Psychoneuroimmunology:
Psychological Influences on Immune Function and Health

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This review focuses on human psychoneuroimmunology studies published in the past decade. Issues discussed include the routes through which psychological factors influence immune function, how a stressor's duration may influence the changes observed, individual difference variables, the ability of interventions to modulate immune function, and the health consequences of psychosocially mediated immune dysregulation. The importance of negative affect and supportive personal relationships are highlighted. Recent data suggest that immune dysregulation may be one core mechanism for a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, Type 2 diabetes, certain cancers, and frailty and functional decline; production of proinflammatory cytokines that influence these and other conditions can be stimulated directly by negative emotions and indirectly by prolonged infection.

In 1964 George F. Solomon coined the term *psychoimmunology* and published a landmark article: "Emotions, Immunity, and Disease: A Speculative Theoretical Integration" (Solomon & Moos, 1964). Despite the importance of this inaugural conceptual article, only a handful of human studies appeared prior to the 1980s. However, the subsequent explosive growth in both animal and human studies has provided a much clearer picture of the ways in which behavior and emotions modulate immune function. This review focused on human psychoneuroimmunology (PNI) studies published during the past decade, particularly those that addressed the health consequences of psychosocially mediated immune alterations.

Various aspects of behavioral influences on immune function have been reviewed elsewhere (Glaser & Kiecolt-Glaser, 1994; Herbert & Cohen, 1993; Kiecolt-Glaser, 1999; Kiecolt-Glaser & Glaser, 1999b; Rabin, 1999; Schedlowski & Tewes, 1999; Uchino,

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Caccioppo, & Kiecolt-Glaser, 1996). For a highly readable discussion of basic immunological material and a broad overview of the field, see Rabin (1999).

Duration of a Stressor: Implications for Immune Function and Health

Laboratory Models (5–60 min)

Acute laboratory stressors that typically last a half hour or less provoke transient immune changes (Brosschot et al., 1994; Kiecolt-Glaser, Cacioppo, Malarkey, & Glaser, 1992; Mills, Dimsdale, Nelesen, & Dillon, 1996; Naliboff et al., 1995; Schedlowski, Jacobs et al., 1993). Both brief and longer term stressors are associated with declines in functional aspects of immunity; however, in contrast to the decrements in lymphocyte numbers associated with longer term naturalistic stressors (Uchino et al., 1996), laboratory stressors appear to increase cell numbers in some lymphocyte subpopulations. Most immune parameters return to resting levels within 1 hour after cessation of laboratory stressors (Kiecolt-Glaser et al., 1992). One possible mechanism may be the acute secretion of stress-responsive hormones, particularly catecholamines, which can alter a number of aspects of immune function (Rabin, 1999).

Cardiovascular and catecholaminergic reactivity tend to covary when assessed under the same conditions, and high reactivity research participants demonstrated greater immunological change than low reactivity participants (Cacioppo et al., 1995; Kiecolt-Glaser et al., 1992). Both the duration and intensity of psychological stressors (as indexed by cardiovascular changes) are related to the breadth and magnitude of immune changes in laboratory studies (Benschop, Rodriguez-Feuerhahn, & Schedlowski, 1996). In

fact, the immunological changes observed following short-term stressors are very similar to those described following epinephrine injections (Schedlowski, Falk, et al., 1993) and likely reflect transient alterations in lymphocyte migration from lymphoid organs and peripheral blood mediated through receptors on lymphocytes or through sympathetic nervous system (SNS) innervation of lymphoid organs like the spleen (Ackerman, Bellinger, Felten, & Felten, 1991). Thus, these transitory changes in the distribution of cells in circulation in peripheral blood (a process called *trafficking*) probably do not represent a real change in cell numbers.

Mouse models suggest the possibility of hyperreaction of at least one aspect of immune function following short-duration stressors; the augmentation of delayed-type hypersensitivity (DTH) responses in the skin appears to be mediated through glucocorticoid and epinephrine stress responses (Dhabhar & McEwen, 1999). One study suggested that this relationship may occur in humans; socially inhibited individuals produced an increased DTH skin response after experiencing a condition of high social engagement, consistent with the hypothesis that social inhibition may be related to physiologic hyperresponsiveness (Cole, Kemeny, Weitznam, Schoen, & Anton, 1999). It should be noted that transient hyperresponsiveness of immune responses in the skin is not necessarily positive, for example, contact allergies and rosacea are maladaptive).

