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Stress, Personal Relationships, and Immune Function: Health Implications

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INTRODUCTION

The invitation to present the Norman Cousins Memorial Lecture to the Psychoneuroimmunology Research Society is a distinct honor; this recognition is clearly shared by my primary collaborator, Ronald Glaser, who has had equal responsibility for the design of our studies and whose laboratory generated most of the immunological data I will describe. We have addressed a number of questions since we initiated our joint research program in 1982: How do commonplace, everyday stressors affect the immune response? What are the health consequences of stress-related immunological changes? Does a chronic stressor promote persistent immunological dysregulation? Does age pose an additional risk factor? I will address each of these topics briefly; however, as a clinical psychologist, the studies of greatest interest to me are those that have examined the links between close personal relationships and immune responses and, in turn, how these elements are translated into important health outcomes. Thus, these issues will be my primary focus.

EARLY WORK: EXAMINATIONS AS A STRESSOR

Prior to the collaborative research we initiated in the early 1980s, the limited knowledge about stress and its impact on immune function in humans came from a handful of studies that dealt with very intense or novel stressors, e.g., bereavement, astronauts' responses to space flight, or 48 h of noise and sleep deprivation (Bartrop, Luckhurst, Lazarus, Kiloh, & Penny, 1977; Kimzey, 1975; Palmblad, 1981). In contrast, our early work addressed the question of whether very commonplace stressors like academic examinations could down-regulate immune function.

A series of prospective studies of medical students' responses to examinations showed transient changes in multiple facets of the cellular immune response and its mediators, including decreased natural killer (NK) cell activity, decreased gamma interferon production by lymphocytes stimulated with Con A, increased plasma and intracellular levels of cyclic AMP, and decreased proliferative responses to mitogens (Glaser et al., 1987; Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986; Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984; Kiecolt-Glaser et al., 1986). These stress-related changes in the competence of the cellular immune response had implications for control of latent herpesviruses (Glaser & Kiecolt-Glaser, 1994; Glaser,

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Kiecolt-Glaser, Speicher, & Holliday, 1985; Glaser et al., 1991). Further work showed decrements in the synthesis of interleukin 2 receptor (IL-2R) mRNA by peripheral blood leukocytes (PBLs), percentages of IL-2R positive cells, and the level of IL-2 in cultures of cells (Glaser et al., 1990); these were the first data to suggest that stress-associated decrements in immunity could be observed at the level of gene expression. Moreover, the incidence of self-reported infectious illness symptoms increased around examination periods (Glaser et al., 1987), evidence that these immunological changes have health consequences.

An additional important finding relevant to health was the demonstration that stress influenced medical students' response to a series of three hepatitis B (Hep B) inoculations, each given on the last day of a 3-day examination series (Glaser, Kiecolt-Glaser, Bonneau, Malarkey, & Hughes, 1992). A quarter of the students (12/48) seroconverted after the first inoculation. These students were significantly less stressed and less anxious than those students who did not seroconvert until after the second inoculation. In addition, students who reported greater social support demonstrated a stronger immune response to the vaccine at the time of the third inoculation, as measured by antibody titers to a Hep B surface antigen (HBsAg) and the blastogenic response to a viral peptide.

The evidence that the immune response to a vaccine can be modulated by a relatively mild stressor in young, healthy adults is a finding with public health implications. Moreover, these data provide a window on the body's response to other pathogens, such as viruses or bacteria. Students who were more stressed and more anxious seroconverted later, suggesting that these same students might also be slower to develop an antibody response to other pathogens; thus, theoretically, they could be at greater risk for more severe illness.

Taken together, these data suggested that academic stress could modulate a variety of different immunological activities, and these changes had health implications. Like most professional students, our medical students were ''experts'' at taking tests—they had long histories of performing well under these very conditions. The fact that something as transient, predictable, and relatively benign as examination stress had significant consequences for immune modulation suggested that other everyday stressors could produce similar alternations.

INTERVENTION STUDIES

Several subsequent studies were designed to assess whether interventions that reduced stress could have positive effects on immune function. To test the hypothesis that a stress-reducing intervention might enhance immunity, 45 older adults were randomly assigned to one of three protocols (relaxation training, social contact, or no intervention). Relaxation subjects showed a significant enhancement in NK cell activity at the end of the 1-month intervention, as well as lower antibody titers to a herpes simplex type I antigen, in comparison to nonsignificant changes in the other two groups (Kiecolt-Glaser et al., 1985). These data provided the first well-controlled demonstration of immune enhancement via a behavioral intervention.

