Psychoneuroimmunology and Psychosomatic Medicine: Back to the Future

JANICE K. KIECOLT-GLASER, PHD, LYNANNE MCGUIRE, PHD, THEODORE F. ROBLES, BS, AND RONALD GLASER, PHD

Objective: Although psychological modulation of immune function is now a well-established phenomenon, much of the relevant literature has been published within the last decade. This article speculates on future directions for psychoneuroimmunology research, after reviewing the history of the field. **Methods:** This review focuses on human psychoneuroimmunology studies published since 1939, particularly those that have appeared in *Psychosomatic Medicine*. Studies were clustered according to key themes, including stressor duration and characteristics (laboratory stressors, time-limited naturalistic stressors, or chronic stress), as well as the influences of psychopathology, personality, and interpersonal relationships; the responsiveness of the immune system to behavioral interventions is also addressed. Additionally, we describe trends in populations studied and the changing nature of immunological assessments. The final section focuses on health outcomes and future directions for the field. **Results:** There are now sufficient data to conclude that immune modulation by psychosocial stressors or interventions can lead to actual health changes, with the strongest direct evidence to date in infectious disease and wound healing. Furthermore, recent medical literature has highlighted a spectrum of diseases whose onset and course may be influenced by proinflammatory cytokines, from cardiovascular disease to frailty and functional decline; proinflammatory cytokine production can be directly stimulated by negative emotions and stressful experiences and indirectly stimulated by chronic or recurring infections. Accordingly, distress-related immune dysregulation may be one core mechanism behind a diverse set of health risks associated with negative emotions. **Conclusions:** We suggest that psychoneuroimmunology may have broad implications for the basic biological sciences and medicine.
Key words: psychoimmunology, social support, neuroimmunomodulation, wound healing, stress.

CRP = C-reactive protein; DTH = delayed-type hypersensitivity; EBV = Epstein-Barr virus; HLA = human leukocyte antigen; HSV = herpes simplex virus; Ig = immunoglobulin; IL = interleukin; NK = natural killer; PHA = phytohemagglutinin; PNI = psychoneuroimmunology; PTSD = posttraumatic stress disorder.

INTRODUCTION

Although psychological modulation of immune function is now a well-established phenomenon, much of the relevant literature has been published within the last decade. Indeed, the bidirectional communication between the immune system and the central nervous system was ignored in immunology textbooks until relatively recently (1). In this article we review the development of the PNI field, and we explore promising directions for future work.

Our literature search focused on human and animal studies published in *Psychosomatic Medicine* since its debut in 1939, with selective inclusion of other relevant work; this journal has been the premier outlet for novel and creative psychologically oriented human PNI studies for many decades. Although not specifically reviewed in this article, it is important to note that PNI emerged within the context of broader psychosomatic investigations, beginning as early as the 1940s. These studies related psychological characteristics, behaviors, and emotions with disease onset and progression, including allergy, asthma, peptic ulcer, cancer, autoimmune diseases, and infectious diseases. Although we do not review the broader psychosomatic literature, the body of knowledge generated by earlier work has clearly informed the development of the PNI field. Indeed, some PNI studies, in which a specific immune variable is examined in the context of psychological processes and health outcomes, are extensions of early psychosomatic studies.

For this PNI review, we searched for articles reporting studies that included immunological assays or those that used an in vivo immune challenge; case studies and reports addressing immunologically related diseases were excluded if they did not fit these criteria (eg, relating life events to the frequency of respiratory infections). Because this review focuses on the pathway leading from psychological states or behavior to immune function and physical health, studies in which behavior was the dependent variable were typically excluded; thus, for example, studies that examined relationships between psychological constructs (eg, personality or mood) and immune-related diseases were not included if there were no immunological data. Similarly, although there are obvious mutual influences, studies that simply used an illness as a stressor, without attempting to relate changes in immune function to physical health, were not considered.

From the Departments of Psychiatry (J.K-G., L.M., T.F.R.), Molecular Virology, Immunology, and Medical Genetics (R.G.), and Psychology (T.F.R.), Ohio State University, and Ohio State Institute for Behavioral Medicine Research (J.K-G., R.G.), Columbus, OH.

Address reprint requests to: Janice K. Kiecolt-Glaser, PhD, Department of Psychiatry, Ohio State University College of Medicine, 1670 Upham Dr., Columbus, OH 43210. Email: kiecolt-glaser.1@osu.edu

Received for publication December 14, 2000; revision received April 20, 2001.

0033-3174/02/6401-0015

As Figure 1 makes clear, PNI research represents a substantial and rapidly growing force in psychosomatic medicine as a field. The sheer number of PNI reports published in this journal over the last decade dictated selectivity for this review. The breadth and complexity of psychological topics examined within PNI has steadily increased over time in the course of development of the field, specifically within *Psychosomatic Medicine*, as is illustrated in Figure 2. Additionally, the PNI-related focus in *Psychosomatic Medicine* has shifted over time toward greater emphasis on studies involving humans and less emphasis on nonhuman animal studies. Other journals that also publish substantial numbers of human PNI studies and behaviorally based animal PNI studies include *Health Psychology, Brain, Behavior, and Immunity, Neuroimmunomodulation,* and the *Journal of Neuroimmunology*; additionally, PNI studies in a number of psychiatric journals have typically addressed immunological correlates of psychiatric diagnoses.

For this review, studies were clustered on the basis of key themes, including stressor duration and characteristics (laboratory stressors, time-limited naturalistic stressors, or chronic stress), as well as the influences of psychopathology, personality, and interpersonal relationships; the responsiveness of immune function to behavioral interventions is also addressed (Figure 2). For each key theme, we link earlier immune-related research (typically pre-1970, depending on the topic) with research from the past two decades. Additionally, we describe trends in populations studied and the changing nature of immunological assessments. The final section focuses on health outcomes and speculation about future directions for the field.

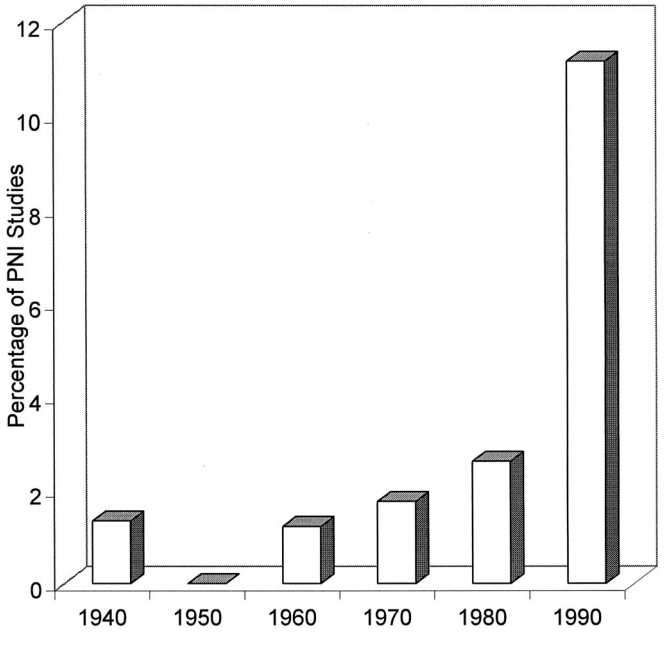

Fig. 1. The explosion of PNI research in the 1990s is illustrated by the increased percentage of PNI original articles, rapid communications, and case reports relative to the total number of such studies published in *Psychosomatic Medicine* by decade. The majority of PNI studies were published in the 1990s, accounting for more than 66% of all the PNI studies published in *Psychosomatic Medicine* from 1939 to 2000.

Two PNI milestones should be highlighted. In 1964 George F. Solomon et al. (2) coined the term "psychoimmunology" and published a landmark paper: "Emotions, immunity, and disease: a speculative theoretical integration." Despite this notable paper, few PNI studies appeared before the 1980s. The explosive growth in both animal and human PNI studies was stimulated by Ader and Cohen's (3) seminal 1975 demonstration of classic conditioning of immune function. For additional historical information, interested readers should consider a chapter by Ader (4), Solomon's entertaining autobiography (5), or an excellent clinically oriented book by Rabin (6).

PSYCHOPATHOLOGY

Interest in the relationship between psychiatric syndromes or symptoms and immune function has been a consistent theme across decades (Figure 2). Early studies of psychiatric patients reported immune alterations in psychotic patients, including numbers of lymphocytes (7, 8) and poorer antibody response to pertussis vaccination (9), compared with nonpsychiatric control subjects. Subsequently, immunological alterations have been reported across a range of psychiatric disorders (10–12). However, the great majority of psychopathologically focused studies have examined immunological alterations associated with affective and anxiety symptoms and disorders (13–27). There is excellent evidence that depression and anxiety enhance the production of proinflammatory cytokines, including IL-6 (13, 28–31), an important finding related to the broad literature on the morbidity and mortality associated with depressive and anxiety disorders (13, 32), as discussed in the final section.

