increases in NK cell number and activity, reductions in the ratio of T helper to T suppressor/cytotoxic cells, and decreases in proliferative responses to PHA and Con A during two cognitive tasks and a public speaking stressor [62]. Similar findings were demonstrated by Benschop et al. [70], who found that the selective beta-2 antagonist propranolol blocked stress-induced rises in NK cell numbers and cytotoxicity.

1. Potential Mechanisms of Sympathetic-Immune Mediation

Precisely how the sympathetic nervous system mediates immune reactions to stress remains unclear. One potential mechanism underlying cell redistribution involves the extrusion of stored lymphocytes from spleen to periphery after the contraction of sympathetically innervated smooth muscle in the spleen [78]. It is also possible that catecholamines may influence leukocyte redistribution between the marginating

pool of blood vessels and the bloodstream by altering adhesion receptor expression on these cells and/or the vasculature. It is now known that blood-borne lymphocytes enter some lymphoid organs by first attaching, via adhesion molecules, to specialized endothelial cells lining the postcapillary venules of lymphatic tissue. In a recent experiment, Benschop, Oostveen, Heijnen, and Ballieux [79] found that NK cell adhesion to endothelial tissue was markedly reduced (36%) *in vitro* after incubation with epinephrine, and that this process was dependent on the generation of adenylate cyclase (cyclic adenosine monophosphate [cAMP]) by NK cells. Finally, altered mitogenesis may, in part, involve sympathetically mediated impairments of IL-2 production by T helper lymphocytes [80], altered IL-2 receptor expression [81], and decreased antigen presentation by macrophages [80].

2. Individual Differences in Stress-Immune Responses

The accumulating evidence supporting sympathetic modulation of immune parameters during stress has implications for individual differences in stress-immune interactions. People are known to vary markedly in the magnitude of their sympathetic-adrenal responsivity to stress, and these differences denote a relatively stable attribute of individuals [82,83]. Recent findings suggest that individuals differ substantially in both neuroendocrine (epinephrine, norepinephrine) and cardiovascular (heart rate, systolic and diastolic blood pressure) indices of sympathetic arousal, and that reactivity in these parameters covaries with cellular immune response to psychological stress [64]. Manuck et al. [64] found that only individuals who were identified as "high sympathetic responders" (on the basis of relatively high catecholamine and cardiovascular responses to mental stress) showed stress-induced increases in T suppressor/cytotoxic cell numbers and a diminished mitogenic response to PHA. Mills et al. [61] extended these findings by demonstrating that individual differences in the magnitude of plasma norepinephrine responses to mental stress and the sensitivity of beta-2 adrenergic receptors on lymphocytes predicted concomitant changes in circulating NK and T suppressor/cytotoxic lymphocytes. Demographic and health variables, such as ethnicity, gender, age, body mass index, blood pressure status (i.e., hypertensive or normotensive blood pressure), and smoking, failed to predict these immune alterations.

Individual differences in several immunological reactions to mental stress are moderately stable over time. Moreover, the propensity for individuals to react to one stressor with heightened sympathetic arousal predicts immunological responses to other stressful situations [60,65,84]. For example, Sgoutas-Emch et al. [65] reported that persons responding with high heart rates when required to give a speech showed greater increases in NK cytotoxicity when exposed to a mental arithmetic task on another day than individuals who demonstrated low heart rate reactions to the speech. Other investigations assessing the stability of cellular immune reactions to laboratory stressors delivered 2 to 6 weeks apart have found significant test-retest correlations for the magnitude of change in proliferative response to PHA, numbers of T suppressor/cytotoxic and NK cells, and ratio of T helper to T suppressor/cytotoxic cells (ranges of .40-.60) [60,84]. Taken together, these findings suggest that individuals differ in the magnitude of immune responses to brief mental stress, that changes in some parameters are moderately reproducible on retesting, and that the magnitude of change may therefore denote a stable dimension of individual differences [60].