A second study investigated the possibility that a hypnotic/relaxation intervention might have prophylactic value for some aspects of cellular immunity if used before a stressor (Kiecolt-Glaser et al., 1986). Half of a group of 34 medical students were randomly assigned to a hypnotic/relaxation group that met in the interval between baseline and examination blood draws. NK cell activity and percentages of helper

T-lymphocytes declined in both groups during examinations. However, subjects in the hypnotic/relaxation group showed wide variability in their frequency of relaxation practice, ranging from 5 to 50 times; regression analyses showed that more frequent practice was associated with higher helper T-lymphocyte percentages during exams after controlling for baseline levels.

In a study that explored the tie between self-disclosure and immune function, 50 undergraduates were randomly assigned to one of two groups: Half the subjects wrote about traumatic or troubling experiences for 20 min on 4 consecutive days, while the remainder wrote about trivial events and experiences (Pennebaker, Kiecolt-Glaser, & Glaser, 1988). Individuals who wrote about traumatic or upsetting events demonstrated a higher mitogen response following baseline than control subjects. Indeed, individuals who wrote about experiences they had not shared previously with other people had a better lymphocyte proliferative response than those subjects who had discussed the experiences previously. Importantly, the intervention was associated with positive health outcomes, in addition to immune change: Trauma subjects' average number of monthly health center visits dropped following the study, while control subjects' visits increased. Thus, these intervention data provided evidence that self-disclosure, an important facet of close personal relationships, was related to immune function and health.

PERSONAL RELATIONSHIPS AND IMMUNE FUNCTION

Other data from our research program have addressed the association between immune function and the quality of personal relationships. For example, lonelier medical students had lower NK cell activity than students who were not as lonely (Kiecolt-Glaser et al., 1984). Medical students who reported greater social support mounted a stronger immune response to hepatitis B vaccine than those with less support (Glaser et al., 1992). Spousal caregivers of dementia sufferers who reported lower levels of social support on entry into our 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 caregivers who showed greater augmentation (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994; Esterling, Kiecolt-Glaser, & Glaser, 1996). However, the support provided by certain key personal relationships is obviously more important than others: Data from national surveys suggest that marital happiness contributes far more to global happiness than any other variable, including satisfaction with work and friendships (Glenn & Weaver, 1981). Marital dissolution has well-documented health consequences; divorced and separated individuals have poorer mental and physical health than comparable widowed, married, or single adults. Indeed, separated and divorced adults have the highest rates of acute medical problems, of chronic medical conditions that limit social activity, and of disability, even when age, race, and income are controlled; of particular relevance for immune function is the fact that separated/divorced individuals have higher rates of mortality from certain infectious diseases, including up to six times as many deaths from pneumonia (Verbrugge, 1982).

While divorce is quite stressful, some individuals adapt much more quickly than others. Evidence from the divorce literature suggests that continued preoccupation with the (ex)spouse, called ''attachment,'' leads to postseparation increases in physi-

cal and psychological symptomatology (Kitson, 1982). Since attachment bonds are normally formed within the first 2 years of marriage, length of marriage is neither a good predictor of attachment nor a good predictor of adjustment following divorce. Factors that have been associated with less attachment include greater time since separation, the development of a new relationship, and being the initiator of the separation (Kitson, 1982).

Psychological adaption following separation may occur over a several-year period. For example, one study (Wallerstein & Kelly, 1980) found that it took 3.3 years after separation before the average woman's life assumed a sense of coherence and stability; however, it is noteworthy that 42% of the women studied had not fully adjusted to their divorce even 5 years after separation. After learning about these relatively long-lasting effects, we wondered if there might be similarly persistent alterations in immune function associated with marital disruption. Thus, we initiated two studies on marital separation/divorce.

When we compared 38 women who had separated from their husbands up to 6 years previously with 38 married women who were comparable in age, education, and number of children, we found that the married women had better immune function (Kiecolt-Glaser et al., 1987). Within the group of separated and divorced women, both shorter separation periods and stronger feelings of attachment were associated with poorer immune function and greater depression and loneliness. Among a group of 32 separated and divorced men, those men who had separated within the last year and those who had initiated the separation were less depressed and lonely than noninitiators.