In addition to syndromal depressive disorders, depressive symptoms can also provoke immune alterations, and this dysregulation may have health consequences. For example, elevated depressive symptoms were associated with lower $CD8^+$ T-lymphocyte counts and a higher rate of genital HSV-2 recurrence over 6 months (18). Depressive symptoms in HIV-seropositive gay men were linked with decreased $CD4^+$ T-cell counts, increased B-cell counts, and increases in an immune activation marker (HLA-DR) even when health behaviors and disease stage were controlled

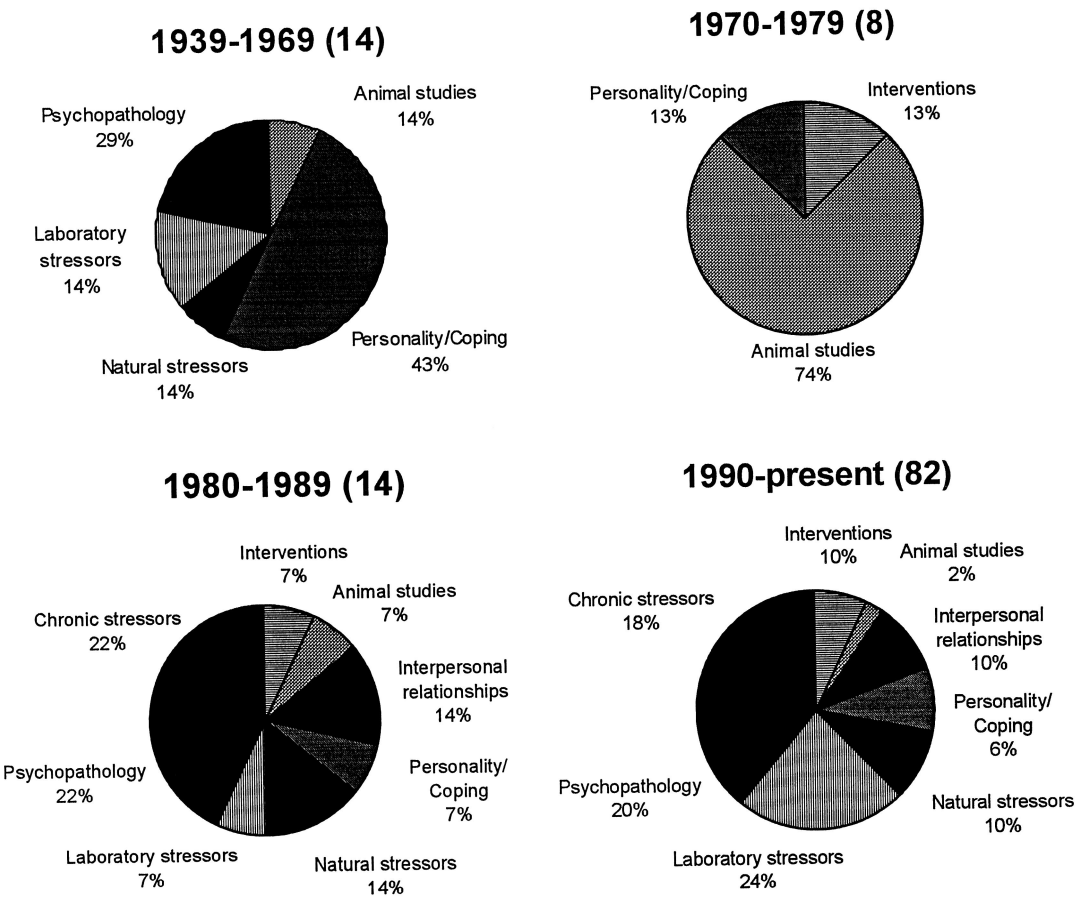

Fig. 2. General categories of psychological focus of PNI studies published in *Psychosomatic Medicine* from 1939 through 2000. Values in parentheses indicate number of studies in each time period.

(27). Interestingly, depressive symptoms were not associated with these effects in HIV-seropositive gay men who had lost a partner to AIDS.

Clinically diagnosed anxiety disorders have also been associated with immune changes. For example, in patients with generalized anxiety disorder, reduced IL-2 receptor expression on lymphocytes (compared with nonpsychiatric control subjects) was associated with higher intrusive thoughts and increased numbers of sick days due to upper respiratory infection (20). Similarly, patients with generalized anxiety disorder or panic disorder had reduced lymphocyte proliferation to PHA and IL-2 production compared with nonpsychiatric control subjects (19). High levels of PTSD symptoms and intrusive thoughts were associated with reduced NK cell lysis in victims of a hurricane compared with laboratory control subjects, and this relationship may have been mediated by onset of sleep problems (26). Vietnam veterans with partial PTSD 20 years after the war had higher total T-cell and $CD4^+$ T-cell counts, and those with other anxiety disorders had higher total T-cell counts and a stronger DTH response to seven antigens compared with Vietnam veterans without psychiatric symptoms or disorders (14). Higher levels of anxiety symptoms have been associated with poorer NK cell lysis 1 week after notification of HIV serostatus among seronegative gay men (15) and with a poorer response to a hepatitis B vaccine among medical students (33).

Health behaviors have been implicated as cofactors in the relationships between psychopathology and immune function; for example, smoking had synergistic effects with depression in reducing NK cell lysis (17), and reduced physical activity mediated the association between depression and lymphocyte proliferation (21). In patients with clinical depression and medical patients with symptoms of depression, objective and subjective indicators of sleep disturbances had significant associations with NK cell lysis (16) and T-cell counts (24) that were independent of depression. Indeed, the sleep disturbances that are characteristic of depression may have a variety of immunological consequences (12, 16, 24, 26).

The evidence for a relationship between psycho-

pathological symptoms and disorders and immunological alterations seems convincing. Furthermore, negative affect, a characteristic of most of the psychopathology spectrum, has been conceptualized as a key pathway for other psychological modifiers of immune function described below, particularly interpersonal relationships and personality.

PERSONALITY AND COPING

Personality characteristics and coping styles reflect individual differences in appraisal and response to stressors that may influence immune function. Reflecting the broader field of psychosomatic medicine at the time, much of the work before 1970 attempted to link personality traits to various diseases. For example, a number of researchers attempted to identify personality variables that predisposed individuals to allergic disorders (34–38); skin reactivity to injected allergens (ie, wheal and flare size) was weaker in individuals with personality styles described as passive, negative, withdrawn, unhappy, anxious, dissatisfied, and impulsive (34–37, 39). In another arena, relatives of patients with rheumatoid arthritis who lacked rheumatoid factor in their serum were more anxious and dysphoric than those who had the factor (40).

Specific personality characteristics such as academic achievement motivation and aggression have been associated with immunological alterations. Among cadets at a military academy, high motivation to perform well interacted with poor actual academic performance and predicted greater susceptibility to EBV infection (41). Aggression, operationalized using DSM-III-R antisocial personality disorder symptoms, was positively associated with T- and B-cell numbers in male military personnel, and this effect was independent of testosterone level, age, or health status or behaviors (42).

Coping styles associated with altered immunity include repression, denial, escape-avoidance, and concealment. Greater reliance on repressive coping was associated with lower monocyte counts, higher eosinophil counts, higher serum glucose, and more self-reported medication reactions in a retrospective chart review of medical outpatients (43), and with higher EBV antibody titers in students, with the latter finding suggesting a decrement in the memory T-cell response to the latent virus (44). Among family members of bone marrow transplant patients, escape-avoidance coping coupled with trait anxiety was associated with fewer total T cells and fewer $CD4^+$ T cells; escape-avoidance coping by itself was associated with increased B-cell counts during the period preceding the transplant (45). Denial coping seemed to have protective effects in gay men anticipating HIV serostatus notification; among seronegative men, denial coping was associated with reduced intrusive thoughts, lower cortisol, and greater lymphocyte proliferation to PHA as men awaited word of their HIV serostatus (46).

Although the majority of these studies were cross-sectional and involved students or young to middle-aged adults, one prospective study provided provocative evidence of notable health consequences. Concealment of homosexual identity predicted an accelerated course of HIV over 9 years as assessed by $CD4^+$ T-cells counts, AIDS diagnosis, and AIDS mortality, even when controlling for demographic, health, and psychopathology factors (47).

Clearly, personality or coping styles associated with emotion or affect regulation are likely to have immunological correlates, as well as those that influence interpersonal relationships. In this context it is not surprising that self-disclosure interventions have immunological consequences. For example, high-hostility subjects exhibited greater increases in NK cell cytotoxicity after self-disclosure than low-hostility subjects, consistent with the authors' hypothesis that persons high in cynical hostility would find disclosure more threatening; no differences between high- and low-hostility subjects were observed in the nondisclosure condition (48). Greater emotional disclosure by students on a written task was associated with lower EBV virus capsid antigen IgG antibody titers compared with students who expressed less emotion when describing a personal stressful event (44). Importantly, self-disclosure is thought to be one factor associated with the health benefits of psychotherapy, consistent with recent evidence of improvements in disease activity after self-disclosure in patients with asthma and arthritis (49).