VII. ACUTE AND CHRONIC STRESS STUDIES: SIMILARITIES AND DIFFERENCES IN IMMUNE RESPONSE

With the exception of increased NK activity, functional immune changes after acute stress usually resemble those accompanying chronic naturalistic stress. More often, though, the direction of quantitative changes in some lymphocyte subpopulations will differ between acute and chronic stressors. Whereas laboratory stressors elicit immediate elevations in NK and T suppressor/cytotoxic lymphocytes, naturalistic stressors tend to be associated with reductions in these cell types [18].

The reasons for these discrepancies are not yet clear but may reflect differences in the hormonal environment surrounding immune cells. Long-term changes in health habits, which influence both immune and neuroendocrine systems, may in part underlie differences that are observed in acute and chronic stress [12,85,86]. Also, it is possible that homeostatic processes, such as receptor down-regulation and desensitization, may be involved. For example, Maisel et al. [87] found that oral administration of the beta-2 agonist terbutaline for 1 week caused a decrease in the number of beta receptors on T suppressor/cytotoxic, NK, and T helper cells, and a substantial drop in isoproterenol-induced cAMP generation in NK and T suppressor/cytotoxic cells in humans. Interestingly, T helper and B lymphocytes showed the least amount of change in either beta-receptor density or cAMP accumulation. If cAMP production is indeed essential in the recruitment of NK cells from the marginating pool of blood vessels to the circulating bloodstream [79], these adaptations may partly explain why peripheral NK cell numbers tend to increase during acute stress conditions and decrease during chronic forms of stress.

Finally, immunological differences may be attributable to a more complex hormonal milieu associated with chronic than acute stress. As slower-responding hormonal systems become activated and release substances such as cortisol, adrenocorticotrophic hormone (ACTH), and β -endorphin, both independent and interactive hormonal effects on immune function are likely to occur. Although reports are few, there is preliminary evidence suggesting that cortisol may play an important role in modulating some immune reactions in chronic stress conditions. As indicated previously, Goodkin et al. [41] found associations between increased plasma cortisol levels and a decreased proliferative response to PHA during bereavement in HIV-infected men. Additionally, in a study assessing cortisol response to HIV testing, Antoni et al. [88] found that anxiety levels and intrusive thoughts before serostatus notification related significantly to higher plasma cortisol levels and lower proliferative responses to PHA. Plasma beta-endorphin levels were also related to reduced lymphocyte proliferation, although associations were less consistent than for cortisol.

VIII. CONCLUSIONS

There is now ample evidence suggesting that stressful life events are related to health outcomes, such as infectious illness, autoimmune disorders, cancer, and wound healing (e.g., Refs. 2-11). The literature in PNI also clearly demonstrates that immunological alterations occur in response to a variety of stressful events in hu-

mans, and it is through such changes that stress may, in part, be linked to disease. Studies conducted in laboratory settings provide particularly strong evidence that the sympathetic nervous system mediates some immunological changes during mental stress. Because individuals differ in the magnitude of immune and sympathoadrenal responsivity to stress, it is conceivable that there is a meaningful distribution of response differences among people which, in turn, may influence their susceptibility to immune-related illness.

Future research in PNI needs to determine whether the nature or magnitude of stress-induced immune alterations bears relevance to increased disease susceptibility and progression. Immune responses of stressed persons generally fall within normal ranges [89], and where reductions in antibody responses to vaccinations are observed, it is unclear whether these decrements are sufficient to influence protection against infection. Additional studies that employ longitudinal designs and measure immune parameters relevant to the disease under study and health outcomes are needed.

It is also likely that stress-related immune alterations may have more pronounced health consequences for individuals with weakened immune systems. It is well known, for example, that aging is associated with a decline in immune function, as indicated by lowering of the proliferative response to mitogens, natural killer cell activity, antibody production, and phagocytic activity [90]. Thus, the significance of stress-related immune alterations may be greater for the elderly or for individuals with HIV infection or autoimmune disorders [15]. With respect to individuals who are HIV-infected, Kemeny et al. [39] reported that elevated neopterin level during bereavement placed some individuals at levels previously shown to be associated with a higher risk of development of AIDS [39,40].

Over the last 20 years, PNI research has established links between psychological stressors and altered functioning in the immune system. This remains one of the most promising pathways through which stress may alter host resistance to disease onset or progression. Prospective studies that measure all aspects of the stress-immune disease model are needed to understand these associations more fully.

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