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Psychoneuroimmunology of Depression: Clinical Implications

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Psychoneuroimmunology is a field that investigates the interactions between the brain and the immune system. One important goal of this field of research is to translate basic research in order to understand how behavior affects health and resistance to disease in humans. This review evaluates the impact of depression on morbidity and mortality risk and asks whether neuroimmune mechanisms contribute to this association. Examples are drawn from three diseases: cardiovascular disease, infectious disease, and rheumatoid arthritis. Finally, the potential for biobehavioral interventions to impact psychological adaptation and the course of immune related disease is discussed.   © 2002 Elsevier Science (USA)

Key Words: depression; immunity; cytokines; cardiovascular disease; infectious disease; rheumatoid arthritis; behavior; interventions.

INTRODUCTION

I am deeply honored and yet also humbled to write this 2001 Presidential Address for the Psychoneuroimmunology Research Society. Psychoneuroimmunology is a field that investigates the interactions between the brain and the immune system as a way of understanding how behavior affects health and resistance to disease. Thus, an important goal of psychoneuroimmunology and its Society is to conduct basic research that can be translated into clinically relevant health applications. For this address, I focus on the psychoneuroimmunology of depression, which has matured from a description of collective immune alterations found in depression to a challenging inquiry that is concerned with the clinical importance of immune abnormalities in depression.

Psychological stress and depressive symptoms are hypothesized to result in increased rates of morbidity and mortality particularly in patients with cardiovascular disease (Barefoot, Brummett, Helms, Mark, Siegler, & Williams, 2000; Covinsky, Kahana, Chin, Palmer, Fortinsky, & Landefeld, 1999; Jiang, Alexander, Christopher, Kuchibhatla, Gaulden, Cuffe, Blazing, Davenport, Califf, Krishnan, & O'Connor, 2001; Wulsin, Vaillant, & Wells, 1999). However, less is known about the effects of major depression on the outcomes of other diseases and whether depression alters the onset and progression of chronic medical disorders such as infectious disease and/or inflammatory disorders. A further question concerns the mechanisms that account for the relationships between depression and the progression of immune-related disorders. The potential role of neuroimmune processes in mediating increases in disease risk in depressed populations has begun to be addressed by evaluating the effects of depression and depressive symptoms on specific immune measures and/or immune markers of disease severity. If it is substantiated that biobehavioral factors impact immune related diseases, then it is equally important to know whether inter-

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ventions that influence psychological adaptation can have attendant effects on immunological and health status outcomes. This address will review and focus on these three major questions as a way of pointing toward future research and opportunities for the field of psychoneuroimmunology.

WHY IS IT IMPORTANT TO STUDY DEPRESSION?

Depression Shows a High Prevalence

Depressive syndromes and major depression are exceedingly common. Lifetime prevalence rates of major depression are estimated to be 20% in women and about 10% in men (Steffens, Skoog, Norton, Hart, Tschanz, Plassman, Wyse, Welsh-Bohmer, & Breitner, 2000). In primary care outpatients, point prevalence rates range from 9% to 20% for all depressive disorders (Barry, Fleming, Manwell, Copeland, & Appel, 1998). In medical patients with chronic diseases, rates are even higher, with 8% for major depression and 15% to 36% for all depressive disorders (Feldman, Mayou, Hawton, Ardern, & Smith, 1987).

In older adults where chronic medical disease is prominent, the clinical course of depression is one that is tenacious and marked by recurrent and remitting episodes (Berger, Small, Forsell, & Backman, 1998). The development of major depression can take many years in the older adult with prodromal and progressive elevation of depressive symptoms, in contrast to the relatively short clinical onset in younger patients (Berger et al., 1998). Moreover, despite up-to-date clinical management, there is often incomplete resolution of depressive symptoms and an increased risk of relapse in the old adult (Lyness, Caine, Conwell, & King, 1993).

The Biopsychosocial Model: Understanding Depression and Its Clinical
    Implications

The factors that contribute to the more chronic nature of depression are not fully known, although the presence of chronic disease, exposure to stressful life events and personal losses, diminished social supports, and declines in self-concepts of efficacy and mastery are suggested (Blazer, 1989). It is also well documented that severity of physical illness is one of the most important variables associated with depression in patients with chronic medical illness (Blazer, 1989). To address the complexity of the relationships between depression and morbidity, assessment of multiple domains (Fig. 1) that takes into account the reciprocal and cascading relationships between severity of chronic disease, other life stresses, social support, self-concept, and coping in the onset of affective disturbance and depressive disorders is needed.

In Fig. 1, it is shown that stressors, including the experience of a chronic disease as well as other stressful life events and/or difficulties, can lead to psychological distress. However, the response to such stressors is variable and individual differences in background characteristics (e.g., age, gender, socioeconomic status), social support, coping, and self-concept (e.g., self-efficacy) can impinge on the stressor domain and outcomes both directly and indirectly. In this formulation, the relationships between environmental and personal factors that lead to affective distress and depressive disorder are emphasized.

Depression: Effects on Health Functioning

The impact of depression on an individual is not trivial nor limited to effects on emotional well-being or social functioning. The occurrence of depression, even sub-
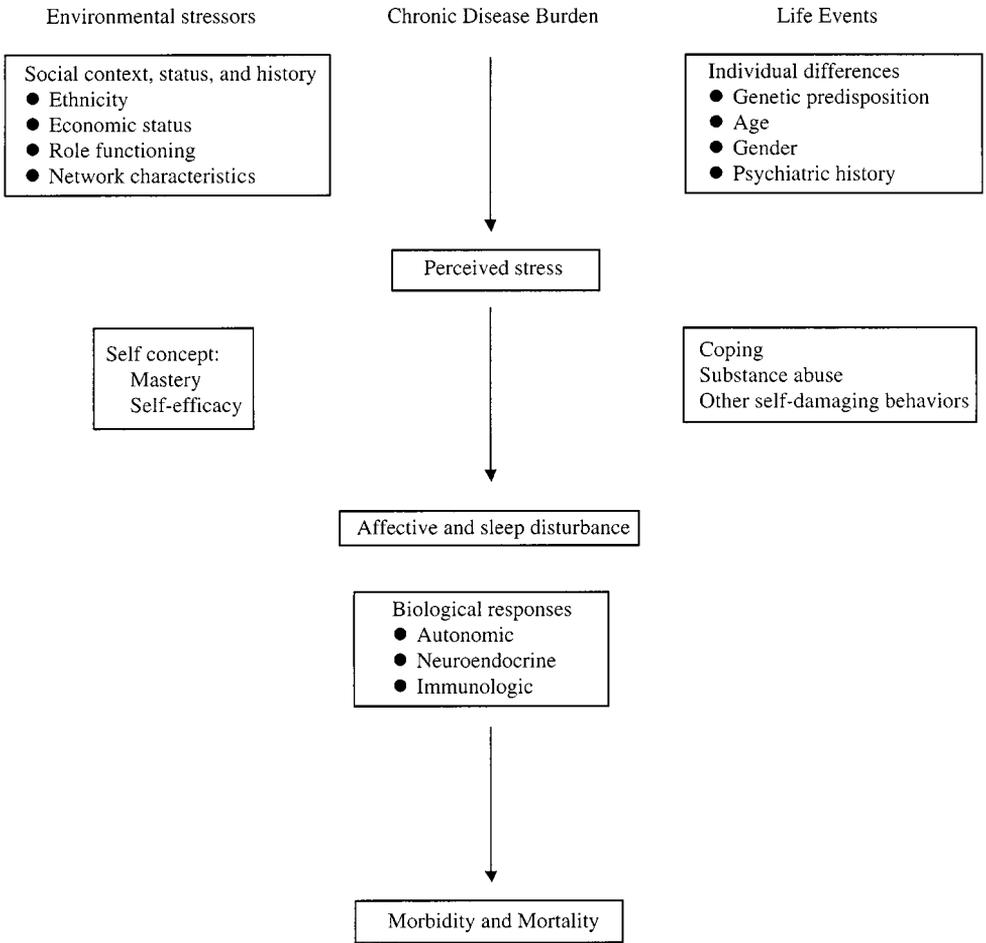
Environmental stressors   Chronic Disease Burden   Life Events