INTERVENTIONS

Behavioral interventions that alter immune responses provide fundamental evidence of psychological influences on immune function. Both earlier and more recent studies have explored participants' ability to alter skin inflammation after antigenic challenge. For example, following hypnotic suggestions, 32 of 38 participants were able to reduce wheal size, and 48% of the variance in wheal size was attributed to systolic blood pressure, irritability, tension, health attributions, and skin temperature (50). A relaxation intervention reduced the flare response to a neurogenic inflammatory stimulus, capsaicin, compared with control or mental stressor conditions (51); norepinephrine, heart rate, and systolic blood pressure during the intervention period predicted flare size, suggesting

sympathetic modulation as a key pathway. In contrast, hypnotic suggestions to alter erythema or wheal size in response to mumps antigen, trypsin, or histamine were unsuccessful in a sample of three students (52), and self-hypnosis training of medical students did not produce immunological differences between intervention and control groups (53). However, greater self-rated relaxation was associated with NK lysis and cell numbers in the latter study (53), consistent with evidence from related work that more frequent practice produces more positive outcomes (54, 55).

Additional research has demonstrated classic conditioning of immune function in humans and immune alterations in HIV-seropositive and at-risk gay men after multicomponent interventions. Human classic conditioning studies were initiated after the demonstration of conditioned immunosuppression in animals (1, 3, 56) and have supported conditioning of DTH (57) and NK cell lysis (58), but not immediate hypersensitivity allergic skin reactions (59). Multifaceted cognitive-behavioral stress management or aerobic exercise reduced EBV virus capsid antigen and human herpesvirus-6 antibody titers in HIV-seropositive and at-risk gay men compared with nonintervention control subjects (60); lower antibody titers are thought to reflect better cellular immune system control over herpesvirus latency.

The majority of the intervention studies have involved young to middle-aged adults experiencing low levels of distress. Such participants likely have normal levels of immune function, and it may not be possible or desirable to enhance immune function beyond its normal levels. Future intervention research should ideally include older adults, more distressed participants, and greater use of longitudinal designs to maximize the ability to demonstrate immunomodulation.

STRESSOR DURATION AND TYPE

Early PNI research typically addressed very intense and novel events, such as bereavement after the death of a spouse (61), 48 hours of sleep deprivation (62), or new cadets' adjustment to life at a military academy (41). Beginning in the 1980s, researchers began to consider whether more commonplace stressful events might also provoke immune alterations; a number of studies demonstrated that brief, time-limited stressors, such as academic examinations, have immunological consequences and, importantly, these immune changes may have relevance for infectious disease and wound healing (33, 53, 63, 64). For example, students who did not seroconvert after an initial inoculation with recombinant hepatitis B vaccine reported greater examination-related anxiety than those who produced measurable antibody (33). Among dental students, healing of an oral punch biopsy wound took 40% longer during exams than during summer vacation, and production of IL-1β mRNA declined 68% in the same interval (64).

Individuals who have experienced more recent stressful life events may show greater immune change in response to minor stressors. For example, men who reported more recent stressful life events demonstrated exaggerated cardiovascular stress responses and greater declines in NK cell function that lasted longer in response to 12 minutes of mental arithmetic than similar men with fewer life changes (65). Similarly, teachers who reported more recent daily hassles showed larger changes in cell numbers when they attempted to teach a confederate how to work out the answer to an unsolvable puzzle; subsequent analyses related changes to differences in perceived controllability (66–68). Hernia surgery patients with higher self-reported life stress before surgery had lower lymphocyte responses to PHA before surgery and to pokeweed mitogen before and after surgery (69); of importance was the fact that increased postoperative complications and longer hospital stays were associated with declines in immune function.

Severe stressors may produce long-term immune dysregulation. Men and women who provide long-term care for a family member with a serious medical condition such as Alzheimer's disease often report high levels of stress, and caregiving has been associated with prolonged immune dysregulation (45, 70–77). Other chronic or longer-term stressors associated with continuing immune alterations include "burnout" at work (78), job strain (79), and unemployment (80). Similarly, continuing immune dysregulation has been described in civilians displaced by war (81) as well as persons living near a damaged nuclear reactor (82). 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 (83); similarly, nonhuman primates with lower social status (a social stressor) were more likely to develop a respiratory infection than those with higher status (84). Marital discord, a persistent interpersonal stressor, has been associated with poorer immune function (85–88).

Under some circumstances, immune dysregulation may persist for months or years after the event. Immunological changes have been documented for weeks or months after such natural disasters as earthquakes and hurricanes (26, 89). Immune dysregulation can persist several years or more after caregiving ends (76). Vietnam "theater" veterans with concurrent PTSD, anxiety, or depressive symptoms or disorders had higher

leukocyte counts than veterans without these disorders 20 years after military service (14). Prolonged intrusive ruminations after a trauma or disaster have been related to maladaptive psychological functioning and may provide one avenue for protracted immune dysregulation as they serve to maintain higher levels of negative affect (14, 20, 26, 82, 90).

Sustained negative affect also has consequences for production of proinflammatory cytokines. Although higher plasma IL-6 levels were associated with greater distress in a sample of community women, the subset of women who were caregiving for a relative with Alzheimer's disease had higher levels of plasma IL-6 than either women who were anticipating a housing relocation or community control subjects (91); the finding was particularly noteworthy because caregivers were 6 to 9 years younger, on average, than women in the other two groups, suggesting that this stressor had accelerated age-related changes. Thus, a chronic stressor may provoke long-term changes in IL-6 production, an important finding related to a broad array of health problems discussed in the final section.

"Laboratory" Stressors

Immune changes in response to very brief stressors have been a central theme in the last decade (Figure 2), but older literature also provides early illustrations; for example, in a study published in 1960, subjects were led to believe that they had accidentally caused serious injury to a companion through misuse of explosives (92). Experimenters obtained blood samples after research participants had struggled for an hour to repair a broken telephone switchboard supposedly needed to summon medical assistance. In contrast to the 30% drop in eosinophils seen in the experimental condition, control subjects who attempted to fix the same switchboard to make routine calls or as a psychomotor test showed only a 7% decline (92). Although the majority of contemporary studies have relied on standard cardiovascular reactivity tasks such as mental arithmetic, Stroop tests, or a speech stressor, investigators have also used acute exercise (93–95), an unsolvable puzzle (66, 67, 96), self-disclosure (48), and mood or fear inductions (97–99).

These acute "laboratory" stressors, which typically last a half hour or less, provoke transient immune changes; they characteristically provoke increases in NK cell activity and cell numbers for some lymphocyte subpopulations, with concurrent decrements in lymphocyte proliferation assays (100). The effects are reasonably consistent across stressors and laboratories, and age has not proven to be a major factor (101–104). The immunological changes observed after short-term stressors likely reflect transient alterations in lymphocyte migration from lymphoid organs and peripheral blood mediated through receptors on lymphocytes or via sympathetic nervous system innervation of lymphoid organs like the spleen (6, 100). Individuals who exhibit the largest sympathetically mediated increases in cardiovascular reactivity in response to acute stressors also show the largest catecholaminergic increases and immune changes (100, 102, 105–110). Adrenergic blockage ameliorates cellular immune responses to mental stress (108).

These transitory increases in the distribution of cells in circulation in peripheral blood (a process called "trafficking") probably do not represent a real change in cell numbers. Indeed, among the studies that continued to assess subjects after the stressor ended, the immunological changes seem relatively short-lived (96), although (not surprisingly) more intense stressors, such as shock, noise, and interpersonal conflict, have somewhat longer-lasting consequences (88, 100).

Mouse models suggest the possibility of hyperreaction of at least one aspect of immune function after short-duration stressors; the augmentation of DTH responses seems to be mediated through glucocorticoid and epinephrine stress responses (111). Interestingly, a 1963 study suggested short-term enhancement of skin inflammation in response to a pain stressor or during strenuous physical exercise in human subjects injected with the enzyme trypsin (39); hyporeactivity was the characteristic response in the recovery period following the brief stressors. Although not studied as extensively, there is evidence that both physical and psychological stressors can provoke transient increases in proinflammatory cytokines (112, 113); in animal models both stress and administration of epinephrine elevate plasma IL-6, consistent with evidence that IL-6 production is stimulated through β-adrenergic receptors among other pathways (114).

Are the individuals who show greater sympathetic nervous system activity or reactivity also at risk for more persistent alterations in immune function? Data from two experimental sessions scheduled 2 weeks apart provided evidence of moderately reproducible results within individuals (106). In addition, individuals characterized by high cardiac sympathetic reactivity to acute psychological stressors also show magnified cortisol responses, providing one mechanism for longer-term immunomodulation (110).

Moreover, one innovative study linked cardiovascular responses to a presurgical cold pressor test (immersion of the hand and forearm in ice water) with postoperative immune and health outcomes (69). High responders to the cold pressor stress (ie, a lower pain threshold and greater sympathetic reactivity) had

poorer proliferative responses to pokeweed mitogen before surgery than low responders. More importantly, however, high responders had poorer postsurgical proliferative responses to pokeweed mitogen after controlling for presurgical values, they required more pain medication, and they had more surgery-related complications. If sympathetic cardiac activation is a marker or determinant of longer-term changes in immune function, then the cardiovascular, endocrine, and immune changes evoked by brief experimental stressors may help to illuminate the nature of the interactions among these physiological systems.