Although loss of a spouse was linked to adverse changes, the simple presence of a spouse was not necessarily protective; lower marital satisfaction was associated with poorer immune function, as well as greater depression and loneliness (Kiecolt-Glaser et al., 1987, 1988). These data were provocative, but the cross-sectional designs precluded inferences about the direction of causality, e.g., people who were more depressed might have viewed their marriages as less supportive, and/or their depressive symptoms might have potentiated immunological down-regulation. Accordingly, we designed a longitudinal study to assess the impact of marital discord prospectively.

MARITAL STUDIES: NEWLYWED COUPLES

We used a rigorous, multistage process to select 90 newlywed couples who met stringent mental and physical health criteria. Each couple was admitted to a hospital research unit for 24 h to provide a detailed assessment of conflict resolution behaviors and changes in autonomic, endocrine, and immune function (Kiecolt-Glaser, Malarkey, Cacioppo, & Glaser, 1994; Kiecolt-Glaser et al., 1993, 1996b; Malarkey, Kiecolt-Glaser, Pearl, & Glaser, 1994).

For frequent, unobtrusive endocrine sampling during the 30-min conflict resolution, a long polyethylene tube was attached to a heparin well in each spouse's arm, allowing nurses to draw blood samples at set intervals, out of couples' sight. These sessions were videotaped and scored for problem-solving behaviors using the Marital Interaction Coding System (MICS; Weiss & Summers, 1983). Negative or hostile behaviors were strongly related, $r = .74$, $p < .001$, so we summed them for each couple, following the convention in other marital research (Ewart, Taylor, Kraemer, & Agras, 1991); also, we were interested in the couple's negative be-

havior total because we assumed that one partner's behavior affected the other. We divided the resulting frequencies at the median to form high and low hostile groups, with higher scores on this dimension reflecting higher frequencies of negative behaviors.

Endocrine data demonstrated the significant impact of hostile behaviors during marital conflict on changes in serum levels of epinephrine (EPI), norepinephrine (NEPI), ACTH, growth hormone (GH), and prolactin (PRL). Moreover, differences in the pattern of change were apparent between the behaviorally defined groups, with more negative couples showing more persistent elevations on EPI, NEPI, ACTH, and GH and continuing 15 min after the problem-solving discussion had ended. These MICS groups did not differ at baseline on hostility or anxiety scales, positive or negative affect scales, social support from other relationships, parental history of hypertension or cardiovascular disease, MICS-coded positive or avoidant behaviors, social desirability responding, or health behaviors.

Two blood samples for immunological analyses were drawn at the beginning and the end of couples' 24-h hospital visit, between 6:00 and 8:00 AM each time to minimize diurnal variation. The immunological battery provided data on functional and quantitative *in vitro* changes in a spectrum of cellular immunological functions (Kiecolt-Glaser et al., 1993). Subjects who exhibited more negative or hostile behaviors during a 30-min discussion of marital problems showed greater decrements over 24 h relative to low negative subjects on four functional immunological assays (NK cell lysis, blastogenic response to two mitogens, and the proliferative response to a monoclonal antibody to the T3 receptor). Women were more likely to show negative immunological changes than men.

EBV VCA IgG antibody titers, assayed only once because of the temporal stability of IgG, were significantly higher among more hostile couples than those who were less hostile. Higher antibody titers to a latent herpesvirus like EBV suggest that the cellular immune response is less competent in controlling the latent virus (Glaser & Kiecolt-Glaser, 1994). The differences found on this assay in the face of its 20-day half-life suggested that the relationships found between marital behavior and immune function were not limited to the laboratory, i.e., the immune changes found over the 24 h parallel longer term processes.

In further analyses, blood samples acquired hourly from 8:00 AM through 10:00 PM were pooled to provide composite daytime values for six hormones; these data allowed us to examine relationships between conflict behaviors observed during the 30-min discussion and more enduring or persistent endocrine changes (Kiecolt-Glaser et al., 1996b). Consistent with the gender differences in immune function, we found stronger and more consistent links between behavior and endocrine function among women than men. For wives, higher probabilities of husband's withdrawal in response to wife's negative behavior were associated with higher NEPI and cortisol levels; this ''demand/withdraw'' sequence has been associated with greater marital distress in a number of marital studies (Christensen, 1987; Heavey, Layne, & Christensen, 1993). In addition, wives who showed higher frequencies of positive behaviors during conflict had lower EPI levels. In contrast, none of the six hormones was significantly associated with husbands' behavioral data.