Social context, status, and history
● Ethnicity
● Economic status
● Role functioning
● Network characteristics

Individual differences
● Genetic predisposition
● Age
● Gender
● Psychiatric history

Perceived stress

Self concept:
Mastery
Self-efficacy

Coping
Substance abuse
Other self-damaging behaviors

Affective and sleep disturbance

Biological responses
● Autonomic
● Neuroendocrine
● Immunologic

Morbidity and Mortality

FIGURE 1

threshold depressive symptoms, produces impairments in measures of physical functioning, pain, and general health, along with decrements in emotional health (Bruce, Seeman, Merrill, & Blazer, 1994; Wells, Stewart, Hays, Burnam, Rogers, Daniels, Berry, Greenfield, & Ware, 1989). Second, limitations in functioning of depressed persons across physical domains are equal to or greater than those found in many major chronic medical conditions (Wells et al., 1989). Third, while impairments can improve over time as might be expected for an episodic disorder, persistent limitations are generally found, supporting the view of depression as a chronic and recurrent disorder with residual disability (Hays, Wells, Sherbourne, Rogers, & Spritzer, 1995). Indeed, depressive symptoms and physical disability can initiate a spiralling decline in physical and psychological health. However, the extent and degrees to which depression adds to functional impairments in adults with pre-existing chronic diseases have received little attention. It is not known, for example, whether ''co-morbidity'' for depression and chronic disease exacerbates limitations in functioning, well-being, and health over time and whether the effects of depressive disorder differ across various patient populations.

Depression: Relation to Morbidity and Mortality

The notion that depressive disorders can increase one's risk for developing disease or influence the severity or rate of progression of disease is controversial and is often ''explained'' by the hypothesis that patients with a psychiatric disorder generally have other risk factors for the development of chronic disease (Hayward, 1995). Alternatively, depression may adversely affect compliance with medical therapy and rehabilitation and increase medical comorbidity via this route (Carney, Freedland, Eisen, Rich, & Jaffe, 1995). However, in the example of cardiovascular disease, analyses of other risk factors (such as hypertension, hypercholesterolemia, nictoine and other substance abuse, and physical inactivity), along with controls for age, gender, and socioeconomic status, implicate depression as an independent risk factor (Glassman & Shapiro, 1998; Lespérance, Frasure-Smith, Juneau, & Théroux, 2000; Musselman, Evans, & Nemeroff, 1998). The presence of depression preceding the onset of ischemic heart disease, the greater risk of sudden death among post-myocardial-infarction patients with depression and arrhythmia, and the predisposition to increased platelet aggregation among depressed patients all point to a causal relationship as reviewed by Musselman et al. (1998). Less is known about other medical illnesses, and one important direction is to determine the role of depression and depressive symptoms (e.g., sleep disturbance) in the progression of infectious and inflammatory diseases such as rheumatoid arthritis using disease-specific and objective clinical outcomes.

Beyond the effects on functioning and morbidity, depression predicts mortality whether it is considered as a disorder or treated as a continuous risk factor (Glassman & Shapiro, 1998; Herrmann et al., 1998; Rovner, 1993). Importantly, findings of increased risk of mortality with depression are not limited to specific physical diseases or to highly selected patient groups, but are reported to occur in mixed patient populations typical of a hospitalized setting (Herrmann et al., 1998) and in elderly persons residing in a nursing home (Rovner, 1993). While conflicting results are also reported, with no higher risk of mortality in depressed populations with cancer or end-stage renal disease (Christensen et al., 1994; Jenkins et al., 1994; Richardson et al., 1990), substantial data in the instance of patients recovering from a myocardial infarction demonstrate that depression significantly predicts mortality even after the effects of previous cardiovascular disease severity and extent of cardiac compromise are considered (Frasure-Smith et al., 1995; Lespérance et al., 2000).

DOES DEPRESSION IMPACT NEUROIMMUNE DISEASE MARKERS?

Relationship of Depression to Cardiovascular Disease: Role of Immune Mediators

Progression of chronic disease shows striking individual differences and one goal of psychoneuroimmunology research is to ascertain what factors come together to exacerbate the progression of disease. Previous cross-sectional and longitudinal studies in depressive disorders involving measures of autonomic, neuroendocrine, and immune function indicate multisystem physiological changes that occur during episodes of depression (Irwin, 1995). However, translation of these observations into clinical and disease-specific outcomes remains incomplete.

Autonomic, neuroendocrine and immune abnormalities found in stress and depressive disorders are thought to contribute to the increased risk of cardiovascular disorders (Musselman et al., 1998). For example, depressed and/or psychologically

stressed persons show elevations of sympathoadrenal activity at rest and in response to acute challenge (Mills, Ziegler, Patterson, Dimsdale, Hauger, Irwin, & Grant, 1997; Pike, Smith, Hauger, Nicassio, Patterson, McClinitick, Costlow, & Irwin, 1997; Irwin, Brown, Patterson, Hauger, Mascovich, & Grant, 1991), and such sympathetic abnormalities correlate with hypertensive cardiovascular disease (Dimsdale & Ziegler, 1991). Sympathoadrenal hyperactivity also contributes to cardiovascular disease through effects of catecholamines upon the heart, blood vessels, and platelets as reviewed by Musselman et al. (1998).

Recent evidence further implicates inflammatory processes in triggering the sequence of events that lead to atherogenesis (Lusis, 2000; Ross, 1993). The presence of numerous macrophages and T-lymphocytes in vascular endothelial lesions indicates that there is an inflammatory reaction secondary to tissue damage as well as a primary immunological response (Lusis, 2000). Activated macrophages secrete pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF). In response to these cytokines, cellular adhesion molecules are expressed on the endothelial membrane, which leads to adhesion of circulating leucocytes to the endothelial cell, transendothelial migration, and further immune cell activation (Lusis, 2000; Ross, 1993). This series of steps is believed to be important in the initiation of atherogenesis; pathological studies have shown increased cellular adhesion molecule expression in several components of the atherosclerotic plaque (Lusis, 2000).