Short-Term or Acute Stressors

A 10-year series of prospective studies of medical students' responses to examinations showed transient changes in multiple facets of the cellular immune response and its mediators (Kiecolt-Glaser, 1999); academic stress has also been widely used as a model by other laboratories (Dobbin, Harth, McCain, Martin, & Cousin, 1991; Marshall et al., 1998; Segerstrom, Taylor, Kemeny, & Fahey, 1998). The importance of these immunological alterations for health is suggested by several studies. For example, stress influenced medical students' response to a series of three hepatitis B (Hep B) vaccinations (Glaser et al., 1992); the students who seroconverted (produced an antibody response to the vaccine) after the first vaccination were significantly less stressed and less anxious than those who did not seroconvert until after the second inoculation. These data suggest that the immune response to a vaccine (and, by implication, to pathogens) can be modulated by a relatively mild stressful event in young, healthy adults.

The immune response plays an important role in the early stages of wound healing, and exam stress also substantially delayed wound repair. Wounds placed on the hard palate 3 days before a major test healed an average of 40% more slowly than those made in the same individuals during summer vacation, and interleukin–1 (IL-1), an important immunological mediator, was also substantially lower during exams (Marucha, Kiecolt-Glaser, & Favagehi, 1998).

Taken together, these data suggest that academic stress (and other relatively short-term, commonplace stressors) can provoke changes in a variety of different immune activities, and these changes can be consequential for health. Of importance, student populations are "experts" at taking tests—they have long histories of performing well under these very conditions. The fact that something as transient, predictable, and relatively benign as exam stress produces immune change suggests that other everyday stressors produce similar alterations.

Chronic Stress

The ability to unwind after stressful encounters (i.e., quicker return to one's neuroendocrine baseline) influences the total burden that stressors place on an individual (Frankenhaeuser, 1986). Stressors that are resistant to behavioral coping, particularly stressors perceived as unpredictable and uncontrollable, may continue to be associated with elevated stress hormones even after repeated exposure (Baum, Cohen, & Hall, 1993). For example, men and women who provide long-term care for a spouse or parent with Alzheimer's disease typically report high levels of stress as they attempt to cope with the family member's problematic behaviors, and this stressor has been associated with prolonged endocrine and immune dysregulation, as well as with health changes, including alterations in vaccine response and wound healing (Castle, Wilkins, Heck, Tanzy, & Fahey, 1995; Irwin et al., 1991; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996; Malarkey et al., 1996; Mills, Yu, Ziegler, Patterson, & Grant, 1999; Vedhara et al., 1999; Vitaliano et al., 1998). Moreover, these changes may persist after caregiving ends (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994; Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998).

Other chronic or longer term stressors associated with immune alterations include burnout at work (Lerman et al., 1999), imprisonment in a prisoner of war camp (Dekaris et al., 1993), isolation and exposure to hostile climate (Muller, Lugg, & Quinn, 1995), living near a damaged nuclear reactor (Baum et al., 1993), job strain (Kawakami et al., 1997), and unemployment (Arnetz et al., 1991). In a study in which volunteers were inoculated with several different strains of cold viruses, stressors that lasted a month or more were the best predictors of developing colds (S. Cohen et al., 1998). Immunological changes have also been documented for weeks or months following such natural disasters as earthquakes and hurricanes (Ironson et al., 1997; Solomon, Segerstrom, Grohr, Kemeny, & Fahey, 1997). Prolonged intrusive ruminations following a trauma or disaster have been related to maladaptive psychological functioning and may provide one avenue for persistent immune dysregulation (Baum et al., 1993). For example, intrusive thoughts were associated with lower levels of natural killer (NK) cell activity among victims of a hurricane (Ironson et al., 1997). Intrusive thoughts may maintain higher levels of distress, as well as stress-related immune change (La Via et al., 1996).

Psychological Modifiers

Negative affect has been associated with immunological dysregulation in studies that have spanned the gamut from clinical depression and chronic stress to transient mood changes induced by laboratory manipulations (Herbert & Cohen, 1993; Kiecolt-Glaser, Malarkey, Cacioppo, & Glaser, 1994). Findings from an innovative daily diary study demonstrated that antibody to an orally ingested antigen was higher in saliva on days when participants reported more positive moods and lower in saliva with more negative moods (Stone et al., 1994). Similarly, negative mood over the course of a day was associated with reduced NK cell lysis among women, and positive mood moderated this association

(Valdimarsdottir & Bovbjerg, 1997). Among healthy older adults, decreased positive mood partially mediated the association between the stressor of moving and reduced NK cell lysis (Lutgendorf, Vitaliano, Tripp-Reimer, Harvey, & Lubaroff, 1999). Individuals with greater right-prefrontal cortex activation had lower levels of NK cell activity than individuals with greater left-frontal activation, and greater right-prefrontal activation was associated with greater decline in NK activity in response to stress (Davidson, Coe, Dolski, & Donzella, 1999). These data are consistent with evidence that left-prefrontal activation is associated with positive emotions, whereas the experience and expression of negative emotions is associated with greater right-prefrontal activation (Davidson, Jackson, & Kalin, 2000). Indeed, negative affect has been conceptualized as a key pathway for other psychological modifiers described later in the article, personal relationships and personality.