INTERPERSONAL RELATIONSHIPS

The support provided by social relationships can serve as a buffer during both acute and chronic stressors, protecting against immune dysregulation. For example, early studies suggested that lonelier medical students and psychiatric inpatients had poorer cellular immune function than their counterparts who reported less loneliness (10, 63). Subsequent investigators reported that lower levels of social support, in the context of naturalistic stressors such as job strain (79), dementia caregiving (70, 76), and surgery (69), were associated with poorer immune function. Social support may also be important for immunity during short-term stressors such as examination stress; greater social support was linked with better immune responses to Hepatitis B vaccine in medical students (33).

The link between personal relationships and immune function is one of the most robust findings in PNI, spanning diverse populations and stressors (115). In a sample of HIV-positive men, low perceived emotional support was associated with a more rapid decline in $CD4^+$ T-cells, an important marker of the progression of HIV infection (116). Better NK cell activity in breast cancer patients was related to high quality emotional support from a spouse, perceived social support from the patient's physician, and actively seeking social support as a coping strategy (117).

Disruption of close relationships has well-documented consequences for immune function, whether the disruption is due to bereavement (27, 61) or divorce (85, 87). In addition, the maintenance of abrasive close relationships also exacts a toll; among newlywed couples engaged in a 30-minute conflict resolution task, individuals who exhibited more hostile or negative behaviors during conflict showed greater decrements in functional immune measures 24 hours later (88) as well as concurrent alterations in stress hormones (118). Similar patterns emerged in older couples who had been married an average of 42 years (86). These results were particularly striking given that the great majority of both young and old couples had happy marriages; thus, these findings may actually underestimate the physiological impact of a troubled relationship (119). In summary, PNI research has contributed to the larger literature on social relationships and health by delineating another pathway through which relationships can be beneficial or detrimental to health outcomes.

METHODOLOGICAL DEVELOPMENTS

The majority of human PNI studies to date have been correlational, which precludes statements of causality among identified psychological, immune, and health outcomes. Stronger evidence for PNI relationships has emerged from randomized intervention trials (reviewed above) that attempt to experimentally manipulate these associations. Further advances in the field require refinement of psychological constructs and processes to identify what specific characteristics, such as personality traits, emotional symptoms, and coping behaviors, are most important for immune dysregulation or modulation in varying situations. These same psychological constructs and processes may then serve as key targets for interventions.

Assays

In the early human studies, the primary immunological outcome was the result of an in vivo immune challenge, typically exposure to allergens by means of skin tests or pollen-laden rooms (34–38); similarly, eosinophil counts were a common in vitro assay (92, 93). As new immunological assays were developed and it became clear that a number of leukocyte subpopulations perform specialized immunologic functions, PNI studies typically used a battery of in vitro assays. In human studies, in vitro assays are generally limited to peripheral blood samples, which may not reflect immunological processes occurring in lymphoid organs or other regions, such as the skin (120). In general, there seems to be an increasing emphasis on qualitative or functional assays, which seem to have greater relevance for health outcomes.

Interestingly, a number of current studies provide conceptual replications of earlier studies; these earlier reports suggest new vistas for future efforts. Early work showed that psychotic patients had a poorer antibody response to pertussis vaccination than nonpsychiatric control subjects (9); subsequent work showed that medical students who reported more stress were slower to develop an antibody response to hepatitis B vaccine than their colleagues who were less distressed (33). After vaccination, IgG antibody titer to a pneu-

mococcal vaccine fell over a 6-month period in dementia caregivers, whereas antibody titers were stable among former caregivers whose spouse had died and control subjects (77). Responses to vaccination provide one proxy for risk of infectious disease because they demonstrate clinically relevant alterations in immunological responses to challenge under well-controlled conditions.

Relatedly, earlier articles emphasized immune down-regulation related to stressors. As data have accumulated, it has become clear that some stressors provoke increases in lymphocyte numbers or activity; moreover, there are times when down-regulation is a biologically useful outcome (eg, dampened skin responses to allergens). Thus, it is more meaningful to broadly characterize psychosocially modulated immunological alterations as immune dysregulation rather than immune suppression or enhancement.

Populations

Although the great majority of studies have sampled young or middle-aged adults (Figure 3), the number of studies with older adults is increasing rapidly, along with a focus on the interactions among age, stressors, and immune function (76, 86, 102). In contrast, only a handful of researchers have studied children or adolescents, in good part because of the difficulty in obtaining blood samples (104, 121, 122). Newer procedures hold promise in this arena (122), and there is evidence that psychosocial factors modify immune function in children and adolescents (104, 121–123).

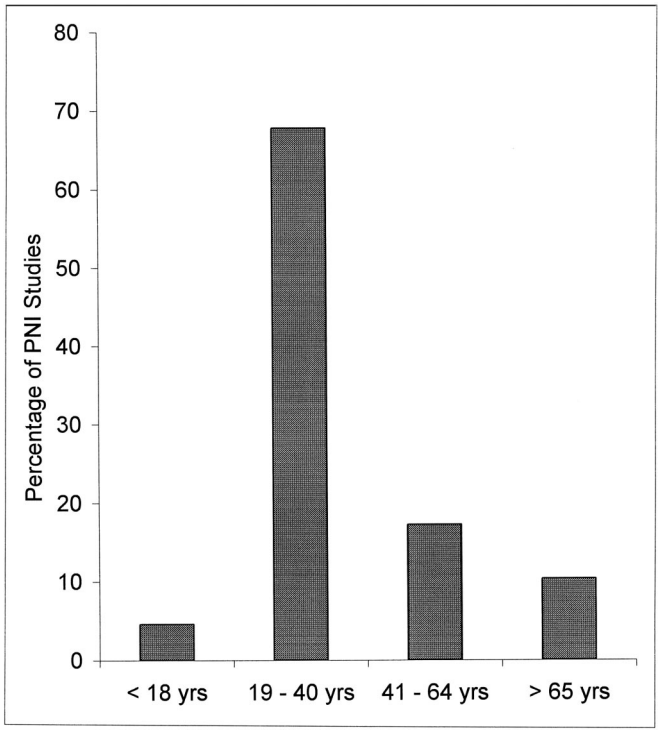

Fig. 3. Distribution of mean subject age per study in PNI studies published in *Psychosomatic Medicine* expressed as a percentage of studies reporting demographic information. In studies that did not report means but did report ranges, the mean was calculated by averaging the upper and lower bound of the range. Total number of studies was 87.

Health Habits

Health-related behaviors, now routinely assessed in most studies as a source of error variance, have become an increasing focus of research in their own right. Sleep deprivation can alter many aspects of immune function (12, 16, 24, 62, 124–128). Similarly, acute exercise produces multiple changes, analogous to other "laboratory" stressors (93, 95); it also seems to have longer-lasting positive consequences as well (21). In general, methodological sophistication has increased markedly, with attention to such issues as circadian influences on immune measures and their relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters (127).

HEALTH CONSEQUENCES

Animal research can provide experimental control over key variables necessary to unequivocally demonstrate the health consequences of behaviorally mediated immune alterations: the nature and intensity of stressors, uniform health challenges (eg, pathogen exposure, and genetic homogeneity). For example, social stress has been induced by varying the number of animals sharing the same cage (129, 130) or by rearranging the dominance hierarchy in primate housing; among rhesus monkeys inoculated with simian immunodeficiency virus, mortality was greater among those whose housing was changed than among those who did not move (131). Moreover, when such changes included social separations from familiar animals, death rates also increased (131). In other work, low social status was associated with increased probability of adenovirus infection among cynomolgus monkeys (84). Studies of conditioned immunosuppression showed alterations in both antibody responses and mortality (3, 56). More detailed reviews of PNI animal studies with additional health data are provided elsewhere (132, 133).

Parallel findings from animal and human studies provide evidence of the effects of stress on infectious illnesses. For example, stressors altered susceptibility to respiratory viruses among mice, cynomolgus monkeys, and humans (83, 84, 134). Experimental stressors

(irregular noise, light, and movement) resulted in delayed antibody formation to bovine serum albumin in mice compared with non-stressed controls (135), similar to the human vaccine data discussed earlier (9, 33, 77). In the case of the vaccine studies, the fact that individuals who were more stressed and more anxious seroconverted later suggested that these same individuals might also be slower to develop an antibody response to other pathogens; thus, theoretically, they could be at greater risk for more severe illness. Accordingly, these data complement the evidence from the respiratory virus studies (83, 84) and provide a window on the body's response to other pathogens.

Other data have suggested that health-associated vulnerabilities are not merely additive. Indeed, individuals who demonstrate larger age-related immunological impairments may manifest the greatest clinical consequences related to stress; for example, antibody responses to an influenza virus vaccine were substantially poorer among chronically stressed spousal caregivers over the age of 70 than among those who were either younger and/or noncaregivers (136). The significantly increased mortality from influenza (as well as other infectious diseases) among older adults emphasizes the meaningfulness of these findings (77, 136).