Psychological and physical stressors increase the release of pro-inflammatory cytokines and alter expression of adhesion molecules. For example, Appels et al. have found that angioplasty patients with feelings of exhaustion and depression have higher levels of IL-1 and TNF (Appels, Bär, Bär, Bruggeman, & de Baets, 2000). Other studies show that acute stress leads to increases in the density of the cellular adhesion molecule, LFA-1, on mixed lymphocytes (Goebel, Mills, Irwin, & Ziegler, 2000). Moreover, stress leads to elevations of plasma levels of soluble isoforms of adhesion molecules such as sICAM, which are implicated as markers of cardiovascular disease risk. In a prospective cohort of 14,916 healthy men, sICAM was measured in 474 participants who developed a first myocardial infarction and 474 participants who remained healthy throughout the 9-year follow-up (Ridker, Hennekens, Roitman-Johnson, Stampfer, & Allen, 1998). Elevated levels of sICAM at baseline were associated with risk of future myocardial infarction, especially among those with sICAM concentrations in the highest quartile, and this association was independent of smoking status and lipid and nonlipid risk factors. A prospective study of similar scope also reported an association between elevated levels of IL-6 and risk of future myocardial infarction (Ridker, Rifai, Stampfer, & Hennekens, 2000).

Depression and Infectious Disease Risk

Compelling evidence has shown that inescapable stress, a putative animal model of depression, increases susceptibility to viral diseases such as herpes simplex, influenza, and coxsackievirus infections via alterations in immune function (Sheridan, Dobbs, Brown, & Zwilling, 1994). However, the immunological consequences of major depression and psychological stress for infectious diseases remain a much needed area of inquiry (Herbert & Cohen, 1993; Stein, Miller, & Trestman, 1991; Zorrilla, Luborsky, McKay, Rosenthal, Houldin, Tax, McCorkle, Seligman, & Schmidt, 2001). Indeed, few clinical studies have begun to address the confluence

of behavioral, immunological and infectious disease outcome variables in the same individuals at the same time.

Prospective epidemiological studies and experimental viral challenge studies show that persons reporting more psychological stress have both a higher incidence and a greater severity of infectious illness (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997; Cohen, Tyrrell, & Smith, 1991; Cohen & Williamson, 1991). Although immune correlates were not determined in these prior studies, this research group recently tested whether local proinflammatory cytokine production might covary with psychological stress and be related with increased susceptibility to upper respiratory illness (Cohen, Doyle, & Skoner, 1999). In 55 subjects experimentally infected with influenza A virus, upper respiratory symptoms were monitored along with nasal levels of IL-6. Consistent with prior findings, severity of psychological stress was associated with more symptoms and signs of upper respiratory infectious illness. Nasal IL-6 production temporally coincided with symptom severity following respiratory viral infection. In addition, those persons with greater psychological stress before inoculation showed greater concentration of IL-6 in their nasal secretions.

Use of a vaccination model has provided another valuable experimental manipulation to examine the disease-specific and integrated *in vivo* action of the immune system in relation to psychological stress. Kiecolt-Glaser and colleagues found that spousal caregivers of dementia patients had a poorer antibody response to influenza vaccination than noncaregivers matched for age and gender (Kiecolt-Glaser, Glaser, Gravenstein, & Malarkey, 1996). Vaccine responders were identified using standard criteria of a fourfold antibody increase to any one of the three vaccine components of the Fluzone vaccine. Caregivers were found to respond less often after vaccination than controls and these differences were amplified in individuals over 70 years of age. For example, in the adults older than 70 years, only 26% of the caregivers responded as compared to 60% of the controls. Differences in vaccine response were related to severity of emotional distress at the time of vaccination, but the two groups were similar in terms of influenza vaccine history, presence of chronic illnesses, medications, income, or age. Further investigations by Vedhara et al. have confirmed these results and further showed that chronic activation of the HPA axis as measured by salivary cortisol over the 6-month follow-up is negatively correlated with antibody levels (Vedhara, Cox, Wilcock, Perks, Hunt, Anderson, Lightman, & Shanks, 1999).

Finally, herpes zoster is another infectious disease model that warrants consideration. Herpes zoster (HZ) or shingles is caused by reactivation of an endogenous varicella zoster virus (VZV) infection that has persisted in a latent form within sensory ganglia following an earlier attack of varicella (chickenpox) (Oxman & Alani, 1993). Both the incidence and the severity of HZ rise markedly with increasing age, and the majority of episodes occur in persons over the age of 60 years (Ragozzino, Melton, Kurland, Chu, & Perry, 1982). Although the factors associated with increased risk of HZ in the older adult and the mechanisms responsible for maintaining VZV in the latent state are not known, there is much evidence that cell-mediated immunity plays a critical role in limiting the occurrence of HZ and its complications (Arvin, 1992). Age-related decline in VZV specific cellular immunity correlates with an increase in the incidence and severity of HZ and its complications (Burke, Steele, Beard, Wood, Cain, & Marmer, 1982), and iatrogenic immunosuppression with diminished VZV specific T lymphocyte proliferation is associated with greater susceptibility to VZV reactivation and HZ. Thus, the effects of depression on herpes zoster

risk were evaluated by assaying the frequency of cells in the peripheral blood capable of proliferating in response to VZV antigen (VZV-responder cell frequency, VZV-RCF) in patients with major depression vs age- and gender-matched normal controls (Irwin, Costlow, Williams, Artin, Levin, Hayward, & Oxman, 1998). VZV-RCF was also concurrently tested in a group of older adults to determine whether the decline in VZV-RCF observed in major depression was comparable in magnitude to that typically found in older persons who are known to be at increased risk of developing HZ. Depressed patients showed significantly lower levels of VZV-RCF than age-matched comparison adults. In addition, depressed patients showed declines of VZV cellular immunity that were comparable to the low levels of older adults 20 years their senior. While the results do not directly link depression with an increase in VZV reactivation and in the incidence of HZ, comparable declines in VZV-specific cellular immunity observed in older adults have been correlated with a significant increase in the incidence of HZ and its complications, an incidence that is more than double that in middle-aged adults (Oxman & Alani, 1993). One study has reported an association between life stress and the onset of herpes zoster in older adults (Schmader, Studenski, MacMillan, Grufferman, & Cohen, 1990).

Stress, Depression, and Rheumatoid Arthritis: Neuroimmune Mechanisms

Cytokines and their receptors are thought to play a fundamental role in the development and maintenance of the inflammatory process in rheumatoid arthritis (Brennan, Maini, & Feldmann, 1998). The macrophage-derived proinflammatory cytokines, IL-1, TNFα, and IL-6, are implicated in cartilage degradation and bone erosion associated with rheumatoid arthritis (Brennan et al., 1998). Indeed, circulating levels of IL-6 and soluble IL-2 receptor (sIL-2R) predict increases of disease severity in longitudinal, prospective studies of rheumatoid arthritis patients (Frank, Herrmann, Hein, Muller, & G, 1997). In addition to the changes of monocyte derived cytokines, it is thought that T lymphocyte activity contributes to disease progression via an imbalance of T-helper 1 (Th1) to Th2 cell activity (Verhoef, van Roon, Vianen, Lafeber, & Bijlsma, 1999). T lymphocytes isolated from peripheral blood or from the joints of patients with rheumatoid arthritis show elevated Th1 cytokine interferon (IFN, IL-2), mRNA, and/or protein expression, while Th2 cytokines are decreased (Verhoef et al., 1999). IL-4 and IL-10 have inhibitory effects on monocyte function, downregulate production of IL-1, IL-6, and TNF, and induce the production of the endogenous inhibitor TNF receptor (Feldmann, Brennan, & Maini, 1996). The promise of specific cytokine inhibitors and the use of anti-inflammatory cytokines in the treatment of rheumatoid arthritis provide converging evidence that a dysregulation of these important immune regulators underlies synovial inflammation in patients with rheumatoid arthritis (Verhoef et al., 1999).