The link between personal relationships and immune function is one of the most robust findings in PNI (Uchino et al., 1996). For example, higher NK cell activity and stronger proliferative responses of peripheral blood leukocytes to mitogen stimulation were associated with higher social support in women whose husbands were being treated for urologic cancer than among those with less support (Baron, Cutrona, Hicklin, Russell, & Lubaroff, 1990). Medical students who reported better social support mounted a stronger immune response to a Hep B vaccine than did those with less support (Glaser et al., 1992). Individuals with fewer social ties were more susceptible to respiratory viruses (S. Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997). Spousal caregivers of dementia sufferers who reported lower levels of social support on entry into a longitudinal study and who were most distressed by dementia-related behaviors showed the greatest and most uniformly negative changes in immune function 1 year later (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991). Spousal caregivers who demonstrated poorer augmentation of NK cell activity to two cytokines reported lower levels of social support and described less closeness in their important relationships than did caregivers who showed greater NK augmentation (Esterling, Kiecolt-Glaser et al., 1994). Data on maternal separation in nonhuman primates provides strong supportive evidence from a well-characterized animal model (Coe, 1993).

However, when close relationships are discordant, they can also be associated with immune dysregulation. For example, pervasive differences in endocrine and immune function were reliably associated with hostile behaviors during marital conflict among diverse samples that included newlyweds selected on the basis of stringent mental and physical health criteria, as well as couples married an average of 42 years (Kiecolt-Glaser et al., 1997; Kiecolt-Glaser et al., 1993; Kiecolt-Glaser, Newton, et al., 1996; Malarkey, Kiecolt-Glaser, Pearl, & Glaser, 1994; Mayne, O'Leary, McCrady, Contrada, & Labouvie, 1997). Thus, although supportive personal relationships are associated with better immune function (Uchino et al., 1996), close personal relationships that are chronically abrasive or stressful may provoke persistent immune dysregulation.

On the basis of findings for negative affect and social support, aspects of personality or coping styles associated with negative moods or social relationships might well demonstrate immunological correlates under certain circumstances. For example, personality and coping styles such as repression, rejection sensitivity,

attributional style, and sociability have been associated with altered leukocyte counts in peripheral blood and dysregulated cellular immune function (Segerstrom, 2000). Indeed, optimism was associated with more positive moods, coping, and differences in response to stress among law students in their 1st year of study, and these differences appeared to mediate optimists' better immune function (Segerstrom et al., 1998). Similarly, in a sample of HIV-infected men, situational optimism about health outcomes was linked to slower immune decline, later symptom onset, and longer survival time among those with AIDS (Kemeny, 1994; Reed, Kemeny, Taylor, & Visscher, 1999). Among healthy older adults, a sense of coherence, an indicator of dispositional resilience, moderated the association between anticipation of moving and reduced NK cell lysis; low sense of coherence was associated with the poorest level of NK cell lysis (Lutgendorf, Vitaliano, et al., 1999).

In another arena, high hostility individuals exhibited greater increases in NK cell cytotoxity following self-disclosure than did those who were low on hostility (Christensen et al., 1996), consistent with the authors' hypothesis that persons high in cynical hostility would find disclosure more threatening; no differences between high- and low- hostility participants were observed in the nondisclosure condition. The data are consistent with prior data linking self-disclosure with heightened SNS activity (Christensen et al., 1996), as well as with the increased NK cell activity that follows short-term laboratory stressors (Kiecolt-Glaser et al., 1992).

The study of individual differences in PNI is still in its infancy, but the data are promising. As the data on personality and coping suggest, differences in perceptions and reactions to the same event can provoke different endocrine and immune responses. In fact, neuroendocrine mechanisms may mediate the associations between personality and coping styles and immune function (Segerstrom, 2000).

Interventions

PNI intervention studies have used a number of diverse strategies including hypnosis, relaxation, exercise, classical conditioning, self-disclosure, exposure to a phobic stressor to enhance perceived coping self-efficacy, and cognitive–behavioral therapies with a range of populations; earlier literature is reviewed elsewhere (Kiecolt-Glaser & Glaser, 1992). On the positive side, intervention work with HIV-seropositive individuals and malignant melanoma patients has produced promising results. An intensive group intervention for malignant melanoma, described in more detail in the *Cancer* section, had positive consequences for mood, immune function, and survival (Fawzy et al., 1993). One excellent series of studies demonstrated that 10-week cognitive–behavioral stress management (CBSM) and aerobic-exercise-training programs both buffered distress responses and immune alterations following notification of HIV seropositivity in asymptomatic men (Antoni, 1997; Schneiderman et al., 1994; Schneiderman, Antoni, Saab, & Ironson, 2001). The CBSM intervention also had positive consequences for mood and immune function in further studies with gay men whose disease had progressed to a symptomatic stage (Lutgendorf et al., 1997, 1998), and such effects have been maintained 6 to 12 months following the interven-

tion (Antoni et al., 2000). Changes in coping and social support related to the intervention appeared to mediate the reductions in distress. Additionally, neuroendocrine mediators of immune cell function associated with the CBSM intervention have been demonstrated (Antoni et al., 2000; Schneiderman et al., 2001).

