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EMOTIONS, MORBIDITY, AND MORTALITY: New Perspectives from Psychoneuroimmunology

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■ **Abstract** Negative emotions can intensify a variety of health threats. We provide a broad framework relating negative emotions to a range of diseases whose onset and course may be influenced by the immune system; inflammation has been linked to a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, certain cancers, Alzheimer's disease, frailty and functional decline, and periodontal disease. Production of proinflammatory cytokines that influence these and other conditions can be directly stimulated by negative emotions and stressful experiences. Additionally, negative emotions also contribute to prolonged infection and delayed wound healing, processes that fuel sustained proinflammatory cytokine production. Accordingly, we argue that distress-related immune dysregulation may be one core mechanism behind a large and diverse set of health risks associated with negative emotions. Resources such as close personal relationships that diminish negative emotions enhance health in part through their positive impact on immune and endocrine regulation.

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INTRODUCTION

The idea that emotions are linked with morbidity and mortality has existed for over two millennia (Sternberg 1997). Hippocrates (c. 500 B.C.) theorized that health was related to the balance of four bodily humors, which contributed to specific temperaments. Galen (A.D. 131–201) took this idea further, proposing that a balance of the "passions" was essential for physical health. Indeed, severe emotional reactions were considered causes of diseases such as stroke, birth defects, asthma, ulcers, and, ultimately, even death (Sternberg 1997). These beliefs persisted through the medieval period and the early Renaissance; in *The Anatomy of Melancholy*, Robert Burton (1621/1893) wrote, "the mind most effectually works upon the body, producing by his passions and perturbations miraculous alterations . . . cruel diseases and sometimes death itself." Although this idea dominated medical practice for much of early civilization, in the modern era the science of the biological bases of health and disease has far surpassed the science of emotions. In this review we consider new evidence that suggests how negative emotions may contribute to disease and death through immune dysregulation.

We first address the evidence that negative emotions are related to morbidity and mortality. We highlight the consequences of depression, anxiety, and hostility, three broad emotions that have been linked to verifiable health outcomes; although there are many potential common paths among the negative emotions, there is also evidence that different emotions may make unique contributions to some disease processes (Leventhal et al. 1998). Next we consider key pathways, focusing on a central immunological mechanism that serves as a gateway for a range of age-associated diseases, the dysregulation of proinflammatory cytokine production. In the final section we consider vulnerability and resilience factors, including sociodemographic variables, personality traits and coping, social relationships, and positive emotions.

Although it is clear that negative emotions can intensify a wide variety of health threats, positive emotions have received considerably less attention, perhaps related to the prevailing view of physical and mental health as the absence of disease and negative emotions (Ryff & Singer 1998), as well as the fact that positive emotions are fewer in number and less differentiated than negative emotions (Ellsworth & Smith 1988). Indeed, although a substantial empirical literature exists for "depression" and objective measures of health, almost none exists for "happiness" and health, and thus we concentrate on the former.

This review concentrates on the pathways from negative emotions to illness and death; the effects of disease on emotional distress will not be addressed in any

detail, although the relationships are clearly bidirectional. Indeed, cytokines have substantial effects on the central nervous system, including production and enhancement of negative moods, physical symptoms including lethargy and fatigue, and a range of sickness behaviors from shivering to loss of appetite (Leventhal et al. 1998, Watkins & Maier 2000); accordingly, negative emotions may also reflect a prodromal or active disease process (Leventhal et al. 1998). In fact, although we focus on the impact of emotions on immune and endocrine responses and disease, there is plausible evidence that the immune system has a role in the neuroendocrine and behavioral features of both depressive and anxiety disorders (Miller 1998).

NEGATIVE EMOTIONS, MORBIDITY, AND MORTALITY: THE EVIDENCE

Depression

Depression is the most common psychiatric illness, and both major depression and subthreshold depressive symptoms carry substantial health risks. A number of well-controlled prospective studies have linked depressive symptoms with coronary heart disease (CHD), the leading cause of death in the United States. For example, a 13-year prospective study suggested that individuals with major depression had a 4.5 times greater risk of a heart attack compared with those with no history of depression (Pratt et al. 1996). Depressive symptoms also place patients at jeopardy; across a series of studies, healthy individuals who had elevated depression scores at baseline had a 1.5- to 2-fold increased risk for a first heart attack (Glassman & Shapiro 1998). Not surprisingly, patients who had preexisting cardiovascular disease also had poorer outcomes if they were depressed (Glassman & Shapiro 1998); mortality among patients who had suffered a heart attack was four times higher among the depressed than the nondepressed (Frasure-Smith et al. 1993).