The mechanisms that account for individual differences and variations in the inflammatory response and disease progression in rheumatoid arthritis patients are not known. However, pharmacologic doses of adrenal steroids have been used as potent immunosuppressive agents in the treatment of rheumatoid arthritis, and it is hypothesized that glucocorticoids might also be responsible under physiological conditions for suppression of an ongoing inflammatory response (McEwen, 1998). Strong support for this hypothesis comes from studies that demonstrate that a negative feedback loop exists between the immune system and the HPA axis and that proinflammatory cytokines (IL-1, TNF, and IL-6) stimulate the HPA axis, which results in the secretion

of glucocorticoids, which suppresses the immune response (McEwen, Biron, Brunson, Bulloch, Chambers, Dhabhar, Goldfarb, Kitson, Miller, Spencer, & Weiss, 1997). Thus, susceptibility to rheumatoid arthritis is carried by the presence of host response genes that contribute to exaggerated immune responses and by deficiencies in the HPA axis such that the host is not capable of mounting an immunosuppressive glucocorticoid response as discussed by Sternberg (Sternberg, 1998). Indeed, animal models of experimental arthritis reveal defects in the homeostatic regulation of the HPA axis at three levels of action: a central hypothalamic defect in the biosynthesis of corticotropin releasing hormone, defective and blunted induction of anterior pituitary ACTH and adrenal steroids, and decreased adrenal steroid receptor activation in immune target tissues (Sternberg, 1998). Taken together, the weak HPA response to inflammatory mediators is thought to be insufficient to suppress the progression of an autoimmune response.

Translation of these basic neuroimmune mechanisms into clinical outcomes is the next step in the psychoneuroimmunology research agenda. Consistent with the findings in animal models, rheumatoid arthritis shows a relative hypofunctioning of the HPA axis despite the degree of inflammation (Cutolo, Villaggio, Foppiani, Briata, Sulli, Pizzorni, Faelli, Prete, Felli, Seriolo, & Giusti, 2000). For example, IL-6 is a potent stimulus of ACTH and cortisol secretion in normal subjects (Späth-Schwalbe, Born, Schrezenmeier, Bornstein, Stromeyer, Drechsler, Fehm, & Porzsolt, 1994), yet Crofford et al. (Crofford, Kalogeras, Mastorakos, Magiakou, Wells, Kanik, Gold, Chrousos, & Wilder, 1997) found that elevations of IL-6 failed to induce increases in ACTH and cortisol in early untreated rheumatoid arthritis patients. In addition, the amplitude of circadian cortisol release is attenuated in rheumatoid arthritis patients with mild to moderate disease and absent in those with severe disease, leading to an overall decrease in cortisol levels as rheumatoid arthritis disease progresses (van den Brink, Blankenstein, Koppeschaar, & Bijlsma, 1993). Along with dysregulation of the neuroendocrine axis, the lymphocytes of rheumatoid arthritis patients may become less sensitive to the effects of glucocorticoids. In rheumatoid arthritis subjects, there appears to be a down-regulation of glucocorticoid receptors (Norbiato, Bevilacqua, Vago, & Clerici, 1997). Th1 and proinflammatory cytokines are reported to decrease glucocorticoid receptor affinity (McEwen et al., 1997), and it is now believed that this vicious circle of immune activation together with insufficient HPA axis restraint of cytokine secretion is a major component of disease progression.

Other agents that also modulate immune function including sympathetic activity and other neuroendocrine hormones, such as prolactin, may provoke dysregulation of neuroimmune mechanisms relevant to rheumatoid arthritis disease progression . For example, there is evidence that immune function is suppressed by activation of the sympathetic nervous system (Friedman & Irwin, 1997). Yet, as is the case for glucocorticoids, the influence of sympathetic activity cannot be interpreted simplistically; the sympathetic nervous system can have both positive and negative influences. Rheumatoid arthritis patients show sympatho-medullary activation, elevated plasma catecholamines, and a down-regulation of β-adrenergic receptor density (Baerwald, Graefe, von Wichert, & Krause, 1992). Moreover, Levine, Coderre, Helms, & Basbaum (1988) have found that β-adrenergic antagonists attenuate disease severity in animal models of arthritis.

Thus, stress, depressive symptoms, and depressive disorders are not believed to be simple correlates or consequences of rheumatoid arthritis disease severity. Rather, stress and depressive symptoms resulting from an inability to regulate negative af-

fective responses to stress are thought to contribute to neuroimmune dysregulation and progression of pathological autoimmune responses in rheumatoid arthritis (Chrousos, 1995). Moreover, stress and depression can induce increases as well as decreases of immune function and cytokine production depending on the immune measures and the chronicity of the stress (Irwin, 1999). For example, cytokine production and function are dynamically regulated at multiple levels in which some substances exert apparently opposing effects at different levels (e.g., increasing mRNA but decreasing protein release) (Watkins, Hansen, Nguyen, Lee, & Maier, 1999).

Depression is associated with complex patterns of changes in immune cell number and function; immune activation with the excessive secretion of proinflammatory cytokine found in depressed persons is coupled with a loss of nonspecific and specific cellular immune responses (Irwin, 1999). For example, depression is correlated with increased *in vivo* and *ex vivo* secretion of the pro-inflammatory cytokine, IL-6 (Zorrilla et al., 2001). Increased circulating concentrations of sIL-2R further support the notion of *in vivo* T cell activation in depressive disorder (Zorrilla et al., 2001). In addition to these findings, acute stress elevates IL-6 whether changes in this cytokine are measured *in vivo* or by *ex vivo* stimulated production (Goebel et al., 2000). Importantly, psychological response to the stressor (e.g., increases in anxiety and depressive symptoms) is critical; those who have increases in depressive symptoms following exposure to acute examination stress show greater production of TNF, IFN, and IL-6 as compared to students with low perceived stress (Maes, Van Der Planken, Van Gastel, Bruyland, Van Hunsel, Neels, Hendriks, Wauters, Demedts, Janca, & Scharpé, 1998). In subjects with multiple sclerosis, acute laboratory stress has also been found to increase the macrophage derived cytokine IL-1 and TNF and to increase the Th1 lymphocyte derived IFN (Ackerman, Martino, Heyman, Moyna, & Rabin, 1998). Studies in rheumatoid arthritis patients are needed to determine whether those patients with depression show exaggerated increases in proinflammatory cytokines in response to stress and/or alterations in the ability of glucocorticoids to restrain inflammatory mediators.