Several researchers reported immunological differences between research participants who disclosed traumatic or upsetting events compared with those in a nondisclosure condition (Christensen et al., 1996; Esterling, Antoni, Fletcher, Margulies, & Schneiderman, 1994; Petrie, Booth, Pennebaker, Davison, & Thomas, 1995). In the typical paradigm, participants were randomly assigned to one of two groups: Half the participants wrote about traumatic or troubling experiences for 20 min on 4 consecutive days, whereas the remainder wrote about trivial events and experiences. Results have been interpreted as evidence for the link between inhibition of strong emotions and the development of physical disease (Petrie et al., 1995). The benefits of disclosure-based interventions may depend on the extent to which individuals become emotionally and cognitively involved in the disclosure process, reorganize the meaning of the traumatic event, and reduce avoidance of the stressful topic (Esterling, Antoni, et al., 1994; Lutgendorf, Antoni, Kumar, & Schneiderman, 1994).

Although classical conditioning of the immune response has been demonstrated in a number of animal studies, parallel studies with humans have been relative rarities. However, there are some provocative data; for example, there may be classical conditioning of immune suppression during chemotherapy (Bovbjerg et al., 1990), an important arena for further research. Among women receiving chemotherapy for ovarian cancer, proliferative responses to T-cell mitogens from peripheral blood samples drawn in the hospital just prior to the treatment showed immune suppression compared with samples obtained at home several days earlier, even after controlling for increased anxiety. Consistent with the interpretation of the process as conditioned immune suppression, patients also demonstrated an increase in conditioned nausea prior to treatment as well. Data from healthy adults demonstrate small increases in NK cell activity in response to neutral stimuli after pairing with injections of epinephrine (Buske-Kirschbaum, Kirschbaum, Stierle, Lehnert, & Hellhammer, 1992). In contrast, an effort to condition allergic skin responses was unsuccessful (Booth, Petrie, & Brook, 1995); further studies are needed to determine whether the lack of conditioning effects are due to small sample size, design of conditioning trials, or differences in conditionability among varying classes of immune variables.

Studies involving hypnotic interventions are suggestive that individuals may be able to alter skin inflammation following antigenic challenge (Zachariae, 2001). Use of the "double arm" technique has provided some of the better controlled hypnotic research. Investigators have used variations of this paradigm with both immediate and delayed hypersensitivity reactions; in these studies, participants were injected with the same antigen in both arms, and suggestions were made that one arm would show certain characteristic changes (e.g., wheal, erythema, itching, burning, and swelling), whereas the other would not. Although a number of prior studies using this methodology have shown positive findings (Kiecolt-Glaser & Glaser, 1992), one very well-controlled study, using a different antigen, found no effects (Locke et al., 1994). Further research is required to resolve whether intervention effects result from specific immune-related imagery and suggestions versus general effects of a relaxed state and to determine the importance of participant characteristics such as hypnotic susceptibility.

Why do some studies show effects but not others? What types of interventions and contexts are most likely to influence immune function? Some aspects of the immune response seem to be relatively insensitive to psychological stress (Herbert & Cohen, 1993); therefore, small effect sizes make it difficult to show relationships. Assays that assess the function or the performance of lymphocytes, rather than simple lymphocyte percentages or counts, are more likely to respond to psychological stress (Herbert & Cohen, 1993); moreover, the former also have greater relevance for health.

Additionally, if an individual's immune system is functioning satisfactorily, it may not be possible to enhance it above normal levels; in fact, it might be undesirable to do so. More is not necessarily better (e.g., an overactive immune system may lead to autoimmune disease). In the absence of any age-, disease-, or stress-related downward alterations in a study population's immune function, any intervention designed to enhance immune function could fail because of homeostatic regulation. As an analogy, if one's blood pressure were 110/70, it might be difficult to lower it further with a behavioral intervention, and it is questionable whether any concrete health benefits would accrue as a consequence.