The magnitude of the relationships were noteworthy: Among women, behavior accounted for 24% of the variance in EPI and cortisol, 29% of the variance in NEPI, and 37% of the variance in prolactin (Kiecolt-Glaser et al., 1996b). To illustrate the

biological implications of the cortisol data, a wife who fell 1.5 SD above the mean for the demand/withdraw behavioral sequence and at the mean on all other predictors (i.e., holding other values constant) would show a predicted cortisol level of 15.28 ng/ml, while a woman 1.5 SD below the mean would have a predicted cortisol of only 7.71 ng/ml—about half as large. Thus, marital conflict behaviors were linked to persistent (and biologically relevant) elevations in cortisol.

Might our pooled endocrine samples simply reflect acute changes during conflict? Both biological and statistical considerations argue strongly against such an interpretation. The pooled endocrine samples represent a summary measure across 15 different time points, from 8 AM through 10 PM. The half-life for cortisol is 90 min, the longest among the six hormones; normal turnover or decay rapidly diminishes any extreme neuroendocrine peaks in the absence of further stimulation. In addition, the conflict discussion and the preparatory interview lasted less than an hour, and a single point would have had to be remarkably high to eclipse the other 14 values; the average magnitude of change across hormones was clearly not sufficient (Malarkey et al., 1994). Accordingly, these pooled data provide a window on endocrine function in couples for whom the day included a disagreement, in accord with the changes in immune function that occurred over the 24 h between couples' hospital admission and discharge. These data suggested that marital discord could indeed produce adverse autonomic, endocrinological, and immunological changes in spite of the high marital satisfaction of our newlywed couples and the healthy lifestyles demanded by our exclusion criteria.

MARITAL STUDIES IN OLDER ADULTS

While the findings from newlyweds provided provocative data on the pathways through which close personal relationships could affect physiological functioning and health, it was unclear if marital discord would continue to provoke physiological change in middle-aged or older couples. For example, the greater predictability of conflicts in longer term marriages might blunt physiological responses over time. Moreover, older couples display less negative behavior and more affectionate behavior during marital conflict than younger couples (Carstensen, Levenson, & Gottman, 1995), and thus physiological responses might similarly be muted. To assess the generalizability of physiological changes observed with younger couples, a similar laboratory paradigm was used to study endocrinological and immunological responses to marital conflict in 31 older couples (mean age = 67) who had been married an average of 42 years (Kiecolt-Glaser et al., 1997). Consistent with the data from newlywed couples, both endocrinological and immunological data showed significant relationships to negative behavior during marital conflict in these older couples.

Among wives, escalation of negative behavior during conflict and marital satisfaction showed strong relationships to endocrine changes, accounting for 16 to 21% of the variance in the rates of change of cortisol, ACTH, and NEPI. In contrast, husbands' endocrine data did not show significant relationships with negative behavior or marital quality. Both men and women who demonstrated relatively poorer immunological responses across three functional assays (the blastogenic response of PBLs to two T-cell mitogens and antibody titers to latent EBV) displayed more negative behavior during conflict; they also characterized their usual marital disagreements as more negative than individuals who showed better immune responses across assays.

These data demonstrate that abrasive marital interactions have physiological conse-

quences even among older adults in long-term marriages. In fact, these data may underestimate the actual physiological impact of marital discord, since the older couples were generally quite happy, and their marriages had endured.

Clearly, marriages can have psychological and physiological repercussions. Indeed, our meta-analysis of autonomic, endocrine, and immune data related to social support showed that family relationships were of particular importance in this regard (Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Thus, these marital studies provided the first ''close-up'' view of endocrine and immune alterations associated with interpersonal behavior in humans.

CONSEQUENCES OF ANOTHER CHRONIC STRESSOR: DEMENTIA CAREGIVING

Men and women who provide long-term care for a spouse with Alzheimer's disease typically report high levels of stress as they attempt to cope with the patient's problematic behaviors (Kiecolt-Glaser et al., 1991; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996a). Consistent with our marital interaction data, a number of studies also suggest that dementia family caregiving, another persistent interpersonal stressor, can have endocrinological and immunological consequences.