Sleep Disturbance: A Key Predictor of Immune Alterations in Clinical Samples

Sleep disturbance is prominent in individuals undergoing stress or depression, and there is emerging data showing that sleep disturbance uniquely contributes to the multisystem physiological effects of depression. For example, sleep disturbance results in sympathoadrenal activation (Irwin, Thompson, Miller, Gillin, & Ziegler, 1999) and is associated with changes in the immune system independent of the presence of a depressive disorder (Irwin, Mascovich, Gillin, Willoughby, Pike, & Smith, 1994; Irwin, McClintick, Costlow, Fortner, White, & Gillin, 1996; Irwin, Smith, & Gillin, 1992). This body of research concerning the consequences of sleep disturbance for measures of immunity and the bidirectional interplay between cytokines and sleep processes in the homeostatic regulations was recently reviewed (Irwin, in press) and will not be discussed in the present review.

DO BEHAVIORAL INTERVENTIONS IMPACT IMMUNITY AND IMMUNE-RELATED DISEASE OUTCOMES?

The model put forward in Fig. 1 posits an interrelationship between stressor, cognitive appraisal of stress, affective integration, and translation of the cognitive and affective processes into physiological responses. In this model, feedback systems are

also operating. Not only can one's appraisal of stressors elicit affective and physiological arousal, but conversely physiological arousal can influence one's cognitions and lead to feelings of anxiety and distress. Consequently, several strategies for intervention can be deduced from the model. One approach involves modifying cognitive appraisal and ameliorating emotional distress, whereas another focuses on reducing psychophysiological arousal through the use of relaxation response based training. In a model that is transactional, reciprocal, and synergistic, the causal priority of the intervention is less of a concern than the view that effective management of stress is related to its impact on the interaction of thoughts, feelings, physiological activity, and behavior (Parker, 1995). Thus, the studies reviewed here provide salient examples of stress-management programs that differ in their therapeutic focus, but nevertheless provide an integrated assessment of psychological and physiological adaptation in an effort to identify individual differences in disease outcomes.

Cognitive–behavioral interventions involve modifying the cognitive–affective mediation of stressful events and focus on the restructuring of appraisal and the amelioration of emotional distress (Bandura, 1977). The clinical effectiveness of cognitive–behavioral interventions in reducing self-reported clinical symptoms has been suggested in studies involving a wide range of chronic illness and disabilities including rheumatoid arthritis, as reviewed by Parker (1995).

Administration of a behavioral intervention has also been found to impact the psychological and medical outcomes of cancer patients. For example, Speigel et al. tested the effects of psychosocial intervention on the time of survival of 86 patients with metastatic breast cancer (Spiegel, Bloom, Kraemer, & Gottheil, 1989). Patients randomized to a weekly group therapy that consisted of support with self-hypnosis for pain lived significantly longer than did controls, by an average of nearly 18 months. Differences in survival between the two groups remained robust even when initial staging and oncological care during follow-up were controlled.

Fawzy et al. extended these observations in cancer outcomes by examining malignant melanoma patients and evaluating psychological, immunological, and recurrence rates in a 6-year longitudinal follow-up (Fawzy, Cousins, Fawzy, Kemeny, Elashoff, & Morton, 1990; Fawzy, Fawzy, Hyun, Elashoff, Guthrie, Fahey, & Morton, 1993). In newly diagnosed postsurgical malignant melanoma patients, a structured psychiatric intervention was found to enhance effective coping, reduce psychological distress, and increase several measures of the NK cell subsystem. Follow-up analyses of 68 patients also revealed an impact of the psychosocial intervention on morbidity and mortality risk. In the control group, 10 of the original 35 patients died and three had recurrences, whereas in the experimental group three of the original 34 patients died and four had recurrences. The number of deaths was significantly less in the experimental group. The relationship between psychosocial treatment group and outcome was further tested, taking into account other predictors such as age, gender, depth of penetration of the melanoma at the time of surgery, and site of the tumor. Two predictors, depth of tumor and treatment group, were associated with recurrence and survival. Indeed, an increase in active-behavioral coping scores following the psychological intervention was related to better survival and recurrence. The mechanisms that account for the association between psychological coping and melanoma outcome 6 years later are not known, although alterations of the NK subsystem at baseline were found to be important; higher levels of NK activity at baseline were related to lower recurrence rates. Together these data demonstrate that individual

variability in outcome of malignant melanoma is related to the levels of affective distress and coping at the time of surgical resection. Interventions that target patients with high levels of distress and low levels of coping are likely to reduce distress, enhance active-behavioral coping, and on average prolong recurrence and survival times.

Are There Critical Elements of a Behavioral Intervention That Lead to Psychological and Health Improvement?

Expressive talking or writing about a traumatic experience may be one salient factor. Pennebaker and Beall asked subjects to engage in a brief emotional exercise that involved writing about a traumatic experience for 20 minutes on three consecutive days per week (Pennebaker & Beall, 1986). As compared to controls who wrote about innocuous subjects without emotional valence, written emotional expression has been found to improve feelings of well-being and decrease the frequency of medical visits (Smyth, 1998). This emotional writing task also appears to have impacts on psychoneuroimmunologic processes. Petrie et al. found that antibody responses to hepatitis immunization were increased in participants who engaged in expressive writing about a traumatic experience prior to vaccination (Petrie, Booth, Pennebaker, Davison, & Thomas, 1995). The relevance of these findings to disease progression is further suggested by evaluation of the effects of writing on symptom reduction in patients with asthma or rheumatoid arthritis (Smyth, Stone, Hurewitz, & Kaell, 1999). In this study, 58 patients with asthma and 49 patients with rheumatoid arthritis underwent baseline assessment and were then randomly assigned to write about the most stressful event of their lives or about an emotionally neutral topic. Follow-up months after the intervention revealed striking improvement in disease-specific symptom measurements. In the asthma patients, the forced expiratory volume improved in the experimental group but not in the controls. For the rheumatoid arthritis patients, blind clinician rating of disease activity, symptom severity (e.g., distribution of pain, tenderness, and swelling throughout the affected joints) and health functioning also showed striking improvements in the intervention group as compared to the controls at 4-month follow-up with intervention patients changing from moderate to mild levels of overall disease activity.

Possible Impact of Pyschophysiological Interventions on Disease

Psychophysiological interventions (e.g., meditation) that involve directly reducing arousal are another approach that may yield benefits for immune-related diseases. Hyman and colleagues conducted a meta-analysis of the effects of relaxation training on somatic symptoms in medical populations and found that various stress-management interventions can lead to a reduction of clinical symptoms (Hyman, Feldman, Harris, Levin, & Malloy, 1989). Other studies have provided evidence that the practice of meditation reduces anxiety and depressive symptoms (Kabat-Zinn, Massion, Kristeller, Peterson, Fletcher, Pbert, Lenderking, & Santorelli, 1992) and lowers blood pressure in hypertensive patients (Alexander, Schneider, Staggers, Sheppard, Clayborne, Rainforth, Salerno, Kondwani, Smith, Walton, & Egan, 1996). In regards to immunologic or inflammatory disease, Kabat-Zinn and colleagues have suggested that mindfulness meditation hastens the remission of psoriasis in patients receiving usual medical care (Kabat-Zinn, Wheeler, Light, Skillings, Scharf, Cropley, Hosmer, & Bernhard, 1998). Psoriasis is thought to be due to an abnormal cutaneous

inflammatory process associated with epidermal hyperproliferation and abnormal differentiation, and most treatments for psoriasis are focused on reducing the inflammatory response and the growth of involved skin cells. Building upon observations that psychological stress is implicated in the onset and severity of psoriatic flare-ups, the effects of a stress reduction intervention on response to standard treatment were tested in 37 patients with psoriasis who were to receive ultraviolet phototherapy or photochemotherapy. In those patients who were randomly assigned to mindfulness meditation and standard treatment, a more rapid clearing of the psoriasis lesions occurred, as evaluated by blind clinician rating of photographs of psoriasis lesions.