One recent well-controlled study found that chronic depressed mood was linked to cancer risk; after adjusting for sociodemograhic variables and risk factors, the hazard ratio across a range of cancers was 1.88 (Penninx et al. 1998b). In contrast to these findings, other researchers have not found evidence for a link between depression and malignant disease (Croyle 1998, Whooley & Browner 1998). However, most prior literature has relied on a single assessment of depressive symptoms; when Penninx et al. (1998b) used a similar strategy with their own data, they did not find the relationship between dysphoria and cancer that emerged when depressive symptoms exceeded cut points at baseline as well as 3 and 6 years before baseline. Thus, some of the inconsistencies among cancer studies may reflect methodological differences. Additionally, it should also be noted that many related cancer studies have assessed a wide range of malignancies with very different etiologies, genetic contributions, behavioral influences (e.g., smoking), etc.; the heterogeneity makes it difficult to assess evidence in this arena. Our mechanistic discussion in the next section suggests that some cancers may show stronger relationships with negative emotions than others (Ershler & Keller 2000).

Depression influences outcomes in a variety of other illnesses. Depressed mood was an independent risk factor for all-cause mortality in medical inpatients (Herrmann et al. 1998). Among 1286 persons who were 71 or older, baseline depressive symptoms predicted greater physical decline over the subsequent 4 years (Penninx et al. 1998a). Depression heightens the risk for osteoporosis; either past or current depression in women was associated with lower bone mineral density (Michelson et al. 1996). Among older men, depressed mood at baseline was associated with an increased risk for declines in muscle strength over a 3-year period; important as an indication of current physical functioning, grip strength is also a powerful predictor of future functional limitations and disability (Rantanen et al. 2000). Depression has also been associated with reduced rehabilitation effectiveness in a spectrum of diseases (e.g., stroke, fractures, and pulmonary disease) (Katz 1996). Similarly, depressed diabetics are less likely to follow recommendations for dietary management and glycemic control (Katon 1998).

Pain, a pervasive medical problem, accounts for substantial levels of disability and contributes greatly to the overall burden of illness (Turk & Melzack 1992). Inextricably linked to depression and other negative moods, pain can increase disease severity and mortality (Staats 1999, Wells et al. 1989). Pain can provoke increases in heart rate and blood pressure, enhance secretion of stress-related hormones including catecholamines and cortisol, and dysregulate a range of immunological activities (Kiecolt-Glaser et al. 1998, Liebeskind 1991). Additionally, pain may disrupt many aspects of physical, mental, and social functioning (Leventhal et al. 1998). Accordingly, depression can amplify morbidity by magnifying pain and disability across a range of acute and chronic health problems.

How large are the effects? For mortality, the increased risk among elderly women in one large study was ". . . similar to that conferred by other cardiovascular risk factors, such as hypertension, cigarette smoking, hyperlipidemia, obesity, and diabetes" (Whooley & Browner 1998, p. 2132). In another study, depression at baseline increased the risk that participants would develop a disability over the next 6 years by 73% (Penninx et al. 1999). Data from 11,242 outpatients in the Medical Outcomes Study showed that patients with either a current depressive disorder or depressive symptoms in the absence of a syndromal disorder had worse physical, social, and role function, worse perceived current health, and greater bodily pain than patients with no chronic conditions (Wells et al. 1989). The poorer functioning that was uniquely associated with depressive symptoms was comparable to—or even worse than—that uniquely associated with eight chronic medical conditions. Thus, the increased morbidity and mortality associated with depression is substantial.

Anxiety

Although depression has been the best-studied negative emotion, anxiety also has adverse effects, particularly in the cardiovascular realm, where it plays a role in the development of CHD and contributes to poorer prognosis after acute coronary events, including death and recurrent ischemic events. Phobic, panic-like anxiety

predicted 3 times the risk of fatal CHD at a 7-year follow-up compared with no anxiety (Haines et al. 1987). In data from the Normative Aging Study higher levels of anxiety were associated with almost double the risk of fatal CHD (Kawachi et al. 1994b). Similarly, men in the Health Professionals Follow-up Study who reported the highest levels of anxiety had more than double the risk for fatal CHD and nonfatal myocardial infarction (Kawachi et al. 1994a). Anxiety symptoms were associated with significantly increased risk of myocardial infarction and coronary-related death over a 20-year period in women who were homemakers (Eaker et al. 1992). Anxiety also has negative consequences for recovery from surgery (Kiecolt-Glaser et al. 1998).

Hostility/Anger

Chronic anger and hostility also negatively impact health. One excellent 9-year population-based study found that men high in hostility had more than twice the risk of all-cause and cardiovascular mortality compared with men low in hostility (Everson et al. 1997). Similarly, a large prospective study of employees found that hostility predicted the total number of long-term medically certified absences over a 4-year period among men but not women (Vahtera et al. 1997). Indeed, a rigorous meta-analysis concluded that hostility was a robust risk factor for CHD, as well as for all-cause mortality (Miller et al. 1996).

Although the weight of the evidence clearly implicates negative emotions, particularly depression, in all-cause mortality, the findings have been inconsistent, the discrepancies undoubtedly fueled by notable methodological shortcomings in a number of studies, including small samples, low mortality, brief follow-up periods, incomplete follow-up, and absence of control for relevant health behaviors or premorbid status (Schulz et al. 2000). Successive assessments that provide information on health problems, medications, smoking, and alcohol use are crucial; indeed, the absence of positive findings in some studies may well be related to failure to assess and control for smoking and alcohol use (Wulsin et al. 1999), key health behaviors that impact a spectrum of diseases (Kiecolt-Glaser & Glaser 1988). The effects are clearly bidirectional, and illness can enhance the risk for the development of depression and anxiety symptoms and disorders (Katz 1996). Despite these methodological shortcomings, it is clear that the burdens and stresses that stimulate psychological morbidity also have clear and notable consequences for physical health.