Two studies demonstrated that stressors enhance susceptibility and severity of the primary infection to a latent herpesvirus as well as clinical recurrence (18, 41). Among West Point cadets who were seronegative to EBV on entry into West Point, data collected over the next 4 years showed that a triad of risk factors (higher levels of motivation for a military career, poorer academic performance, and having a father who was an "overachiever") predicted three important illness indices: an increased risk of seroconversion, longer hospitalization in the infirmary after seroconversion (presumably reflecting more severe illness episodes), and higher antibody titers to EBV among those who seroconverted in the absence of clinical symptoms (41). Similarly, among individuals already infected with another herpesvirus, HSV, elevated depressive symptoms were associated with lower $CD8^+$ counts and a higher rate of genital HSV recurrence over 6 months (18). These findings were consistent with demonstrations of stress-related changes in herpesvirus latency in a number of studies (44, 60, 70, 71, 85–88, 122).

Researchers have also attempted to relate psychological variables to immune change and disease progression in people infected with another virus, HIV. Two studies suggest that nondisclosure of important personal information is related to HIV progression (47, 123), consistent with evidence that self-disclosure has positive immunological consequences (44, 48, 137). Clearly behavior has clinically important consequences for infectious disease.

A number of studies in the psychosomatic medicine literature have shown that greater fear or distress before surgery is associated with poorer outcomes, including longer hospital stays, more postoperative complications, and higher rates of rehospitalization (69, 138). One key psychobiological mechanism is suggested by evidence that stress slows wound healing, an immunologically mediated process (138). For example, wounds placed on the hard palate 3 days before a major academic examination healed an average of 40% more slowly than those made in the same individuals during summer vacation (64); wound healing and postsurgical recovery are notable areas for future PNI exploration.

Promising new directions are suggested by the evidence that stress can potentiate the effects of a high-lipid diet and initiate formation of macrophage-related lesions of early atherosclerosis (139). Similarly, the role of *Helicobacter pylori* in ulcer diathesis, along with demonstrations of stress-related alterations in wound repair, provides a PNI context for future ulcer research (140). In addition to newer vistas, data are also emerging in more traditional PNI arenas such as autoimmune disease and cancer (24, 117, 141, 142).

More broadly, recent evidence implicates dysregulation of proinflammatory cytokines, particularly IL-6, as a central component across a range of diseases in older adults. The immune system's inflammatory response can be triggered in a variety of ways, including infection and trauma, and the mechanisms associated with inflammation are critical to resolving infections and repairing tissue damage; however, chronic or recurring infections can provoke pathological changes (143). For example, low levels of persistent inflammation may result when chronic infectious processes such as periodontal disease, urinary tract infections, chronic pulmonary disease, and chronic renal disease persistently stimulate the immune system, with the greatest repercussions among older adults who already show age-related increases in IL-6 production (144).

In fact, 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 (145). The association between cardiovascular disease and IL-6 is related in part to the central role that this cytokine plays in promoting the production of CRP, recently recognized as an important risk factor for myocardial infarction (114). For example, high concentrations of

CRP predicted the risk of future cardiovascular disease in apparently healthy men (146). Further studies provided mechanistic links: chronic infections amplified the risk for development of atherosclerosis four-fold in subjects who were free of carotid atherosclerosis at baseline, conferring increased risk even in subjects lacking conventional vascular risk factors (147). Indeed, the increased risk for artery-clogging plaque was greater than that conferred by elevated blood pressure or cholesterol (147). Cardiovascular disease is the leading cause of death, and individuals with high levels of both IL-6 and CRP were 2.6 times more likely to die over a 4.6-year period than those who were low on both (148).

Importantly, chronic inflammation has been suggested as one key biological mechanism that may fuel declines in physical function leading to frailty, disability, and ultimately death (143, 149). For example, elevated serum IL-6 levels predicted future disability in older adults, a finding the authors suggest may reflect the effects of the cytokine on muscle atrophy and/or the pathophysiologic role played by the cytokine in particular diseases (150). Proinflammatory cytokines, including IL-6, may slow muscle repair after injury and accelerate muscle wasting (151); indeed, IL-6 and CRP also play a pathogenic role in a range of diseases associated with disability among the elderly (osteoporosis, arthritis, and congestive heart failure among others) (150). In this context it is interesting that IL-6 is also associated with self-rated health (152), a robust predictor of mortality (153). In fact, IL-6 may function as a ". . .global marker of impending deterioration in health status in older adults" (150); 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 (150).

As discussed earlier, depression and distress enhance the production of proinflammatory cytokines, including IL-6 (13, 28–31, 91, 113). A particularly notable finding was the demonstration of an association between depressive symptomatology and inflammation in patients with stable angina (13). 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 (eg, IL-2, an important defense against infection), and thus may contribute to the immunodepression of aging (154). Certainly there is excellent evidence that stress impedes the immune response to infectious challenges, amplifying risks for contagion and prolonged illness episodes (18, 41, 77, 83, 84, 131, 134–136); distress also provokes substantial delays in wound healing (64, 138) and enhances the risk of wound infection after injury (155). 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 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.

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 risks across diverse conditions and diseases related to proinflammatory cytokines (114, 143, 145, 148–152). The PNI field has grown tremendously in the last two decades, and the future looks quite promising.

Work on this paper was supported by National Institutes of Health Grants R37 MH42096, K02 MH01467, T32 MH18831, P01 AG16321, and P50 DE17811.

REFERENCES

1. Ader R. Presidential address—1980. Psychosomatic and psychoimmunologic research. Psychosom Med 1980;42:307–21.
2. Solomon GF, Moos RH. Emotions, immunity, and disease: a speculative theoretical integration. Arch Gen Psychiatry 1964; 11:657–74.
3. Ader R, Cohen N. Behaviorally conditioned immunosuppression. Psychosom Med 1975;37:333–40.
4. Ader R. Historical perspectives on psychoneuroimmunology. In: Friedman H, Klein TW, Friedman AL, editors. Psychoneuroimmunology, stress, and infection. Boca Raton (FL): CRC Press; 1996. p. 1–24.
5. Solomon GF. From psyche to soma and back: tales of biopsychosocial medicine. Philadelphia: Xlibris; 2000.
6. Rabin BS. Stress, immune function, and health: the connection. New York: Wiley-Liss & Sons; 1999.
7. Freeman H, Elmadjian F. The relationship between blood sugar and lymphocyte levels in normal and psychotic subjects. Psychosom Med 1947;9:226–33.
8. Phillips L, Elmadjian F. A Rorschach tension score and the diurnal lymphocyte curve in psychotic subjects. Psychosom Med 1947;9:364–71.
9. Vaughan WTJ, Sullivan JC, Elmadjian F. Immunity and schizophrenia. Psychosom Med 1949;11:327–33.
10. Kiecolt-Glaser JK, Ricker D, George J, Messick G, Speicher CE, Garner W, Glaser R. Urinary cortisol levels, cellular immunocompetency, and loneliness in psychiatric inpatients. Psychosom Med 1984;46:15–24.
11. Nagata T, Tobitani W, Kiriike N, Iketani T, Yamagami S. Ca-