Taken together, these data suggest that behavioral interventions can lead to changes in self-report clinical symptoms. By targeting specific disease populations and simultaneously evaluating psychological, physiological, and disease specific outcomes, the efficacy of cognitive behavioral or psychophysiological interventions can be more firmly established. In addition, a better understanding of the degrees and ways in which cognitive–behavioral treatment and/or relaxation-response-based interventions exert their effects on disease outcomes in distinct and homogeneous patient populations is needed.

SUMMARY

I have tried to summarize many of the approaches my colleagues and I have used in our studies of depression and health. The most productive insights in psychoneuroimmunology will come from studies that are sensitive to the broad nuances of psychological and behavioral determinants and to how these factors alter immunity and predict individual differences in progression and severity of specific disease outcomes. Understanding these relationships is critical to the development of behavioral and/or psychopharmacological interventions that have the potential to alter neuroimmune mechanisms and clinical outcomes in medical disorders.

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REFERENCES

Ackerman, K.D., Martino, M., Heyman, R., Moyna, N.M., & Rabin, B.S. (1998). Stressor-induced alteration of cytokine production in multiple sclerosis patients and controls. *Psychosom. Med.* **60,** 484–491.

Alexander, C.N., Schneider, R.H., Staggers, F., Sheppard, W., Clayborne, B.M., Rainforth, M., Salerno, J., Kondwani, K., Smith, S., Walton, K.G., & Egan, B. (1996). Trial of stress reduction for hypertension in older African Americans. II. Sex and risk subgroup analysis. *Hypertension* **28,** 228–237.

Appels, A., Bär, F.W., Bär, J., Bruggeman, C., & de Baets, M. (2000). Inflammation, depressive symptomtology, and coronary artery disease. [Comment In: *Psychosom. Med.* 2000 Sep–Oct; 62(5):606–607]. *Psychosom. Med.* **62,** 601–605.

Arvin, A.M. (1992). Cell-mediated immunity to varicella–zoster virus. *J. Infect. Dis.* **166,** S35–S41.

Baerwald, C., Graefe, C., von Wichert, P., & Krause, A. (1992). Decreased density of beta-adrenergic receptors on peripheral blood mononuclear cells in patients with rheumatoid arthritis. *J. Rheumatol.* **19,** 204–210.

Bandura, A. (1977). *A social learning theory.* Prentice–Hall: Englewood Cliffs, NJ.

Barefoot, J.C., Brummett, B.H., Helms, M.J., Mark, D.B., Siegler, I.C., & Williams, R.B. (2000). Depressive symptoms and survival of patients with coronary artery disease. *Psychosom. Med.* **62,** 790–795.

Barry, K.L., Fleming, M.F., Manwell, L.B., Copeland, L.A., & Appel, S. (1998). Prevalence of and factors associated with current and lifetime depression in older adult primary care patients. *Fam. Med.* **30,** 366–371.

Berger, A.K., Small, B.J., Forsell, Y., & Backman, L. (1998). Preclinical symptoms of major depression in very old age: A prospective longitudinal study. *Am. J. Psychiatr.* **155,** 1039–1043.

Blazer, D. (1989). Depression in the elderly. *New Engl. J. Med.* **320,** 164–166.

Brennan, F.M., Maini, R.N., & Feldmann, M. (1998). Role of pro-inflammatory cyotkines in rheumatoid arthritis. *Springer Sem. Immunopathol.* **20,** 133–147.

Bruce, M.L., Seeman, T.E., Merrill, S.S., & Blazer, D.G. (1994). The impact of depressive symptomatology on physical disability: MacArthur studies of successful aging. *Am. J. Pub. Health* **84,** 1796–1799.

Burke, B.L., Steele, R.W., Beard, O.W., Wood, J.S., Cain, T.D., & Marmer, D.J. (1982). Immune response to varicella–zoster in the aged. *Arch. Intern. Med.* **142,** 291–293.

Carney, R.M., Freedland, K.E., Eisen, S.A., Rich, M.W., & Jaffe, A.S. (1995). Major depression and medication adherence in elderly patients with coronary artery disease. *Health Psychol.* **14,** 88–90.

Christensen, A.J., Wiebe, J.S., Smith, T.W., & Turner, C.W. (1994). Predictors of survival among hemodialysis patients: Effect of perceived family support. *Health Psychol.* **13,** 521–525.

Chrousos, P. (1995). The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. *N. Engl. J. Med.* **332,** 1351–1362.

Cohen, S., Doyle, W.J., & Skoner, D.P. (1999). Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosom. Med.* **61,** 175–180.

Cohen, S., Doyle, W.J., Skoner, D.P., Rabin, B.S., & Gwaltney, J.M. (1997). Social ties and susceptibility to the common cold. *JAMA* **277,** 1940–1944.

Cohen, S., Tyrrell, D.A., & Smith, A.P. (1991). Psychological stress and susceptibility to the common cold. *N. Engl. J. Med.* **325**(9), 606–656.

Cohen, S., & Williamson, G. (1991). Stress and infectious disease in humans. *Psychol. Bull.* **109**(1), 5–24.

Covinsky, K.E., Kahana, E., Chin, M.H., Palmer, R.M., Fortinsky, R.H., & Landefeld, C.S. (1999). Depressive symptoms and 3-year mortality in older hospitalized medical patients. *Ann. Intern. Med.* **130,** 563–569.

Crofford, L.J., Kalogeras, K.T., Mastorakos, G., Magiakou, M.A., Wells, J., Kanik, K.S., Gold, P.W., Chrousos, G.P., & Wilder, R.L. (1997). Circadian relationships between interleukin (IL)-6 and hypothalamic–pituitary–adrenal axis hormones: Failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. *J. Clin. Endocrinol. Metab.* **82,** 1279–1283.

Cutolo, M., Villaggio, B., Foppiani, L., Briata, M., Sulli, A., Pizzorni, C., Faelli, F., Prete, C., Felli, L., Seriolo, B., & Giusti, M. (2000). The hypothalamic–pituitary–adrenal and gonadal axes in rheumatoid arthritis. *Ann. N.Y. Acad. Sci.* **917,** 835–843.

Dimsdale, J.E., & Ziegler, M.G. (1991). What do plasma and urinary measures of catecholamines tell us about human response to stressors? *Circulation* **83,** 36–42.

Fawzy, F.I., Cousins, N., Fawzy, N.W., Kemeny, M.E., Elashoff, R., & Morton, D. (1990). A structured psychiatric intervention for cancer patients. I. Changes over time in methods of coping and affective disturbance. *Arch. Gen. Psychiatry* **47**(8), 720–725.

Fawzy, F.I., Fawzy, N.W., Hyun, C.S., Elashoff, R., Guthrie, D., Fahey, J.L., & Morton, D.L. (1993). Malignant melanoma: Effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. *Arch. Gen. Psychiatry* **50,** 681–689.