PATHWAYS

Morbidity, Mortality, and Aging: Central Immunological Mechanisms

Emotions can affect health through many pathways; these influences may occur indirectly, through health behaviors or compliance with medical regimens, and directly, through alterations in the functioning of the central nervous system, immune,

endocrine, and cardiovascular systems. The primary focus of our mechanistic discussion will be the immune and endocrine pathways to age-related changes in health; our choice is based on recent evidence that implicates dysregulation of proinflammatory cytokines, particularly interleukin 6 (IL-6), as a central component across a range of diseases in older adults. We first provide a brief introduction to cytokines, followed by a review of evidence relating cytokine dysregulation to a spectrum of health problems.

Cytokines are protein substances released by cells that serve as intercellular signals to regulate the immune response to injury and infection. The relevance of cytokines to the biobehavioral sciences is illustrated by the appearance of reviews of cytokine biology in psychiatric and psychological literature (Kronfol & Remick 2000, Maier & Watkins 1998). The signaling properties of cytokines are similar to classic hormones of the endocrine system, and cytokines can be differentiated into two basic classes based on their effects on the immune response, proinflammatory and antiinflammatory. The proinflammatory cytokines include IL-1, IL-6, and tumor necrosis factor (TNF); they promote inflammation, a beneficial reaction in early immune responses to infection and injury (Glaser et al. 1999a). The primary actions of these cytokines are attracting immune cells to the site of infection or injury and causing them to become activated to respond. Secondary actions include changes in physiology that promote inflammation, such as alterations in metabolism and temperature regulation. Antiinflammatory cytokines such as IL-10 and IL-13 dampen the immune response, causing, for instance, decreased cell function and synthesis of other cytokines.

The immune system's inflammatory response can be triggered in a variety of ways, including infection and trauma. The mechanisms associated with inflammation are critical to resolving infections and repairing tissue damage; however, chronic or recurring infections can provoke pathological changes (Hamerman 1999). 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 (Cohen 2000).

Indeed, inflammation has recently been linked to a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, certain lymphoproliferative diseases or cancers (including multiple myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia), Alzheimer's disease, and periodontal disease (Ershler & Keller 2000). 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 C-reactive protein (CRP), recently recognized as an important risk factor for myocardial infarction (Papanicolaou et al. 1998). For example, high concentrations of CRP predicted the risk of future cardiovascular disease in apparently healthy men (Ridker et al. 1997). Further studies provided mechanistic links: chronic infections amplified the risk for development of atherosclerosis fourfold in subjects who were free of carotid

atherosclerosis at baseline, conferring increased risk even in subjects lacking conventional vascular risk factors (Kiechl et al. 2001). Indeed, the increased risk for artery-clogging plaque was greater than that conferred by elevated blood pressure or cholesterol (Kiechl et al. 2001). 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 (Harris et al. 1999).

More globally, chronic inflammation has been suggested as one key biological mechanism that may fuel declines in physical function leading to frailty, disability, and, ultimately, death (Hamerman 1999, Taaffe et al. 2000). 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 to the pathophysiologic role played by the cytokine in particular diseases (Ferrucci et al. 1999). Proinflammatory cytokines including IL-6 may slow muscle repair following injury and accelerate muscle wasting (Cannon 1995); indeed, IL-6 and CRP also play a pathogenic role in a range of diseases associated with disability among the elderly (e.g., osteoporosis, arthritis, and congestive heart failure) (Ferrucci et al. 1999). In this context it is interesting that IL-6 is also associated with self-rated health (Cohen et al. 1997a), a robust predictor of mortality (Leventhal et al. 1998). Thus, the clinical importance of immunological dysregulation for older adults is highlighted by increased risks across diverse conditions and diseases.

Emotions and Immune System Alterations

There is excellent evidence that depression and anxiety enhance the production of proinflammatory cytokines, including IL-6 (Dentino et al. 1999; Lutgendorf et al. 1999; Maes et al. 1995, 1999, 1998). Higher plasma IL-6 levels were associated with greater distress in a sample of community women (Lutgendorf et al. 1999). 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 controls (Lutgendorf et al. 1999); the finding was particularly noteworthy because caregivers were 6–9 years younger, on average, than women in the other two groups. Chronic fatigue patients showed increases in IL-6 following a severe life stressor (Hurricane Andrew) (Costello et al. 1998). Following successful pharmacologic treatment, elevated IL-6 levels declined in patients with a major depression diagnosis (Sluzewska et al. 1995).