pacity to produce cytokines during weight restoration in patients with anorexia nervosa. Psychosom Med 1999;61:371–7.
12. Appelberg B, Katila H, Rimon R. Plasma interleukin-1 beta and sleep architecture in schizophrenia and other nonaffective psychoses. Psychosom Med 1997;59:529–32.
13. Appels A, Bar FW, Bar J, Bruggeman C, de Baets M. Inflammation, depressive symptomatology, and coronary artery disease. Psychosom Med 2000;62:601–5.
14. Boscarino JA, Chang J. Higher abnormal leukocyte and lymphocyte counts 20 years after exposure to severe stress: research and clinical implications. Psychosom Med 1999;61:378–86.
15. Ironson G, LaPerriere A, Antoni M, O'Hearn P, Schneiderman N, Klimas N, Fletcher MA. Changes in immune and psychological measures as a function of anticipation and reaction of news of HIV-1 antibody status. Psychosom Med 1990;52: 247–70.
16. Irwin M, Smith TL, Christian G. Electroencephalographic sleep and natural killer activity in depressed patients and control subjects. Psychosom Med 1992;54:10–21.
17. Jung W, Irwin M. Reduction of natural killer cytotoxic activity in major depression: interaction between depression and cigarette smoking. Psychosom Med 1999;61:263–70.
18. Kemeny M, Cohen F, Zegens L. Psychological and immunological predictors of genital herpes recurrence. Psychosom Med 1989;51:195–208.
19. Koh KB, Lee BK. Reduced lymphocyte proliferation and interleukin-2 production in anxiety disorders. Psychosom Med 1998;60:479–83.
20. La Via MF, Munno I, Lydiard RB, Workman EW, Hubbard JR, Michel Y, Paulling E. The influence of stress intrusion on immunodepression in generalized anxiety disorder patients and controls. Psychosom Med 1996;58:138–42.
21. Miller GE, Cohen S, Herbert TB. Pathways linking major depression and immunity in ambulatory female patients. Psychosom Med 1999;61:850–60.
22. Ravindran AV, Griffiths J, Merali Z, Anisman H. Lymphocyte subsets associated with major depression and dysthymia: modification by antidepressant treatment. Psychosom Med 1995; 57:555–63.
23. Ravindran AV, Griffiths J, Merali Z, Anisman H. Circulating lymphocyte subset in major depression and dysthymia with typical or atypical features. Psychosom Med 1998;60:283–9.
24. Savard J, Miller SM, Mills M, O'Leary A, Harding H, Douglas SD, Mangan CE, Belch R, Winokur A. Association between subjective sleep quality and depression on immunocompetence in low-income women at risk for cervical cancer. Psychosom Med 1999;61:496–507.
25. Locke SE, Kraus L, Leserman J, Hurst MW, Heisel JS, Williams RM. Life change stress, psychiatric symptoms, and natural killer cell activity. Psychosom Med 1984;46:441–53.
26. Ironson G, Wynings C, Schneiderman N, Baum A, Rodriguez M, Greenwood D, Benight C, Antoni M, LaPerriere A, Huang HS, Klimas N, Fletcher MA. Posttraumatic stress symptoms, intrusive thoughts, loss, and immune function after Hurricane Andrew. Psychosom Med 1997;59:128–41.
27. Kemeny ME, Weiner H, Duran R, Taylor SE, Visscher B, Fahey JL. Immune system changes after the death of a partner in HIV-positive gay men. Psychosom Med 1995;57:547–54.
28. Dentino AN, Pieper CF, Rao KMK, Currie MS, Harris T, Blazer DG, Cohen HJ. Association of interleukin-6 and other biologic variables with depression in older people living in the community. J Am Geriatr Soc 1999;47:6–11.
29. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 1995;9:853–8.
30. Maes M, Song C, Lin A, De JR, Van GA, Kenis G, Bosmans E, De MI, Benoy I, Neels H, Demedts P, Janca A, Scharpe S, Smith R. The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. Cytokine 1998;10:313–8.
31. Maes M, Lin A, Delmeire L, Van Gastel A, Kenis G, De Jongh R, Bosmans E. Elevated serum interleukin-6 (IL-6) and IL-6 receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events. Biol Psychiatry 1999; 45:833–9.
32. Kiecolt-Glaser JK, McGuire L, Robles TR, Glaser R. Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. Annu Rev Psychol. In press.
33. Glaser R, Kiecolt-Glaser JK, Bonneau RH, Malarkey W, Kennedy S, Hughes J. Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. Psychosom Med 1992;54:22–9.
34. Mitchell JH, Curran CA, Myers RN. Some psychosomatic aspects of allergic diseases. Psychosom Med 1947;9:184–91.
35. Feingold BF, Gorman FJ, Singer MT, Schlesinger K. Psychological studies of allergic women: the relation between skin reactivity and personality. Psychosom Med 1962;24:193–202.
36. Freeman EH, Gorman FJ, Singer MT, Affelder MT, Feingold BF. Personality variables and allergic skin reactivity: a cross-validation study. Psychosom Med 1967;29:312–22.
37. Cassell WA, Fisher S. Body image boundaries and histamine flare reaction. Psychosom Med 1963;25:344–50.
38. Jacobs MA, Friedman MA, Franklin MJ, Anderson LS, Muller JJ, Eisman HD. Incidence of psychosomatic predisposing factors in allergic disorders. Psychosom Med 1966;28:679–95.
39. Ely NE, Verhey JW, Holmes TH. Experimental studies of skin inflammation. Psychosom Med 1963;25:264–84.
40. Solomon GF, Moos RH. The relationship of personality to the presence of rheumatoid factor in asymptomatic relatives of patients with rheumatoid arthritis. Psychosom Med 1965;27: 350–60.
41. Kasl SV, Evans AS, Niederman JC. Psychosocial risk factors in the development of infectious mononucleosis. Psychosom Med 1979;41:445–66.
42. Granger DA, Booth A, Johnson DR. Human aggression and enumerative measures of immunity. Psychosom Med 2000;62: 583–90.
43. Jamner LD, Schwartz GE, Leigh H. The relationship between repressive and defensive coping styles and monocyte, eosinophil, and serum glucose levels: support for the opioid peptide hypothesis of repression. Psychosom Med 1988;50:567–75.
44. Esterling B, Antoni M, Kumar M, Schneiderman N. Emotional repression, stress disclosure responses, and Epstein-Barr viral capsid antigen titers. Psychosom Med 1990;52:397–410.
45. Futterman AD, Wellisch DK, Zighelboim J, Luna-Raines M, Weiner H. Psychological and immunological reactions of family members to patients undergoing bone marrow transplantation. Psychosom Med 1996;58:472–80.
46. Antoni MH, August BA, LaPerriere A, Baggett HI, Klimas N, Ironson G, Schneiderman N, Fletcher MA. Psychological and neuroendocrine measures related to functional immune changes in anticipation of HIV-1 serostatus notification. Psychosom Med 1990;52:496–510.
47. Cole SW, Kemeny M, Taylor SE, Visscher B, Fahey J. Accelerated course of human immunodeficiency virus infection in gay men who conceal their homosexual identity. Psychosom Med 1996;58:219–31.

48. Christensen AJ, Edwards DL, Wiebe JS, Benotsch EG, McKelvey L, Andrews M, Lubaroff DM. Effect of verbal self-disclosure on natural killer cell activity: moderating influence of cynical hostility. Psychosom Med 1996;58:150–5.
49. Smyth JM, Stone AA, Hurewitz A, Kaell A. Effects of writing about stressful experiences on symptom reduction in patients with asthma or rheumatoid arthritis: a randomized trial. JAMA 1999;17:1304–9.
50. Laidlaw TM, Booth RJ, Large RG. Reduction in skin reactions to histamine after a hypnotic procedure. Psychosom Med 1996; 58:242–8.
51. Lutgendorf SK, Logan H, Kirchner L, Rothrock N, Svengalis S, Iverson K, Lubaroff D. Effects of relaxation and stress on the capsaicin-induced local inflammatory response. Psychosom Med 2000;62:524–34.
52. Beahrs JO, Harris DR, Hilgard ER. Failure to alter skin inflammation by hypnotic suggestion in five subjects with normal skin reactivity. Psychosom Med 1970;32:627–31.
53. Whitehouse WG, Dinges DF, Orne EC, Keller SE, Bates BL, Bauer NK, Morahan P, Haupt BA, Carlin MM, Bloom PB, Zaugg L, Orne MT. Psychosocial and immune effects of self-hypnosis training for stress management throughout the first semester of medical school. Psychosom Med 1996;58:249–63.
54. Kiecolt-Glaser JK, Glaser R, Strain EC, Stout JC, Tarr K, Holliday J, Speicher C. Modulation of cellular immunity in medical students. J Behav Med 1986;9:311–20.
55. Kiecolt-Glaser JK, Marucha PT, Atkinson C, Glaser R. Hypnosis as a modulator of cellular immune dysregulation during acute stress. J Consult Clin Psychol 2001;69:674–82.
56. Ader R. Behaviorally conditioned immunosuppression [letter]. Psychosom Med 1974;36:183–4.
57. Smith GR, McDaniels SM. Psychologically mediated effect on the delayed hypersensitivity reaction to tuberculin in humans. Psychosom Med 1983;45:65–70.
58. Buske-Kirschbaum A, Kirschbaum C, Stierle H, Lehnert H, Hellhammer D. Conditioned increase of natural killer cell activity (NKCA) in humans. Psychosom Med 1992;54:123–32.
59. Booth RJ, Petrie KJ, Brook RJ. Conditioning allergic skin responses in humans: a controlled trial. Psychosom Med 1995; 57:492–5.
60. Esterling BA, Antoni MH, Schneiderman N, Carver CS, LaPerriere A, Ironson G, Klimas NG, Fletcher MA. Psychosocial modulation of antibody to Epstein-Barr viral capsid antigen and human herpesvirus type-6 in HIV-1-infected and at-risk gay men. Psychosom Med 1992;54:354–71.
61. Bartrop R, Luckhurst E, Lazarus L, Kiloh LG, Penny R. Depressed lymphocyte function after bereavement. Lancet 1977; 1:374–7.
62. Palmblad J, Petrini B, Wasserman J, Akerstedt T. Lymphocyte and granulocyte reactions during sleep deprivation. Psychosom Med 1979;41:273–8.
63. Kiecolt-Glaser JK, Garner W, Speicher C, Penn GM, Holliday J, Glaser R. Psychosocial modifiers of immunocompetence in medical students. Psychosom Med 1984;46:7–14.
64. Marucha PT, Kiecolt-Glaser JK, Favagehi M. Mucosal wound healing is impaired by examination stress. Psychosom Med 1998;60:362–5.
65. Pike JL, Smith TL, Hauger RL, Nicassio PM, Patterson TL, McClintick J, Costlow C, Irwin MR. Chronic life stress alters sympathetic, neuroendocrine, and immune responsivity to an acute psychological stressor in humans. Psychosom Med 1997; 59:447–57.
66. Brosschot JF, Godaert GL, Benschop RJ, Olff M, Ballieux RE, Heijnen CJ. Experimental stress and immunological reactivity: a closer look at perceived uncontrollability. Psychosom Med 1998;60:359–61.
67. Brosschot JF, Benschop RJ, Godaert GL, Olff M, De Smet M, Heijnen CJ, Ballieux RE. Influence of life stress on immunological reactivity to mild psychological stress. Psychosom Med 1994;56:216–24.
68. Peters ML, Godaert GL, Ballieux RE, Brosschot JF, Sweep FC, Swinkels LM, van Vliet M, Heijnen CJ. Immune responses to experimental stress: effects of mental effort and uncontrollability. Psychosom Med 1999;61:513–24.
69. Linn BS, Linn MW, Klimas NG. Effects of psychophysical stress on surgical outcome. Psychosom Med 1988;50:230–44.
70. Kiecolt-Glaser JK, Dura JR, Speicher CE, Trask OJ, Glaser R. Spousal caregivers of dementia victims: longitudinal changes in immunity and health. Psychosom Med 1991;53:345–62.
71. Kiecolt-Glaser JK, Glaser R, Shuttleworth EC, Dyer CS, Ogrocki P, Speicher CE. Chronic stress and immunity in family caregivers for Alzheimer's disease victims. Psychosom Med 1987; 49:523–35.
72. Mills PJ, Ziegler MG, Patterson TL, Dimsdale JE, Hauger RL, Irwin M, Grant I. Plasma catecholamine and lymphocyte β_2-adrenergic receptor alternations in elderly Alzheimer caregivers under stress. Psychosom Med 1997;59:251–6.
73. Mills PJ, Yu H, Ziegler MG, Patterson TL, Grant I. Vulnerable caregivers of patients with Alzheimer's disease have a deficit in circulating CD62L-T lymphocytes. Psychosom Med 1999;61: 168–74.
74. Grant I. Caregiving may be hazardous to your health. Psychosom Med 1999;61:420–3.
75. Scanlan JM, Vitaliano PP, Ochs H, Savage MV, Borson S. CD4 and CD8 counts are associated with interactions of gender and psychosocial stress. Psychosom Med 1998;60:644–53.
76. Esterling BA, Kiecolt-Glaser JK, Glaser R. Psychosocial modulation of cytokine-induced natural killer cell activity in older adults. Psychosom Med 1996;58:264–72.
77. Glaser R, Sheridan JF, Malarkey WB, MacCallum RC, Kiecolt-Glaser JK. Chronic stress modulates the immune response to a pneumococcal vaccine. Psychosom Med 2000;62:804–7.
78. Lerman Y, Melamed S, Shragin Y, Kushnir T, Rotgoltz Y, Shirom A, Aronson M. Association between burnout at work and leukocyte adhesiveness/aggression. Psychosom Med 1999; 61:828–33.
79. Theorell T, Orth-Gomer K, Eneroth P. Slow-reacting immunoglobulin in relation to social support and changes in job strain: a preliminary note. Psychosom Med 1990;52:511–6.
80. Arnetz BB, Brenner SO, Levi L, Hjelm R, Petterson IL, Wasserman J, Petrini B, Eneroth P, Kallner A, Kvetnansky R, Vigas M. Neuroendocrine and immunologic effects of unemployment and job insecurity. Psychother Psychosom 1991;55:76–80.
81. Sabioncello A, Kocijan-Hercigonja D, Rabatic S, Tomasic J, Jeren T, Matijevic L, Rijavec M, Dekaris D. Immune, endocrine, and psychological responses in civilians displaced by war. Psychosom Med 2000;62:502–8.
82. Baum A, Cohen L, Hall M. Control and intrusive memories as possible determinants of chronic stress. Psychosom Med 1993; 55:274–86.
83. Cohen S, Frank E, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM. Types of stressors that increase susceptibility to the common cold in healthy adults. Health Psychol 1998;17:214–23.
84. Cohen S, Line S, Manuck SB, Rabin BS, Heise ER, Kaplan JR. Chronic social stress, social status, and susceptibility to upper respiratory infections in nonhuman primates. Psychosom Med 1997;59:213–21.
85. Kiecolt-Glaser JK, Fisher LD, Ogrocki P, Stout JC, Speicher CE,