Feldman, E., Mayou, R., Hawton, K., Ardern, M., & Smith, E.B. (1987). Psychiatric disorder in medical in-patients. *Q. J. Med.* **63,** 405–412.

Feldmann, M., Brennan, F.M., & Maini, R.N. (1996). Role of cytokines in rheumatoid arthritis. *Annu. Rev. Immunol.* **14,** 397–440.

Franke, S., Herrmann, D., Hein, G., Muller, A., & Stein, G. (1997). Interleukin-6, soluble interleukin-

2 receptor and soluble interleukin-6 receptor in sera of patients with rheumatoid arthritis: Influences of disease activity and drug therapy. *Eur. J. Med. Res.* **2,** 401–406.

Frasure-Smith, N., Lespérance, F., & Talajic, M. (1995). Depression and 18-month prognosis after myocardial infarction [see comments] [published erratum appears in *Circulation* 1998 Feb 24;97(7): 708]. *Circulation* **91,** 999–1005.

Friedman, E.M., & Irwin, M.R. (1997). Modulation of immune cell function by the autonomic nervous system. *Pharmacol. Ther.* **74,** 27–38.

Glassman, A.H., & Shapiro, P.A. (1998). Depression and the course of coronary artery disease. *Am. J. Psychiatry* **155,** 4–11.

Goebel, M.U., Mills, P.J., Irwin, M.R., & Ziegler, M.G. (2000). Interleukin-6 and tumor necrosis factor-alpha production after acute psychological stress, exercise, and infused isoproterenol: Differential effects and pathways. *Psychosom. Med.* **62,** 591–598.

Hays, R.D., Wells, K.B., Sherbourne, C.D., Rogers, W., & Spritzer, K. (1995). Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses. *Arch. Gen. Psychiatry* **52,** 11–19.

Hayward, C. (1995). Psychiatric illness and cardiovascular disease risk. *Epidemiol. Rev.* **17,** 129–138.

Herbert, T.B., & Cohen, S. (1993). Depression and immunity—A meta-analytic review. *Psychol. Bull.* **113,** 472–486.

Herrmann, C., Brand-Driehorst, S., Kaminsky, B., Leibing, E., Staats, H., & Rüger, U. (1998). Diagnostic groups and depressed mood as predictors of 22-month mortality in medical inpatients. *Psychosom. Med.* **60,** 570–577.

Hyman, R.B., Feldman, H.R., Harris, R.B., Levin, R.F., & Malloy, G.B. (1989). The effects of relaxation training on clinical symptoms: A meta-analysis. *Nurs Res.* **38,** 216–220.

Irwin, M. (1995). Psychoneuroimmunology of depression. In F. E. Bloom and D. J. Kupfer (Eds.), *Psychopharmacology: The fourth generation of progress,* pp. 983–998. Raven: New York.

Irwin, M. (1999). Immune correlates of depression. *Adv. Exp. Med. Biol.* **461,** 1–24.

Irwin, M., Brown, M., Patterson, T., Hauger, R., Mascovich, A., & Grant, I. (1991). Neuropeptide Y and natural killer cell activity: Findings in depression and Alzheimer caregiver stress. *FASEB J.* **5,** 3100–3107.

Irwin, M., Costlow, C., Williams, H., Artin, K.H., Levin, M.J., Hayward, A.R., & Oxman, M.N. (1998). Cellular immunity to varicella–zoster virus in depression. *J. Infect. Dis.* **178,** S104–108.

Irwin, M., Mascovich, A., Gillin, J.C., Willoughby, R., Pike, J., & Smith, T.L. (1994). Partial sleep deprivation reduces natural killer cell activity in humans. *Psychosom. Med.* **56,** 493–498.

Irwin, M., McClintick, J., Costlow, C., Fortner, M., White, J., & Gillin, J.C. (1996). Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. *FASEB J.* **10,** 643–653.

Irwin, M., Smith, T.L., & Gillin, J.C. (1992). Electroencephalographic sleep and natural killer activity in depressed patients and control subjects. *Psychosom. Med.* **54,** 10–21.

Irwin, M., Thompson, J., Miller, C., Gillin, J.C., & Ziegler, M. (1999). Effects of sleep and sleep deprivation on catecholamine and interleukin-2 levels in humans: clinical implications. *J. Clin. Endocrinol. Metab.* **84,** 1979–1985.

Jenkins, P.L., Lester, H., Alexander, J., & Whittaker, J. (1994). A prospective study of psychosocial morbidity in adult bone marrow transplant recipients. *Psychosomatics* **35,** 361–367.

Jiang, W., Alexander, J., Christopher, E., Kuchibhatla, M., Gaulden, L.H., Cuffe, M.S., Blazing, M.A., Davenport, C., Califf, R.M., Krishnan, R.R., & O'Connor, C.M. (2001). Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Arch. Intern. Med.* **161,** 1849–1856.

Kabat-Zinn, J., Massion, A.O., Kristeller, J., Peterson, L.G., Fletcher, K.E., Pbert, L., Lenderking, W.R., & Santorelli, S.F. (1992). Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *Am. J. Psychiatry* **149,** 936–943.

Kabat-Zinn, J., Wheeler, E., Light, T., Skillings, A., Scharf, M.J., Cropley, T.G., Hosmer, D., & Bernhard, J.D. (1998). Influence of a mindfulness meditation-based stress reduction intervention on rates of

skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA). *Psychosom. Med.* **60,** 625–632.

Kiecolt-Glaser, J.K., Glaser, R., Gravenstein, S., & Malarkey, W.B. (1996). Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proc. Natl. Acad. Sci. USA* **93,** 3043–3047.

Lespérance, F., Frasure-Smith, N., Juneau, M., & Théroux, P. (2000). Depression and 1-year prognosis in unstable angina. *Arch. Intern. Med.* **160,** 1354–1360.

Levine, J.D., Coderre, T.J., Helms, C., & Basbaum, A.I. (1988). β2-adrenergic mechanisms in experimental arthritis. *Proc. Natl. Acad. Sci. USA* **85,** 4553–4556.

Lusis, A.J. (2000). Atherosclerosis. *Nature* **407,** 233–241.

Lyness, J.M., Caine, E.D., Conwell, Y., & King, D. (1993). Depressive symptoms, medical illness, and functional status in depressed psychiatric inpatients. *Am. J. Psychiatry* **150,** 910–915.

Maes, M., Van Der Planken, M., Van Gastel, A., Bruyland, K., Van Hunsel, F., Neels, H., Hendriks, D., Wauters, A., Demedts, P., Janca, A., & Scharpé, S. (1998). Influence of academic examination stress on hematological measurements in subjectively healthy volunteers. *Psychiatry Res.* **80,** 201–212.

McEwen, B.S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Ann. N.Y. Acad. Sci.* **840,** 33–44.

McEwen, B.S., Biron, C.A., Brunson, K.W., Bulloch, K., Chambers, W.H., Dhabhar, F.S., Goldfarb, R.H., Kitson, R.P., Miller, A.H., Spencer, R.L., & Weiss, J.M. (1997). The role of adrenocorticoids as modulators of immune function in health and disease: Neural, endocrine and immune interactions. *Brain Res. Rev.* **23,** 79–133.