Both physical and psychological stressors can provoke transient increases in proinflammatory cytokines (DeRijk et al. 1997, Zhou et al. 1993); in animal models both stress and administration of epinephrine elevated plasma IL-6, consistent with evidence that IL-6 production is stimulated through β-adrenergic receptors, among other pathways (Papanicolaou et al. 1998). Thus, production of IL-6 and other proinflammatory cytokines can be directly stimulated by negative emotions and stressful experiences, providing one direct pathway.

Negative emotions also contribute indirectly to the immune dysregulation evidenced by proinflammatory cytokine overproduction. Repeated, chronic, or slow-resolving infections or wounds enhance secretion of proinflammatory cytokines, a process that can serve to further inhibit certain aspects of immune responses (e.g., IL-2, an important defense against infection), and thus may contribute to the immunodepression of aging (Catania et al. 1997). Stress impedes the immune response to infectious challenges, amplifying risks for contagion and prolonged illness episodes (Glaser et al. 1999b, Kiecolt-Glaser et al. 1996a, Sheridan et al. 1991); distress also provokes substantial delays in wound healing (Glaser et al. 1999a, Kiecolt-Glaser et al. 1995, Marucha et al. 1998) and enhances the risk for wound infection after injury (Rojas et al. 2001). 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.

Although our focus thus far has been on the health consequences associated with secretion of proinflammatory cytokines, negative emotions can also have direct adverse effects on a variety of other immunological mechanisms; both animal and human studies have provided convincing evidence that these immune alterations are consequential for health. For example, to help demonstrate causal relationships between psychosocial stressors and the development of infectious illness, investigators have inoculated subjects with a variety of vaccines (Glaser et al. 1992, 2000, Kiecolt-Glaser et al. 1996a, Morag et al. 1999, Vedhara et al. 1999). Vaccine responses demonstrate clinically relevant alterations in immunological responses to challenge under well-controlled conditions; accordingly, they serve as a proxy for response to an infectious agent. More distressed and anxious individuals produced immune responses to vaccines that were delayed, substantially weaker, and/or shorter lived; as a consequence, it is reasonable to assume these same individuals would also be slower to develop immune responses to other pathogens; thus, they could be at greater risk for more severe illness. Consistent with this argument, adults who show poorer responses to vaccines also experience higher rates of clinical illness, as well as longer-lasting infectious episodes (Burns & Goodwin 1990, Patriarca 1994). In addition, other researchers have shown that distress can alter susceptibility to cold viruses (Cohen et al. 1998).

Increased susceptibility to pathogens is a serious health problem for older adults. For example, although influenza is rarely fatal among healthy younger adults, together influenza and pneumonia, a common complication of influenza virus infection, constitute the fourth leading cause of death among individuals who are 75 or older (Yoshikawa 1983); distressed older adults demonstrate poorer responses to both influenza and pneumococcal vaccines (Glaser et al. 2000, Kiecolt-Glaser et al. 1996a, Vedhara et al. 1999). Thus, data from human studies now provide solid

evidence that negative emotions can increase susceptibility to infectious disease via alterations in the immune response.

Emotions and Neuroendocrine Alterations

The endocrine system serves as one prominent gateway across a spectrum of diseases because emotions provoke the release of pituitary and adrenal hormones that have multiple effects, including alterations in cardiovascular and immune function (Glaser & Kiecolt-Glaser 1994, Rozanski et al. 1999). Both anxious and depressed moods can activate the sympathetic-pituitary-adrenal medullary axis, as well as the hypothalamic-pituitary-adrenocortical (HPA) axis (Miller 1998). Numerous studies have suggested that a variety of emotion-responsive hormones including the catecholamines (norepinephrine and epinephrine), adrenocorticotropin hormone, cortisol, growth hormone, and prolactin can impel quantitative and qualitative changes in immune function, and there is bi-directional feedback between the endocrine and immune systems (Rabin 1999). For example, depression can substantially boost cortisol, and elevations in cortisol can provoke multiple adverse immunological changes including defects in vaccine responses (Vedhara et al. 1999) and wound healing (Padgett et al. 1998). In contrast to the generally negative effects of cortisol, growth hormone can enhance many aspects of immune function (Malarkey et al. 1996); growth hormone is lower in depressed patients (Dinan 1998), and growth hormone gene expression is altered in mononuclear cells of chronically distressed caregivers (Malarkey et al. 1996). Additionally, both anxious and depressive disorders and symptoms can elevate catecholamines; although brief increases in response to acute stressors may be advantageous under many circumstances, longer-term increases are generally associated with immunological down-regulation (Malarkey et al. 1996).

The hypercortisolemia associated with clinical depression is well documented (DeRijk et al. 1997); however, the endocrine system's involvement in the pathogenesis of many stress-related disease processes is also likely mediated in part through frequent small daily excursions in hormonal levels following stressful events, and/or through disturbance of diurnal rhythms (Dhabhar & McEwen 1997). The ability to "unwind" after stressful encounters, i.e., quicker return to one's neuroendocrine baseline, influences the total burden that stressors place on an individual (Frankenhaeuser 1986). Stressors that are resistant to behavioral coping, particularly stressors perceived as unpredictable and uncontrollable, may continue to be associated with elevated stress hormones even after repeated exposure (Baum et al. 1993).