It seems reasonable to assume that, in general, the narrower the scope of a behavioral intervention and the shorter its time course, the smaller and less enduring the impact, either psychological or immunological; a number of interventions have been brief, often limited to single sessions using imagery and hypnosis. In addition, longer follow-up periods are certainly desirable and may show changes not visible earlier, and this is likely to be particularly important for more intensive interventions (e.g., Fawzy et al., 1993).

Distress and poorer personal relationships appear to be associated with the down-regulation of immunity across a number of studies. Psychological or behavioral therapies are often targeted at one or both of these dimensions, and the addition of immunological measures to therapy outcome studies could produce very interesting results. Although studies to date suggest promising immune-related intervention effects, much methodological and dismantling work remains to be done to advance the current state of knowledge about important client characteristics (e.g., health status, stressors, age, hypnotic susceptibility), active and independent intervention components (e.g., relaxation/hypnosis, cognitive–behavioral strategies, social support, specific vs. nonspecific factors), intervention characteristics (duration, frequency, individual vs. group), and client-intervention matching and mediating mechanisms (e.g., negative affect, neuroendocrine) for producing health-relevant alterations in immune function.

Health Consequences

A growing literature supports the hypothesis that psychosocial factors have clinically significant relationships with immune-related health outcomes, including infectious disease, cancer, wound healing, autoimmune disease, and HIV. At the same time, there is limited direct empirical evidence for immune pathways responsible for these links, in part because of methodological issues (e.g., timing of blood samples). As the field advances, and new immunological technologies are developed, it is increasingly

clear that immune cell subpopulations perform specialized immunologic functions. Thus, future work should identify and examine immune measures that are directly relevant to particular health conditions. Of importance, PNI studies typically use a battery of in vitro assays; in human studies, in vitro assays are generally limited to peripheral blood samples, which may not reflect important immunological processes occurring in lymphoid organs or other regions, such as the skin (Glaser et al., 1999).

Infectious Disease

Infectious illnesses occur relatively infrequently in the general population, with most adults reporting only a few illness episodes a year. As a consequence, alterations in low base rates are difficult to detect, particularly with the relatively small sample sizes necessitated by the time and expense inherent in PNI research. As an alternative, to help demonstrate causal relationships between psychosocial stressors and the development of infectious illness, investigators have inoculated participants with a pathogen or a vaccine. For example, four laboratories have demonstrated that psychosocial factors can modulate the response to a Hep B vaccination (Glaser et al., 1992; Jabaaij et al., 1993; Marsland, Cohen, Rabin, & Manuck, 2001; Petrie et al., 1995). In data from two studies, spousal dementia caregivers were significantly less likely to show a clinically significant response to influenza virus vaccine than were noncaregivers (Kiecolt-Glaser, Glaser et al., 1996; Vedhara et al., 1999). Following vaccination, antibody titers to a pneumococcal vaccine fell over a 6-month period in dementia caregivers, whereas antibody titers were stable among former caregivers whose spouse had died and noncaregivers (Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000). Among a population of girls who had no previous exposure to rubella virus, those with higher negative affect and lower self-esteem were more likely to have lower antibody titers to a rubella virus vaccine at 10 weeks postvaccination (Morag, Morag, Reichenberg, Lerer, & Yirmiya, 1999). Volunteers who reported more enduring interpersonal difficulties with family or friends were substantially more likely to develop a cold following inoculation with a rhinovirus (S. Cohen et al., 1998). Moreover, increased IL-6 production was associated with greater self-reported and objective (mucus weight) symptoms of infection with influenza A virus and may be one mediator of the relationship between stress and symptoms of infection (S. Cohen, Doyle, & Skoner, 1999).

Studies such as these in which participants are inoculated with a pathogen or a vaccine provide researchers with a means of controlling exposure and dosage; moreover, because immune function may be assessed prior to the infectious challenge, these studies provide better data on causality than is possible with naturally occurring infections. Because individuals who were more stressed and more anxious showed a delay in the immune response to the vaccine (or showed no response), these same individuals might also be impaired in developing protective immunity to other pathogens; thus, they could be at greater risk for more severe illness. Indeed, adults who show poorer responses to vaccines also experience higher rates of clinical illness (Burns & Goodwin, 1990).