Mills, P.J., Ziegler, M.G., Patterson, T., Dimsdale, J.E., Hauger, R., Irwin, M., & Grant, I. (1997). Plasma catecholamine and lymphocyte beta 2-adrenergic receptor alterations in elderly Alzheimer caregivers under stress. *Psychosom. Med.* **59,** 251–256.

Musselman, D.L., Evans, D.L., & Nemeroff, C.B. (1998). The relationship of depression to cardiovascular disease: Epidemiology, biology, and treatment. *Arch. Gen. Psychiatry* **55,** 580–592.

Norbiato, G., Bevilacqua, M., Vago, T., & Clerici, M. (1997). Glucocorticoids and Th-1, Th-2 type cytokines in rheumatoid arthritis, osteoarthritis, asthma, atopic dermatitis and AIDS. *Clin. Exp. Rheumatol.* **15,** 315–323.

Oxman, M.N., & Alani, R. (1993). Varicella and herpes zoster. In T. B. Fitzpatrick *et al.* (Eds.), *Dermatology in general medicine,* pp. 2543–2572. McGraw–Hill: New York.

Parker, J.C. (1995). Stress management. In P. Nicassio and T. Smith (Eds.), *Managing chronic illness: A biopsychosocial perspective,* pp. 285–312. Am. Psychol. Assoc.: Washington, D.C.

Pennebaker, J.W., & Beall, S.K. (1986). Confronting a traumatic event: Toward an understanding of inhibition and disease. *J. Abnorm. Psychol.* **95,** 274–281.

Petrie, K.J., Booth, R.J., Pennebaker, J.W., Davison, K.P., & Thomas, M.G. (1995). Disclosure of trauma and immune response to a Hepatitis B vaccination program. *J. Consult. Clin. Psychol.* **63,** 787–792.

Pike, J.L., Smith, T.L., Hauger, R., Nicassio, P.M., Patterson, T.L., McClinitick, J., Costlow, C., & Irwin, M.R. (1997). Chronic life stress alters sympathetic, neuroendocrine, and immune responsivity to an acute psychological stressor in humans. *Psychosom. Med.* **59,** 447–457.

Ragozzino, M.W., Melton, L.J., Kurland, L.T., Chu, C.P., & Perry, H.O. (1982). Population-based study of herpes zoster and its sequelae. *Medicine* **61,** 310–316.

Richardson, J.L., Zarnegar, Z., Bisno, B., & Levine, A. (1990). Psychosocial status at initiation of cancer treatment and survival. *J. Psychosom. Res.* **34,** 189–201.

Ridker, P.M., Hennekens, C.H., Roitman-Johnson, B., Stampfer, M.J., & Allen, J. (1998). Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men [see comments]. *Lancet* **351,** 88–92.

Ridker, P.M., Rifai, N., Stampfer, M.J., & Hennekens, C.H. (2000). Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* **101,** 1767–1772.

Ross, R. (1993). The pathogenesis of atherosclerosis: A perspective for the 1990s. *Nature* **362,** 801–809.

Rovner, B.W. (1993). Depression and increased risk of mortality in the nursing home patient. *Am. J. Med.* **94,** 19S–22S.

Schmader, K.E., Studenski, S., MacMillan, J., Grufferman, S., & Cohen, H.J. (1990). Are stressful life events risk factors for herpes zoster? *Am. J. Geriatr. Soc.* **38,** 1188–1195.

Sheridan, J.F., Dobbs, C., Brown, D., & Zwilling, B. (1994). Psychoneuroimmunology: Stress effects on pathogenesis and immunity during infection. *Clin. Microbiol. Rev.* **7,** 200–212.

Smyth, J.M., Stone, A.A., Hurewitz, A., & Kaell, A. (1999). Effects of writing about stressful experiences on symptom reduction in patients with asthma or rheumatoid arthritis: A randomized trial [see comments]. *JAMA* **281,** 1304–1309.

Smyth, J.M. (1998). Written emotional expression: Effect sizes, outcome types, and moderating variables. *J. Consult. Clin. Psychol.* **66,** 174–184.

Späth-Schwalbe, E., Born, J., Schrezenmeier, H., Bornstein, S.R., Stromeyer, P., Drechsler, S., Fehm, H.L., & Porzsolt, F. (1994). Interleukin-6 stimulates the hypothalamus–pituitary–adrenocortical axis in man. *J. Clin. Endocrinol. Metab.* **79,** 1212–1214.

Spiegel, D., Bloom, J., Kraemer, H.C., & Gottheil, E. (1989). The beneficial effect of psychosocial treatment on survival of metastatic breast cancer patients: A randomized prospective outcome study. *Lancet* **10/14,** 888–891.

Steffens, D.C., Skoog, I., Norton, M.C., Hart, A.D., Tschanz, J.T., Plassman, B.L., Wyse, B.W., Welsh-Bohmer, K.A., & Breitner, J.C. (2000). Prevalence of depression and its treatment in an elderly population: The Cache County study. *Arch. Gen. Psychiatry* **57,** 601–607.

Stein, M., Miller, A.H., & Trestman, R.L. (1991). Depression, the immune system, and health and illness. *Arch. Gen. Psychiatry* **48,** 171–177.

Sternberg, E.M. (1998). Overview of the conference and the field. *Ann. N.Y. Acad. Sci.* **840,** 1–8.

van den Brink, H.R., Blankenstein, M.A., Koppeschaar, H.P., & Bijlsma, J.W. (1993). Influence of disease activity on steroid hormone levels in peripheral blood of patients with rheumatoid arthritis. *Clin. Exp. Rheumatol.* **11,** 649–652.

Vedhara, K., Cox, N.K., Wilcock, G.K., Perks, P., Hunt, M., Anderson, S., Lightman, S.L., & Shanks, N.M. (1999). Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination [see comments]. *Lancet* **353,** 627–631.

Verhoef, C.M., van Roon, J.A., Vianen, M.E., Lafeber, F.P., & Bijlsma, J.W. (1999). The immune suppressive effect of dexamethasone in rheumatoid arthritis is accompanied by upregulation of interleukin 10 and by differential changes in interferon gamma and interleukin 4 production. *Ann. Rheum. Dis.* **58,** 49–54.

Watkins, L.R., Hansen, M.K., Nguyen, K.T., Lee, J.E., & Maier, S.F. (1999). Dynamic regulation of the proinflammatory cytokine, interleukin-1beta: Molecular biology for non-molecular biologists. *Life Sci.* **65,** 449–481.

Wells, K.B., Stewart, A., Hays, R.D., Burnam, M.A., Rogers, W., Daniels, M., Berry, S., Greenfield, S., & Ware, J. (1989). The functioning and well-being of depressed patients. *JAMA* **262,** 914–919.

Wulsin, L.R., Vaillant, G.E., & Wells, V.E. (1999). A systematic review of the mortality of depression [see comments]. *Psychosom. Med.* **61,** 6–17.

Zorrilla, E.P., Luborsky, L., McKay, J.R., Rosenthal, R., Houldin, A., Tax, A., McCorkle, R., Seligman, D.A., & Schmidt, K. (2001). The relationship of depression and stressors to immunological assays: A meta-analytic review. *Brain Behav. Immun.* **15,** 199–226.