Our prior discussion focused on age-related immune dysregulation; thus, it is important to note that cytokines such as IL-6 also influence the functioning of the endocrine system, one of the many bi-directional relationships between the two systems. IL-6 is a potent stimulator of corticotropin-releasing hormone production, a mechanism that leads to heightened HPA activity, including elevated levels of plasma adrenocorticotropin hormone, followed by increased cortisol levels

(Dentino et al. 1999). Thus, negative emotions that dysregulate IL-6 secretion may also promote neuroendocrine alterations that have immune consequences.

The complexity of these potential interactions is further underscored by one line of research that suggests that once cortisol levels rise, they can initiate, perpetuate, or aggravate syndromal depression, depression-like behaviors, and depressive symptoms such as anxiety, insomnia, and poor memory (Wolkowitz & Reus 1999). Such data are consistent with the conceptualization of major depression as a dysfunction in the stress response (Sternberg et al. 1992), as well as evidence that both emotional distress and disease may be prompted by common genetic and constitutional variables (Leventhal et al. 1998). For example, first-degree relatives of depressed patients who have never been clinically depressed have HPA axis responses similar to their affected relatives and different from controls (Holsboer et al. 1995). Similarly, a 10-year follow-up of adolescents who had served as part of a normal control group showed that the baseline pattern of sleep-related growth hormone secretion was predictive of subsequent depressive episodes (Coplan et al. 2000). Accordingly, the health hazards associated with negative emotions are likely to reflect multiple interacting risk factors, including important genetic influences.

Although there are common genetic influences for depression and neuroendocrine dysregulation, sufficiently stressful circumstances can also produce clinically significant immune and endocrine dysregulation in individuals who are not at risk. For example, the chronic strains of dementia spousal caregiving were related to the onset of syndromal depressive disorders in older adults who had no prior evidence of vulnerability through either personal or family history (Dura et al. 1990). Moreover, although only a minority of caregivers develop syndromal disorders, men and women who provide long-term care for a spouse or parent with Alzheimer's disease typically report high levels of distress as they attempt to cope with the family member's problematic behaviors; this stressor has been associated with prolonged endocrine and immune dysregulation, as well as health changes, including alterations in vaccine response and wound healing (Castle et al. 1995; Esterling et al. 1994, 1996; Glaser et al. 1998; Irwin et al. 1991; Kiecolt-Glaser et al. 1996a; Malarkey et al. 1996; Mills et al. 1999; Vedhara et al. 1999; Wu et al. 1999).

Health Behaviors

In addition to the direct influences of psychological states on physiological function, distressed individuals are more likely to have health habits that put them at greater risk, including poorer sleep, a greater propensity for alcohol and drug abuse, poorer nutrition, and less exercise, and these health behaviors have cardiovascular, immunological, and endocrinological consequences (Kiecolt-Glaser & Glaser 1988). Psychosocial stressors that increase adverse health behaviors also provoke maladaptive physiological changes. For example, deep sleep provides the normal stimulus for much of the release of growth hormone, which enhances multiple aspects of immune function; thus, stressors that modify the architecture of

sleep also lessen secretion of growth hormone (Veldhuis & Iranmanesch 1996). Moreover, even partial sleep loss one night results in elevated cortisol levels the next evening (Leproult et al. 1997). Adverse health behaviors can interact with one another; for example, heavy alcohol use is linked to poorer sleep and nutrition. Smoking makes substantial contributions to morbidity and mortality; depressed patients are more likely to smoke and less likely to quit than nondepressed individuals (Wulsin et al. 1999). Depressed patients may be less likely to seek medical care and take prescribed medications than those who are not depressed (Penninx et al. 1999, Whooley & Browner 1998).

Higher plasma IL-6 and CRP levels are associated with adverse health habits: Values for both are higher in smokers than nonsmokers, in individuals who report less physical activity, and in those with a higher body mass index (Ferrucci et al. 1999, Taaffe et al. 2000). However, health habits including smoking, physical activity, and alcohol use have typically explained only a small part of the excess mortality associated with depression among older adults, e.g., Penninx et al. (1999). Similarly, IL-6 has robust relationships with morbidity and mortality, even after controlling for health behaviors (Ferrucci et al. 1999, Taaffe et al. 2000); more broadly, behavioral studies have demonstrated reliable psychological influences on immune function in populations selected in part on the basis of health habits (Kiecolt-Glaser et al. 1993). Thus, health behaviors, although obviously important, are not sufficient to explain the relationship between emotions and disease.

We have focused on the immune and endocrine systems, but there are obviously many other physiological pathways through which emotions can influence health, including cardiovascular and neurobiological circuitry (Davidson et al. 2001, Krantz & McCeney 2001, Leventhal et al. 1998). However, many lines of evidence now indicate that IL-6 may function as a "... global marker of impending deterioration in health status in older adults" (Ferrucci et al. 1999, p. 645). We have argued that negative emotions directly prompt immune dysregulation, and these processes may lead to subsequent maladaptive immune and endocrine changes. Thus, research that addresses the dysregulation of the immune and endocrine systems associated with negative emotions could substantially enhance our understanding of psychological influences on health, particularly among the elderly.