Cancer

Research that has attempted to link psychosocial stressors with tumor development or progression has faced many obvious difficulties, including etiology, treatment effects, tumor type, and stage of disease (Andersen, Kiecolt-Glaser, & Glaser, 1994; Kiecolt-Glaser & Glaser, 1999b). Cancer is composed of a heterogeneous group of diseases with multiple etiologies (Andersen et al., 1994), and immunological involvement varies across different cancers. Those cancers that are induced by chemical carcinogens (e.g., lung cancer) may be less influenced by psychological, behavioral, and immunological factors than are cancers that are associated with a virus such as Epstein–Barr Virus (EBV), which are immunogenic. Suppression of cellular immunity is associated with higher incidence of certain types of tumors, particularly leukemias and lymphoproliferative diseases in transplantation patients and Kaposi's sarcoma and EBV-associated B-cell lymphoma in AIDS patients (Herberman, 2001). Compelling evidence exists for the role of other cells of the immune system, particularly NK cells, in resisting the progression and metastatic spread of tumors once they have developed (Herberman, 2001). To establish clear links between psychosocial factors and tumor development and progression, the magnitude of immune dysregulation induced by behavioral and psychological factors must exceed the immune dysregulation associated with the malignant disease processes and treatment. Stage of disease can have profound effects on how patients feel, and cancer treatments such as chemotherapy and radiation therapy are associated with a number of side effects, including immunological toxicity. Despite these problems, several lines of work appear promising.

Substantial evidence has linked psychological stress with immune down-regulation, particularly alterations in NK cell activity (for a review see Kiecolt-Glaser & Glaser, 1999b). A study of breast cancer patients found that psychological stress predicted lower NK cell lysis and NK responses to cytokine stimulation (Andersen et al., 1998). However, although the immune system is likely a primary defense against only a subset of malignancies (many tumors are not recognized as foreign by the immune system and thus do not stimulate an immune response), stress may also enhance carcinogenesis through hormones, alterations in cellular DNA repair mechanisms, and/or effects on apoptosis (Kiecolt-Glaser & Glaser, 1999b). For instance, psychological stress was associated with higher blood levels of prostate-specific antigen, a marker for the development of prostate cancer; the specific physiological mechanisms underlying this relationship have yet to be identified (Stone, Mezzacappa, Donatone, & Gonder, 1999). These studies, along with the finding that depression and smoking had synergistic effects on reduced NK cell lysis (Jung & Irwin, 1999), underscore the importance of psychological variables in cancer risk assessments (Kiecolt-Glaser & Glaser, 1999c).

Fawzy et al. (1993) evaluated both the immediate and longer term effects of a 6-week structured group intervention that consisted of health education, enhancement of problem-solving skills regarding diagnosis, and stress management techniques. Among malignant melanoma patients, noteworthy intervention effects included reduced psychological distress and significant immunological changes compared with controls. A 6-year follow-up of these patients showed a trend toward greater recurrence, as well as significantly higher mortality in the control group than in intervention patients (Fawzy et al., 1993). Although the data are still quite limited, these studies and others suggest that psychological or behavioral factors may influence the initiation and/or progression

of cancer, at least in part, through psychosocial influences on hormones and immune function.

Wound Healing

Stress impedes wound healing, as well as some of the key immunological mediators in the early phases of wound repair, such as the proinflammatory cytokines. In studies that assessed repair of standardized wounds, the stress-related delays in healing ranged from 24% to 40% and the effect sizes (using a squared simple correlation as a measure of the proportion of variance in healing time accounted for by stress) were between .30 and .74 (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998); unquestionably, these effects are both statistically significant and clinically meaningful. Further work suggested a possible mechanism: Psychological stress has measurable negative consequences for proinflammatory cytokine production in the local wound environment (Glaser et al., 1999).

Indeed, the stress-related deficits in wound repair are consistent with a number of studies that have shown that greater fear or distress prior to surgery is associated with poorer outcomes, including longer hospital stays, more postoperative complications, and higher rates of rehospitalization (Contrada, Leventhal, & Anderson, 1994; Johnston & Vogele, 1993). Given the substantial consequences of stress for wound repair, and immune changes associated with distress, even relatively small alterations in anxiety could have substantial clinical consequences, both directly through physiological mechanisms and indirectly through increased pain and decreased compliance (Kiecolt-Glaser et al., 1998).

Autoimmune Diseases

In autoimmune diseases, a hyperactive immune response produces problems because it is unable to discriminate self from nonself and, as a consequence, attacks the body's own tissues. Suppression of the immune response is one treatment frequently used, with selection of medications, such as steroids, which inhibit various aspects of the immune response. Although there is ample anecdotal evidence linking stress with both exacerbation and remission of symptoms, the processes likely show considerable variability across the spectrum of autoimmune disorders and are not well understood (Rabin, 1999).

For example, animal and human data suggest that stress may play a role in the development and course of multiple sclerosis (MS); thus, to assess the possibility that differences in subjective and physiological responses to stress might underlie susceptibility of MS patients to stress-related exacerbations, researchers in one well-designed study compared patients' and controls' cytokine responses with a laboratory stressor (Ackerman, Martino, Heyman, Moyna, & Rabin, 1998). Although patients' and controls' stress responses did not differ, the authors suggested that psychological stress may enhance certain cellular immune responses that are potentially harmful to MS patients. Similar results were found in adolescents with and without asthma. Immune changes were observed during academic examination and laboratory stressors, but they did not differ between asthmatics and controls, and lung function did not decline in asthmatics during examination stress (Kang, Coe, & McCarthy, 1996).