In an early study, we assessed changes in depression, immune function, and health in 69 spousal caregivers who had already been caregiving for an average of 5 years (Kiecolt-Glaser et al., 1991). Between the initial sample (''intake'') and the follow-up data collected an average of 13 months later, these caregivers showed decrements relative to 69 sociodemographically matched control subjects on three measures of cellular immunity; the former also reported significantly more days of infectious illness, primarily upper respiratory tract infections, than the latter. Caregivers who reported lower levels of social support at intake and who were most distressed by dementia-related behaviors showed the greatest and most uniformly negative changes in immune function at follow-up.

In a further study, we examined differences among current dementia spousal caregivers, former (bereaved) caregivers whose spouse had died, and noncaregiving controls (Esterling et al., 1994). Although an average of over 2 years had elapsed since bereavement, former caregivers did not differ from continuing caregivers on depressive symptomatology or perceived distress; moreover, both groups were more depressed and reported more stress than control subjects. As was true in data from another caregiver project (Irwin et al., 1991), we found no differences in NK cell cytotoxicity between either the continuing or former caregiver groups or control subjects in the absence of cytokine stimulation. However, continuing and former caregivers did differ in the ability of their NK cells to respond to recombinant interferon-gamma and recombinant interleukin-2 (rIFN-γ and rIL-2) *in vitro:* Both caregiver groups had a poorer response than controls.

The NK cell cytotoxicity of the continuing and former caregivers was highly skewed toward low responding (i.e., responding below the median for the population) following stimulation with either rIFN-γ or rIL-2. Compared to caregivers who were high responders to at least one cytokine, caregivers who were low responders to both cytokines reported significantly less positive social support, less emotional closeness in their social contacts, and more physician visits for infectious illness symptoms. Even though our former caregivers could still be defined as compromised in their response to cytokine stimulation even 2 years postbereavement, there may be even-

tual recovery; caregivers who had been bereaved for longer periods of time had significantly better responses to both cytokines.

A follow-up study using cell preparations enriched for NK cells (approximately 90%) replicated the previously observed group differences between caregivers (current and former) and controls (Esterling et al., 1996). In addition, higher levels of social support were associated with heightened NK cell responses to cytokines, independent of level of depression.

Thus, caregiving has immunological consequences, and the immunological dysregulation of this chronic stressor can continue at measureable levels, even after cessation of actual caregiving activities. The fact that former caregivers continue to be more distressed than controls may account, in part, for the persistent maladaptive changes; our longitudinal data suggest that caregivers continue to show higher rates of syndromal depressive and anxiety disorders than controls for as long as 3 years after bereavement, the maximum period for which we currently have analyzed our follow-up data (Bodnar & Kiecolt-Glaser, 1994). In addition to their greater risk for syndromal affective disorders, bereaved caregivers continue to report significantly more depressive symptoms than controls. We cannot disentangle the effects of bereavement from caregiving, because we do not have similar longitudinal data on bereaved noncaregivers; however, the persistent affective symptomatology in our bereaved caregivers differs from the typical patterns following bereavement for noncaregivers (Harlow, Goldberg, & Comstock, 1991; Thompson, Gallagher-Thompson, Futterman, Gilewski, & Peterson, 1991).

Caregivers' high levels of syndromal depressive disorders both during and after caregiving are particularly noteworthy in light of recent evidence that the long-term outcome of depressive episodes may be much less favorable than had been previously assumed, with many depressed individuals either failing to recover or frequently relapsing (Alexopoulos, Young, Abrams, Meyers, & Shamoian, 1989). Moreover, an increased relapse rate is associated with an older age of onset for depressive episodes (Alexopoulos et al., 1989). In addition, impaired social relationships are characteristic of both currently depressed individuals and remitted depressives (George, Blazer, Hughes, & Fowler, 1989). Both size of social network and subjective social support are significant predictors of follow-up depressive symptoms, after controlling for initial depressive symptoms (George et al., 1989). Since caregivers have smaller networks and describe their relationships as less supportive than controls before bereavement (Kiecolt-Glaser et al., 1991), there are additional reasons for concern about recurrent depression after bereavement.