Allostatic Load: Conceptual Similarities and Differences

The immune dysregulation we are discussing is consistent with the broad allostatic load formulation, the "... long-term effect of the physiologic response to stress" (McEwen 1998, p. 171); however, the breadth of disease outcomes addressed and the operationalization of the concepts and pathways are somewhat different. Investigators have used a broad battery of measures to gauge allostatic load, including blood pressure, overnight urinary cortisol and catecholamine excretion, waist to hip ratio, glycosylated hemoglobin, the ratio of serum high-density lipoprotein in the total serum cholesterol concentration, and dehydroepiandrosterone (DHEA)

sulfate; individuals with higher scores on this broad battery were more likely to have incident cardiovascular disease as well as declines in cognitive and physical function when assessed at a 3-year follow-up (Seeman et al. 1997).

In concert with the underlying tenets of the allostatic load formulation (McEwen 1998), emotional influences on the HPA and sympathetic-pituitary-adrenal medullary axes—and potential long-term changes in each—are a central focus of our mechanistic discussion. Within both frameworks chronic stress is highlighted, with its capacity for inducing long-term decline via overexposure to stress hormones. However, our mechanistic path focuses more narrowly on the implications of adverse neuroendocrine changes for immune modulation, as well as the bidirectional feedback from the immune system to the endocrine system—the stimulation of corticotropin-releasing hormone by IL-6—on the spectrum of inflammation-related health outcomes discussed earlier. Clearly, the battery of health indices described above (Seeman et al. 1997) have important prognostic value; however, even after the point at which risk factors such as cholesterol, hypertension, and obesity predict health deterioration less successfully among the very old, chronic inflammation continues to be an important marker (Ferrucci et al. 1999). Finally, we place a greater emphasis on the toll that daily stress plays via immune dysregulation—the extent to which negative emotions contribute to prolonged infection and delayed wound healing, processes that fuel sustained proinflammatory cytokine production. Thus, in the final section we address the enormous variability in stress responsiveness by reviewing literature related to resilience and vulnerability factors identified in psychoneuroimmunology research to date.

VULNERABILITY AND RESILIENCE FACTORS

Sociodemographic Variables

AGE Biologically, the largest deleterious or enhancing consequences of negative and positive emotions are likely to occur when biological vulnerability is greatest: early and late in life. Although our primary focus has been on aging, intense emotional experiences have the capacity to permanently alter neuroendocrine and autonomic responses, and these may be most consequential when they occur early in life. For example, women with a history of childhood abuse are at substantially greater risk for depressive and anxiety disorders; they also show larger pituitary-adrenal and autonomic responses to laboratory stressors than controls (Heim et al. 2000, Lemieux & Coe 1995) and possibly experience long-term immunological alterations (De Bellis et al. 1996). Data on maternal separation in nonhuman primates provides strong supportive evidence from a well-characterized animal model (Coe 1993).

Changes in immune function associated with aging have already been addressed. In addition, however, older adults appear to show greater immunological impairments associated with distress or depression than younger adults (Herbert &

Cohen 1993, Kiecolt-Glaser et al. 1996a, Schleifer et al. 1989). Further, older adults may be more vulnerable to negative emotions due to smaller social support networks (Carstensen 1992). In contrast, however, the intensity of emotional reactions may also decline with aging, providing some protection (Leventhal et al. 1998).

Finally, the impact of age may vary through its association with other individual differences, related to changes in social, psychological, and biological resources (Leventhal et al. 1998). For example, age of onset of depression interacted with gender such that onset after age 70 in women most strongly predicted increased morbidity and mortality among adults seeking treatment for depression (Philibert et al. 1997). Thus, aging can interact with distress and depression to enhance risks for morbidity and mortality among older adults.

GENDER There are established gender differences in well-being, including differences in major psychopathology (e.g., depression is more common in women) and negative and positive moods, that may derive from biological, personality, and sociocultural influences (Nolen-Hoeksema & Rusting 1999). Surprisingly, there has been inconsistent attention paid to possible gender differences in emotion and health relationships, making it difficult to draw conclusions at this time. Some studies have used only males or females, and others have not systematically examined gender effects. For example, a meta-analysis of hostility and health concluded that too few studies have reported results by sex to draw conclusions at this time (Miller et al. 1996).

Estrogen and androgens can repress IL-6 expression, and thus age-related increases in IL-6 gene expression and serum levels are thought to be related in part to the aging of the endocrine system (Ershler & Keller 2000). These linkages suggest that longitudinal comparisons of postmenopausal women who are taking hormone replacement therapy with those who are not would be one potentially profitable avenue for exploration.