In contrast, researchers in another study successfully predicted changes in rheumatoid arthritis disease states using a priori decision rules. Women with rheumatoid arthritis were followed for 12 weeks (Zautra et al., 1998); although T cell numbers, soluble IL-2 receptors, and clinician's ratings of disease activity increased during a week of increased interpersonal stress, women who reported more positive spousal interaction patterns and less spouse criticism or negativity did not show as large an increase in clinical symptoms. In this context, it is interesting to note that perturbations in the communication between the immune system and the brain have been hypothesized to produce inflammatory diseases such as rheumatoid arthritis, as well as affective disorders like major depression (Sternberg, Chrousos, Wilder, & Gold, 1992).

HIV

As described earlier, intervention work with HIV-seropositive individuals has produced promising results. In addition, several laboratories have attempted to relate psychological variables to immunological change and disease progression in people infected with HIV. More rapid disease progression has been associated with greater concealment of homosexual identity (Cole, Kemeny, Taylor, Visscher, & Fahey, 1996) and more cumulative stressful life events and less cumulative social support over a 5-year period (Leserman et al., 1999). Among Black women co-infected with HIV-1 and human papillomavirus (a viral indicator of cervical cancer), greater pessimism was associated with reduced NK cell lysis, indicating possible greater risk for future invasive cervical cancer, a Centers for Disease Control and Prevention-classified AIDS-defining disease (Byrnes et al., 1998). Alternatively, more deliberate cognitive processing about the death of a close friend or partner was associated with greater likelihood of finding positive meaning in the loss, less rapid decline in CD4+ cell levels, and lower rates of AIDS-related mortality over a 9-year period in HIV-seropositive men (Bower, Kemeny, Taylor, & Fahey, 1998). Among men with AIDS, situational optimism about health outcomes was linked to slower decline of immune function, later symptom onset, and longer survival time (Kemeny, 1994).

A number of additional studies have provided evidence of psychosocial correlates, for example Kemeny and her colleagues (Kemeny, 1994; Kemeny et al., 1995) compared men who had lost one or more close friends to AIDS in the prior year with men who had not. Higher levels of depressed mood were associated with lower numbers of CD4+ cells and increased expression of activation markers on lymphocytes in nonbereaved men, but not in bereaved men, a pattern that replicated across two cohorts. She suggested that higher depression scores may represent different processes in the two groups (e.g., grief in the bereaved, depressed mood in the nonbereaved), and the two processes may have different immunological correlates. In addition, men characterized by chronic and severe depression over a 2-year period demonstrated a sharper decline in CD4+ cells than nondepressed men who were matched on age and CD4+ levels at baseline (Kemeny, 1994). It should be noted that some researchers have found no ties between depression and progression (Lyketsos et al., 1993); however, others have argued that possible reasons for null findings may be related to heterogeneity of research populations on such key factors as disease stage, drug abuse history, gender, health behaviors, and age (Goodkin et al., 1994).

How Do Psychological Factors Influence Immune Function?

The endocrine system serves as one central gateway for psychological influences on health; stress and depression can provoke the release of pituitary and adrenal hormones that have multiple effects on immune function (Rabin, 1999). For example, social stressors can substantially elevate key stress hormones, including catecholamines and cortisol, and these hormones have multiple immunomodulatory effects on immune function (Glaser & Kiecolt-Glaser, 1994). In addition, distressed individuals are more likely to have multiple health behaviors that put them at greater risk, including poorer sleep, a greater propensity for alcohol and drug abuse, poorer nutrition, and less exercise, and these health behaviors have immunological and endocrinological consequences (Kiecolt-Glaser & Glaser, 1988). For instance, deep sleep is the normal stimulus for much of the release of growth hormone, a hormone that enhances a number of aspects of immune function (Veldhuis & Iranmanesch, 1996); thus, stressors that modify the architecture of sleep may also lessen growth hormone secretion. Moreover, even partial sleep loss 1 night results in elevated cortisol levels the next evening (Leproult, Copinschi, Buxton, & Cauter, 1997).