While the immune dysregulation can be explained by such psychosocial processes, there are also important biological processes to consider. Indeed, it is possible that the continuing immune dysregulation reflects other mechanisms. In particular, the glucocorticoid cascade hypothesis suggests that chronic stress may accelerate the process of immune down-regulation associated with aging (Sapolsky, Krey, & McEwen, 1986). Thus, the chronic stress of caregiving may also serve to accelerate the aging of the immune response. The final section provides additional data on immunological changes observed in caregivers and addresses their significance for health.

HEALTH IMPLICATIONS

The immunological decrements associated with the stress of caregiving are of particular concern because older individuals' age-related reductions in cellular immune

function have important health consequences: Respiratory infections such as influenza and pneumonia are major causes of morbidity and mortality among the elderly, and many older adults do not respond to influenza virus vaccines (or other novel antigens) as efficiently as younger adults (Burns & Goodwin, 1990; Hobson, Curry, & Beare, 1972; Patriarca, 1994; Phair, Kauffmann, Bjornson, Adams, & Linnemann, 1978). Adults who show poorer responses to vaccines and other antigenic challenges also experience higher rates of clinical illness, including influenza virus infection (Burns & Goodwin, 1990; Gravenstein et al., 1994; Hobson et al., 1972). Thus, we examined the immune responses to influenza virus vaccination in spousal caregivers and matched noncaregiving control subjects.

Caregivers exhibited significant deficits relative to controls in antibody and virus specific T-cell responses to an influenza virus vaccine (Kiecolt-Glaser et al., 1996a); the former were less likely to display a fourfold increase in antibody titers 4 weeks after vaccination, they had lower levels of *in vitro* stimulated IL-1β, and their PBLs produced lower levels of IL-2 in response to vaccine (antigen) stimulation. These data suggest that caregivers are more vulnerable than their age peers to influenza virus infection and, potentially, to other infectious agents (Burns & Goodwin, 1990; Hobson et al., 1972).

Moreover, the stress-related differences in IL-1β observed in our influenza virus vaccine study may have implications for health beyond infectious disease. Proinflammatory cytokines such as IL-1 play a role in wound healing by preparing injured tissue for repair and enhancing phagocytic cell recruitment (Lowry, 1993). Indeed, we found similar differences in IL-1β in a separate study using an additional 13 caregivers and 13 matched controls (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995); in addition, those 13 caregivers took an average of 9 days longer to heal a 3.5-mm punch biopsy wound than controls, i.e., 24% longer to repair a small, standardized wound.

Further research assessed the impact of academic examinations on alterations in mucosal wound repair. As described earlier, our prior work demonstrated that medical students' cellular immune responses during examinations were poorer than those measured in the same individuals during lower stress periods (Kiecolt-Glaser & Glaser, 1991); thus, we were interested in whether the distress associated with exams would modulate mucosal wound healing among a group of 11 dental students (Marucha, Kiecolt-Glaser, & Favagehi, 1998). Wounds placed 3 days before a major test healed an average of 40% more slowly than those made during summer vacation, and the differences were quite reliable: No student healed as rapidly during this stressful period as during vacation, and no student produced as much IL-1. While this study demonstrated differences in mucosal wounds, the critical early events in the wound healing process are virtually identical for oral and dermal wounds (Wikesjö, Nilvéus, & Selvig, 1992). Accordingly, these stress-related deficits have broad implications for surgical recovery (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998), consistent with evidence that greater distress or anxiety prior to surgery is associated with a slower and more complicated postoperative recovery (Johnston & Wallace, 1990; Mathews & Ridgeway, 1981).

A central question throughout much of the PNI literature has been the extent to which stress-induced immune changes have consequences for morbidity and mortality. These newer data on wound repair provide clear evidence of important health effects in one domain. As already discussed, several studies have demonstrated stress-related modulation of vaccine responses in both younger and older subjects (Glaser

et al., 1992; Jabaaij et al., 1993; Kiecolt-Glaser et al., 1996a), one proxy for infectious illness risk because they demonstrate alterations in immunological responses to challenge under well-controlled conditions. In addition, other researchers (Cohen, Tyrrell, & Smith, 1991) have shown that stress can alter susceptibility to cold viruses. Thus, data from human studies now provide solid evidence that psychological stress can have important consequences for both immune function and health.

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