More broadly, gender effects have been demonstrated both in emotional experiences (e.g., cognitive, physiological responses), and in health outcomes (Frankenhaeuser 1991, Stoney et al. 1987, Verbrugge 1982). Differential rates of depression, anxiety, and hostility in men and women may lead to different overall associations between gender and health outcomes. Furthermore, men and women may experience similar emotions differently, perhaps in part due to different constellations of additional vulnerability and resilience factors (e.g., age, social support), resulting in different associations with health outcomes (Kiecolt-Glaser & Newton 2001, Taylor et al. 2000b). For example, an interaction between depression severity, age, and gender was recently found such that among the elderly, severe depression was associated with increased mortality in men and women, whereas mild depression predicted increased mortality solely in men (Schoevers et al. 2000). In another example, among community dwelling adults, chronic strain, low sense of mastery, and rumination were more common in women than in men and mediated the greater prevalence of depression in women (Nolen-Hoeksema et al. 1999). It is possible that differences in the qualitative experience of emotions may be

associated with different health behavior and physiological reactivity patterns, leading to different health outcomes. An important focus for future research is the manner in which gender may act as a vulnerability or resilience factor in its interaction with emotion and health outcomes, and the contribution of additional contextual variables such as age and social support in these relationships.

SOCIOECONOMIC STATUS Socioeconomic status (SES), typically measured by education, income, and occupation, has inverse relationships with major depression, depressive symptoms, and hostility (Adler et al. 1994). SES also shows strong inverse relationships with most major causes of morbidity and mortality across populations (Taylor et al. 1997). The relationships are so strong that although lower SES groups have higher rates of morbidity and mortality, differences in social position relate to risk even at the upper levels of the hierarchy (Adler et al. 1994). The longer-term stressors associated with immune alterations include "burnout" at work (Lerman et al. 1999), job strain (Kawakami et al. 1997), and unemployment (Arnetz et al. 1991). Taylor and colleagues (1997) suggest that social class and race provide a context for understanding the impact of unhealthy environments, with one initial route to increased risk via obvious differential exposures to chronic stress.

RACE Racial and ethnic disparities in morbidity and mortality exist in a number of health-related conditions, including cancer, cardiovascular disease, diabetes, HIV/AIDS, and preventable infectious illness (Williams 1997), all of which involve the immune system. These differences are due in part to dispositional risk factors, health behavioral risk factors (Myers et al. 1995), and SES, which are not exclusive to particular ethnic groups. For example, a higher prevalence of AIDS indicator conditions (e.g., tuberculosis, pneumonia) has been found in HIV-positive racial and ethnic minorities compared with HIV-positive whites, and is probably influenced by differential exposure to etiologic agents, diagnosis and reporting, and access to treatment (Hu et al. 1995). Racial and ethnic differences in health-related outcomes may be associated with mental health disparities, such as rates of depression, that may be driven by SES and ethnic differences in seeking treatment (US Dep. of Health and Human Services 1999). At the same time, there appear to be direct relationships between ethnicity and health, such as poorer health outcomes among African Americans across the socioeconomic strata (Williams & Collins 1995).

The immunological and genetics literatures generally suggest a genetic contribution to disease risk stratified by race/ethnicity, particularly for autoimmune disorders (Hess & Farhey 1994, Kalman & Lublin 1999), and these differences may be due to genetic factors such as cytokine polymorphisms. Despite these genetic stratifications, the concept of "race" is not a true biological characteristic, and the construct of "ethnicity" is atheoretical; both can lead to simplistic interpretations of intergroup differences (Meyerowitz et al. 1998, Williams 1997). Moreover, given that genetic factors generally determine susceptibility, but not development of disease, racial and ethnic influences on emotions, immunity, and health may be

best understood along multiple dimensions, including culture, ethnic identity, and minority status (Phinney 1996).

Personality Traits and Coping

Personality and coping styles reflect individual differences in appraisal and response to stressful situations, and both have been associated with the onset and course of chronic and progressive health problems (Scheier & Bridges 1995). In fact, in longitudinal studies, personality and coping characteristics have predicted physical illness and mortality in initially healthy adults (Maruta et al. 2000, Peterson et al. 1988), as well as in HIV-seropositive gay men (Cole et al. 1997, 1996; Reed et al. 1999) and adults undergoing bone marrow transplant (Molassiotis et al. 1997). There is evidence that personality, coping, and emotions may interact to increase or decrease individuals' risk of negative health outcomes. For example, the co-existence of the type "D" distressed personality style, including depressive and anxiety symptoms, and social inhibition, predicted cardiac morbidity and mortality over a 10-year period (Denollet & Brutsaert 1998, Denollet et al. 1996), whereas greater optimism, indicative of a positive emotion personality style, predicted better health outcomes among cardiac patients (Scheier et al. 1999).