Although the endocrine system and health behaviors are likely the primary avenues whereby psychological factors influence immune function, there are other pathways, such as by means of SNS-innervation of lymphoid organs like the spleen (Ackerman et al., 1991). The endocrine system and SNS play central roles in the concept of "allostatic load," the cumulative long-term effects of physiological responses to stress (McEwen, 1998). In this conceptualization, the neuroendocrine system and SNS are considered primary mediators of allostatic processes, as they play central roles in a variety of adaptive processes and deleterious physiological outcomes. However, the strongest evidence implicating the neuroendocrine system and SNS as primary mediators in immune change in humans comes from laboratory studies of acute stress. Neuroendocrine and SNS mediation of immune changes related to chronic stress may also exist; for instance, lymphocyte insensitivity to glucocorticoids resulting from chronically elevated cortisol has been reported in Alzheimer's caregivers (Bauer et al., 2000), but such mediation has not been consistently demonstrated. Further work in this area is needed; these interactions are complex and require careful attention to methodological refinements in both endocrine and immune measures.

More broadly, recent evidence has implicated dysregulation of proinflammatory cytokines, a marker of chronic inflammation, as a central component across a range of diseases in older adults; particular emphasis has been placed on IL-6. Depression and distress enhance the production of proinflammatory cytokines, including IL-6 (Dentino et al., 1999; Lutgendorf, Garand, et al., 1999; Maes et al., 1995, 1999; Zhou, Kusnecov, Shurin, DePaoli, & Rabin, 1993). In addition, negative emotions may also contribute indirectly to the immune dysregulation evidenced by proinflammatory cytokine overproduction; repeated, chronic, or slow-resolving infections or wounds enhance secretion of proinflammatory cytokines, a process that can serve to further inhibit certain aspects of immune responses (e.g., IL-2, an important defense against infection), and thus may contribute to the immunodepression of aging (Catania et al., 1997). Certainly there is excellent evidence that stress impedes the immune response to infectious challenges, amplifying risks for contagion and prolonged-illness episodes; distress also provokes substantial delays in wound healing and enhances the risk for wound infection after injury (Rojas, Padgett, Sheridan, & Marucha, 2002).

Thus, negative emotions such as depression or anxiety can directly affect the cells of the immune system and either up- or down-regulate the secretion of proinflammatory cytokines. In addition, negative emotions may also contribute to prolonged or chronic infections or to delayed wound healing, processes that indirectly fuel proinflammatory cytokine production. These changes are likely to be greatest, and to carry the highest health risks, among the elderly, who already show age-related increases in IL-6 production (H. J. Cohen, 2000). Indeed, inflammation has recently been linked to a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, Type 2 diabetes, certain lymphoproliferative diseases or cancers (including multiple myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia), Alzheimer's disease, and periodontal disease (Ershler & Keller, 2000). Chronic inflammation has been suggested as one key biological mechanism that may fuel declines in physical function, leading to frailty, disability, and, ultimately, death (H. J. Cohen, Pieper, Harris, Rao, & Currie, 1997; Hamerman, 1999; Taaffe, Harris, Ferrucci, Rowe, & Seeman, 2000). For example, elevated serum IL-6 levels predicted future disability in older adults (Ferrucci et al., 1999), a finding the authors suggest may reflect the effects of the cytokine on muscle atrophy, and/or to the pathophysiologic role played by the cytokine in particular diseases. In fact, IL-6 may function as a "global marker of impending deterioration in health status in older adults" (Ferrucci et al., 1999, p. 645); even after the point at which risk factors such as cholesterol, hypertension, and obesity predict health deterioration less successfully among the very old, chronic inflammation continues to be an important marker (Ferrucci et al., 1999).

Future Directions

A well-functioning immune system is central to good health. Maladaptive immunological alterations may influence the etiology, progression, and/or severity of a variety of disorders or diseases; whereas infectious disease, certain cancers, wound healing, and autoimmune disease have been addressed in this brief review, the potential range is much broader, from ulcers to atherosclerosis (Rabin, 1999). Given its centrality, it is not surprising that conditions or processes that influence immune function can have diverse consequences for health. The field of PNI holds rich promise for helping to understand the interplay between psychological functioning and health.

Immune function declines with age, particularly functional aspects of the cellular immune response (Burns & Goodwin, 1990); these age-related decrements are thought to be associated with the greatly increased morbidity and mortality from infectious illness (and perhaps cancer) in the elderly. Furthermore, older adults show greater immunological impairments related to depression or stress than younger adults (Kiecolt-Glaser & Glaser, 1999a). Thus, older adults represent a particularly important population for PNI research and are likely to be a central focus in the future (Kiecolt-Glaser & Glaser, 2001).

There are now sufficient data to conclude that immune modulation by psychosocial stressors and/or interventions can lead to actual health changes. Although changes related to infectious disease and wound healing have provided the strongest evidence to date, the clinical importance of immunological dysregulation is highlighted by increased morbidity and mortality risks across diverse conditions and diseases related to proinflammatory cytokines (Harris et al., 1999; Papanicolaou, Wilder, Manolagas, & Chrousos, 1998). The PNI field has grown tremendously in the past 2 decades, and the future appears quite promising.

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