Glaser R. Marital quality, marital disruption, and immune function. Psychosom Med 1987;49:31–4.
86. Kiecolt-Glaser JK, Glaser R, Cacioppo JT, MacCallum RC, Snydersmith M, Kim C, Malarkey WB. Marital conflict in older adults: endocrinological and immunological correlates. Psychosom Med 1997;59:339–49.
87. Kiecolt-Glaser JK, Kennedy S, Malkoff S, Fisher L, Speicher CE, Glaser R. Marital discord and immunity in males. Psychosom Med 1988;50:213–29.
88. Kiecolt-Glaser JK, Malarkey WB, Chee M, Newton T, Cacioppo JT, Mao H, Glaser R. Negative behavior during marital conflict is associated with immunological down-regulation. Psychosom Med 1993;55:395–409.
89. Solomon GF, Segerstrom SC, Grohr P, Kemeny M, Fahey J. Shaking up immunity: psychological and immunologic changes after a natural disaster. Psychosom Med 1997;59: 114–27.
90. Delahanty DL, Dougall AL, Craig KJ, Jenkins FJ, Baum A. Chronic stress and natural killer cell activity after exposure to traumatic death. Psychosom Med 1997;59:467–76.
91. Lutgendorf SK, Garand L, Buckwalter KC, Reimer TT, Hong S, Lubaroff DM. Life stress, mood disturbance, and elevated interleukin-6 in healthy older women. J Gerontol A Biol Sci Med Sci 1999;54A:M434–9.
92. McDonald RD, Yagi K. A note on eosinopenia as an index of psychological stress. Psychosom Med 1960;22:149–50.
93. McDonald RD, Yagi K, Stockton E. Human eosinophil response to acute physical exertion. Psychosom Med 1961;23:63–6.
94. Goebel MU, Mills PJ. Acute psychological stress and exercise and changes in peripheral leukocyte adhesion molecule expression and density. Psychosom Med 2000;62:664–70.
95. Goebel MU, Mills PJ, Irwin MR, Ziegler MG. Interleukin-6 and tumor necrosis factor-α production after acute psychological stress, exercise, infused isoproterenol: differential effects and pathways. Psychosom Med 2000;62:591–8.
96. Brosschot JR, Benschop RJ, Godaert GLR, de Smet MB, Olif M, Heijnen CJ, Ballieux RE. Effects of experimental psychological stress on distribution and function of peripheral blood cells. Psychosom Med 1992;54:394–406.
97. Futterman AD, Kemeny ME, Shapiro D, Fahey JL. Immunological and physiological changes associated with induced positive and negative mood. Psychosom Med 1994;56:499–511.
98. Knapp PH, Levy E, Giorgi RG, Black PH, Fox BH, Herren TC. Short-term immunological effects of induced emotion. Psychosom Med 1992;54:133–48.
99. Gerritsen W, Heijnen CJ, Wiegant VM, Bermond B, Frijda NH. Experimental social fear: immunological, hormonal, and autonomic concomitants. Psychosom Med 1996;58:273–86.
100. Kiecolt-Glaser JK, Cacioppo JT, Malarkey WB, Glaser R. Acute psychological stressors and short-term immune changes: what, why, for whom, and to what extent? Psychosom Med 1992;54: 680–5.
101. Benschop RJ, Geenen R, Mills PJ, Naliboff BD, Kiecolt-Glaser JK, Herbert TB, van der Pomp G, Miller GE, Matthews KA, Godaert GLR, Gilmore SL, Glaser R, Heijnen CJ, Dopp JM, Bijlsma JWJ, Solomon GF, Cacioppo JT. Cardiovascular and immune responses to acute psychological stress in young and old women: a meta-analysis. Psychosom Med 1998;60:290–6.
102. Naliboff BD, Benton D, Solomon GF, Morley JE, Fahey JL, Bloom ET, Makinodan T, Gilmore SL. Immunological changes in young and old adults during brief laboratory stress. Psychosom Med 1991;53:121–32.
103. Burleson MH, Malarkey WB, Cacioppo JT, Poehlmann KM, Kiecolt-Glaser JK, Berntson GG, Glaser R. Postmenopausal hormone replacement: effects on autonomic, neuroendocrine, and immune reactivity to brief psychological stressors. Psychosom Med 1998;60:17–25.
104. Liang SW, Jemerin JM, Tschann JM, Wara DW, Boyce WT. Life events, frontal electroencephalogram laterality, and functional immune status after acute psychological stressors in adolescents. Psychosom Med 1997;59:178–86.
105. Herbert TB, Cohen S, Marsland AL, Bachen EA, Rabin BS, Muldoon MF, Manuck SB. Cardiovascular reactivity and the course of immune response to an acute psychological stressor. Psychosom Med 1994;56:337–44.
106. Marsland AL, Manuck SB, Fazzari TV, Stewart CJ, Rabin BS. Stability of individual differences in cellular immune responses to acute psychological stress. Psychosom Med 1995; 57:295–8.
107. Bachen EA, Manuck SB, Marsland AL, Cohen S, Malkoff SB, Muldoon MF, Rabin BS. Lymphocyte subset and cellular immune responses to a brief experimental stressor. Psychosom Med 1992;54:673–9.
108. Bachen EA, Manuck SB, Cohen S, Muldoon MF, Raible R, Herbert TB, Rabin BS. Adrenergic blockade ameliorates cellular immune responses to mental stress in humans. Psychosom Med 1995;57:366–72.
109. Matthews KA, Caggiula AR, McAllister CG, Berga SL, Owens JF, Flory JD, Miller AL. Sympathetic reactivity to acute stress and immune response in women. Psychosom Med 1995;57: 564–71.
110. Cacioppo JT, Malarkey WB, Kiecolt-Glaser JK, Uchino BN, Sgoutas-Emch SA, Sheridan JF, Berntson GG, Glaser R. Heterogeneity in neuroendocrine and immune responses to brief psychological stressors as a function of autonomic cardiac activation. Psychosom Med 1995;57:154–64.
111. Dhabhar FS, McEwen BS. Enhancing versus suppressive effects of stress hormones on skin immune function. Proc Natl Acad Sci U S A 1999;96:1059–64.
112. DeRijk R, Michelson D, Karp B, Petrides J, Galliven E, Deuster P, Paciotti G, Gold PW, Sternberg EM. Exercise and circadian rhythm-induced variations in plasma cortisol differentially regulate interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) production in humans: high sensitivity of TNF-α and resistance of IL-6. J Clin Endocrinol Metab 1997;82: 2182–92.
113. Zhou D, Kusnecov AW, Shurin MR, DePaoli M, Rabin BS. Exposure to physical and psychological stressors elevates plasma interleukin 6: relationship to the activation of hypothalamic-pituitary-adrenal axis. Endocrinology 1993;133: 2523–30.
114. Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophysiologic roles of interleukin-6 in human disease. Ann Intern Med 1998;128:127–37.
115. Uchino BN, Cacioppo JT, Kiecolt-Glaser JK. The relationship between social support and physiological processes: a review with emphasis on underlying mechanisms. Psychol Bull 1996; 119:488–531.
116. Theorell T, Blomkvist V, Jonsson H, Schulman S, Berntorp E, Stigendal L. Social support and the development of immune function in human immunodeficiency virus infection. Psychosom Med 1995;57:32–6.
117. Levy SM, Herberman RB, Whiteside T, Sanzo K, Lee J, Kirkwood J. Perceived social support and tumor estrogen/ progesterone receptor status as predictors of natural killer cell activity in breast cancer patients. Psychosom Med 1990;52: 73–85.
118. Malarkey W, Kiecolt-Glaser JK, Pearl D, Glaser R. Hostile be-