A potent resilience factor for health outcomes may be the induction and maintenance of positive emotion through personality and coping styles. The broaden-and-build model of positive emotions (Fredrickson 1998) posits a broadening of the individual's scope of attention, cognition, and action, and building of physical, intellectual, and social resources. Positive emotion may include, but is not limited to, positive reappraisal of stressful life events (Folkman & Moskowitz 2000), finding meaning (Taylor 1983), developing positive illusions (Taylor et al. 2000a), and situational or dispositional optimism (Scheier & Carver 1992, Taylor 1989). Furthermore, positive emotions might "undo" the aftereffects of negative emotions, particularly in physiological recovery (Fredrickson 1998). Positive emotion has been associated with better health outcomes, for example among male heart attack survivors (Affleck et al. 1987) and HIV-seropositive men experiencing bereavement (Bower et al. 1998). The pathways through which positive emotions impact health outcomes are not well known at this point, but likely occur through endocrine and immune mechanisms, as well as indirectly through health behaviors (Aspinwall & Brunhart 1996, Shepperd et al. 1996).

Personality and coping styles may predispose individuals toward greater relative negative or positive emotions, thereby maintaining physiological alterations associated with emotions. For example, personality and coping styles, such as repression, rejection sensitivity, attributional style, and sociability, have been associated with altered immune cell counts in peripheral blood and dysregulated cellular immune function (Segerstrom 2000). Notably, given our earlier discussion, one positive coping strategy, attendance at religious services, has been associated with lower levels of IL-6 in a large community sample of older adults (Koenig et al. 1997). Thus, the relationships among personality and coping styles and health outcomes

may be mediated by their influences on negative and positive emotions and immune function, and these relationships are likely to be strongest in the context of relevant stressful events.

Social Relationships

Data from large, well-controlled epidemiological studies suggest that social isolation constitutes a major risk factor for morbidity and mortality, with statistical effect sizes comparable to those of such well-established health risk factors as smoking, blood pressure, blood lipids, obesity, and physical activity (House et al. 1988). Immunological alterations provide one possible physiological pathway: the link between personal relationships and immune function is one of the most robust findings in psychoneuroimmunology (Uchino et al. 1996). For example, better responses on two immunological assays were associated with higher social support in women whose husbands were being treated for urologic cancer (Baron et al. 1990). Medical students who reported better social support mounted a stronger immune response to a hepatitis B vaccine than those with less support (Glaser et al. 1992). Individuals with fewer social ties were more susceptible to respiratory viruses (Cohen et al. 1997b). Spousal caregivers of dementia sufferers who reported lower levels of social support on entry into a longitudinal study and who were most distressed by dementia-related behaviors showed the greatest and most uniformly negative changes in immune function one year later (Kiecolt-Glaser et al. 1991). Several researchers reported immunological differences between subjects who disclosed traumatic or upsetting events, compared with those in a nondisclosure condition (Christensen et al. 1996, Esterling et al. 1990, Pennebaker et al. 1988, Petrie et al. 1995). Loss of a spouse or partner through bereavement or divorce is associated with poorer immune function for a period of time (Irwin et al. 1987; Kemeny et al. 1995; Kiecolt-Glaser et al. 1987, 1988; Schleifer et al. 1983).

Marriage is obviously an important relationship, and marital quality has been associated with immune and endocrine function (Kiecolt-Glaser & Newton 2001). For example, women with rheumatoid arthritis were followed for 12 weeks (Zautra et al. 1998); although both immune function and clinician's ratings changed during a week of increased interpersonal stress, women who reported more positive spousal interaction patterns and less spousal criticism or negativity did not show as large an increase in clinical symptoms.

However, when close relationships are discordant, they can also be associated with depression and immune dysregulation. Both syndromal depression and depressive symptoms were strongly associated with marital discord (Beach et al. 1998, Fincham & Beach 1999). In addition, pervasive differences in endocrine and immune function were reliably associated with hostile behaviors during marital conflict among diverse samples that included newlyweds selected on the basis of stringent mental and physical health criteria, as well as couples married an average of 42 years (Kiecolt-Glaser et al. 1997, 1993, 1996b; Malarkey et al. 1994). Thus, although supportive personal relationships are associated with better

immune function (Kiecolt-Glaser & Newton 2001, Uchino et al. 1996), close personal relationships that are chronically abrasive or stressful may provoke depression and other negative emotions as well as persistent immune and endocrine dysregulation.

CONCLUSIONS

We suggest that researchers interested in psychological influences on health should expand their consideration of the range of diseases whose onset and course may be influenced by the immune system; 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, Alzheimer's disease, frailty and functional decline, and periodontal disease (Ershler & Keller 2000). Production of IL-6 and other proinflammatory cytokines that influence these and other conditions can be directly stimulated by negative emotions and stressful experiences, providing one direct pathway from emotions to health. In addition, negative emotions may also contribute to prolonged infection or delayed wound healing, processes that fuel sustained proinflammatory cytokine production. Accordingly, we argue that distress-related immune dysregulation may be one core mechanism behind the health risks associated with negative emotions. These direct and indirect processes pose the greatest health risks for older adults who already show age-related increases in proinflammatory cytokine production. Thus, aging interacts with negative emotions to enhance risks for morbidity and mortality among older adults. Finally, the psychoneuroimmunology literature provides evidence that resources such as close personal relationships or personality and coping styles that diminish negative emotions may enhance health in part through their positive impact on immune and endocrine regulation.

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