havior during marital conflict alters pituitary and adrenal hormones. Psychosom Med 1994;56:41–51.
119. Kiecolt-Glaser JK, Newton T. Marriage and health: his and hers. Psychol Bull. In press.
120. Glaser R, Kiecolt-Glaser JK, Marucha PT, MacCallum RC, Laskowski BF, Malarkey WB. Stress-related changes in proinflammatory cytokine production in wounds. Arch Gen Psychiatry 1999;56:450–6.
121. Boyce WT, Chesney M, Alkon A, Tschann JM, Adams S, Chesterman B, Cohen F, Kaiser P, Folkman S, Wara D. Psychobiologic reactivity to stress and childhood respiratory illnesses: results of two prospective studies. Psychosom Med 1995;57:411–22.
122. McDade TW, Stallings JF, Angold A, Costello EJ, Burleson M, Cacioppo JT, Glaser R, Worthman CM. Epstein-Barr virus antibodies in whole blood spots: a minimally invasive method for assessing an aspect of cell-mediated immunity. Psychosom Med 2000;62:560–8.
123. Sherman BF, Bonanno GA, Wiener LS, Battles HB. When children tell their friends they have AIDS: possible consequences for psychological well-being and disease progression. Psychosom Med 2000;62:238–47.
124. Moldofsky H, Lue FA, Eisen J, Keystone E, Gorczynski RM. The relationship of interleukin-1 and immune functions to sleep in humans. Psychosom Med 1986;48:309–18.
125. Uthgenannt D, Schoolmann D, Pietrowsky R, Fehm HL, Born J. Effects of sleep on the production of cytokines in humans. Psychosom Med 1995;57:97–104.
126. Irwin M, Mascovich A, Gillin JC, Willoughby R, Pike J, Smith TL. Partial sleep deprivation reduces natural killer cell activity in humans. Psychosom Med 1994;56:493–8.
127. Kronfol Z, Nair M, Zhang Q, Hill EE, Brown MB. Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Psychosom Med 1997;59:42–50.
128. Hall M, Baum A, Buysse DJ, Prigerson HG, Kupfer DJ, Reynolds CF III. Sleep as a mediator of the stress-immune relationship. Psychosom Med 1998;60:48–51.
129. Friedman SB, Glasgow LA, Ader R. Differential susceptibility to a viral agent in mice housed alone or in groups. Psychosom Med 1970;32:285–99.
130. Edwards EA, Dean LM. Effects of crowding of mice on humoral antibody formation and protection to lethal antigenic challenge. Psychosom Med 1977;39:19–24.
131. Capitanio JP, Lerche NW. Social separation, housing relocation, and survival in simian AIDS: a retrospective analysis. Psychosom Med 1998;60:235–44.
132. Moynihan JA, Ader R. Psychoneuroimmunology: animal models of disease. Psychosom Med 1996;58:546–58.
133. Coe CL. Psychosocial factors and immunity in nonhuman primates: a review. Psychosom Med 1993;55:298–308.
134. Feng NF, Pagniano R, Tovar CA, Bonneau RH, Glaser R, Sheridan JF. The effect of restraint stress on the kinetics, magnitude, and isotype of the humoral immune response to influenza virus infection. Brain Behav Immun 1991;5:383–7.
135. Hill CW, Greer WE, Felsenfeld O. Psychological stress, early response to foreign protein, and blood cortisol in vervets. Psychosom Med 1967;29:279–83.
136. Kiecolt-Glaser JK, Glaser R, Gravenstein S, Malarkey WB, Sheridan J. Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc Natl Acad Sci U S A 1996;93:3043–7.
137. Suedfeld P, Pennebaker JW. Health outcomes and cognitive aspects of recalled negative life events. Psychosom Med 1997;59:171–7.
138. Kiecolt-Glaser JK, Page GG, Marucha PT, MacCallum RC, Glaser R. Psychological influences on surgical recovery: perspectives from psychoneuroimmunology. Am Psychol 1998;53:1209–18.
139. Adams DO. Molecular biology of macrophage activation: a pathway whereby psychosocial factors can potentially affect health. Psychosom Med 1994;56:316–27.
140. Levenstein S, Ackerman S, Kiecolt-Glaser JK, Dubois A. Stress and peptic ulcer disease. JAMA 1999;281:10–1.
141. Ackerman KD, Martino M, Heyman R, Moyna NM, Rabin BS. Stressor-induced alteration of cytokine production in multiple sclerosis patients and controls. Psychosom Med 1998;60:484–91.
142. Byrnes DM, Antoni MH, Goodkin K, Efantis-Potter J, Asthana D, Simon T, Munajj J, Ironson G, Fletcher MA. Stressful events, pessimism, natural killer cell cytotoxicity, and cytotoxic/suppressor T cells in HIV^+ black women at risk for cervical cancer. Psychosom Med 1998;60:714–22.
143. Hamerman D. Toward an understanding of frailty. Ann Intern Med 1999;130:945–50.
144. Cohen HJ. In search of the underlying mechanisms of frailty [editorial]. J Gerontol A Biol Sci Med Sci 2000;55:M706–8.
145. Ershler W, Keller E. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annu Rev Med 2000;51:245–70.
146. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–9.
147. Kiechl S, Egger G, Mayr M, Wiedermann CJ, Bonora E, Oberhollenzer F, Muggeo M, Xu Q, Wick G, Poewe W, Willeit J. Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study. Circulation 2001;103:1064–70.
148. Harris T, Ferrucci L, Tracy R, Corti M, Wacholder S, Ettinger WJ, Heimovitz H, Cohen H, Wallace R. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am J Med 1999;106:506–12.
149. Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur Studies of Successful Aging. J Gerontol A Biol Sci Med Sci 2000;55:M709–15.
150. Ferrucci L, Harris T, Guralnik J, Tracy R, Corti M, Cohen H, Penninx B, Pahor M, Wallace R, Havlik R. Serum IL-6 level and the development of disability in older persons. J Am Geriatr Soc 1999;47:639–46.
151. Cannon J. Cytokines in aging and muscle homeostasis. J Gerontol A Biol Sci Med Sci 1995;50:120–3.
152. Cohen H, Pieper C, Harris T, Rao K, Currie M. The association of plasma IL-6 levels with functional disability in community-dwelling elderly. J Gerontol A Biol Sci Med Sci 1997;52:M201–8.
153. Leventhal H, Patrick-Miller L, Leventhal EA, Burns EA. Does stress-emotion cause illness in elderly people? In: Schaie KW, Lawton MP, editors. Annual review of gerontology and geriatrics. Vol 17: Focus on emotion and adult development. New York; Springer Publishing; 1998. p. 138–84.
154. Catania A, Airaghi L, Motta P, Manfredi MG, Annoni G, Pettenati C, Brambilla F, Lipton JM. Cytokine antagonists in aged subjects and their relation with cellular immunity. J Gerontol A Biol Sci Med Sci 1997;52A:B93–7.
155. Rojas I, Padgett DA, Sheridan JF, Marucha PT. Stress-induced susceptibility to bacterial infection during cutaneous wound healing. Brain Behav Immun. In press.