ACADEMIC PRESS

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Brain, Behavior, and Immunity 17 (2003) S98–S105

BRAIN, BEHAVIOR, and IMMUNITY

www.elsevier.com/locate/ybrbi

Loneliness and pathways to disease

Louise C. Hawkley* and John T. Cacioppo

Institute for Mind and Biology, The University of Chicago, 940 E. 57th Street, Chicago, IL 60637, USA

Received 9 April 2002; received in revised form 18 July 2002; accepted 18 July 2002

Abstract

Social isolation predicts morbidity and mortality from cancer, cardiovascular disease, and a host of other causes. The mechanisms by which the social world impacts on health are poorly understood, in part because of lack of specificity in the conceptualization and operationalization of relevant aspects of social relationships and physiological processes. Perceived social isolation, commonly termed loneliness, may represent a link between the epidemiological and biological levels of analysis. Research is presented that investigates loneliness as a social factor of importance in three predisease pathways: health behaviors, excessive stress reactivity, and inadequate or inefficient physiological repair and maintenance processes. Empirical evidence of autonomic, endocrine, and immune functioning suggests that the physiological effects of loneliness unfold over a relatively long time period. For cancer patients, interventions should be aimed at providing instrumental support for the immediate demands of the disease.
© 2002 Elsevier Science (USA). All rights reserved.

Keywords: Loneliness; Social isolation; Social support; Cancer; Cardiovascular disease; Health behaviors; Autonomic reactivity; Cortisol; Immunity; Sleep

1. Introduction

Social relationships are fundamental to emotional fulfillment, behavioral adjustment, and cognitive function. They can also be severely challenged by the diagnosis, treatment, and progression of cancer (Rokach, 2000; Spiegel, 2001). Recent research has shown that emotional closeness in relationships increases with age (Carstensen, Pasupathi, Mayr, & Nesselroade, 2000; Fung, Carstensen, & Lang, 2001). Yet the number of social relationships decreases and social events triggering loneliness continue in older adults. Physical aging and diminished resilience enhance the likelihood that these psychosocial challenges could leave older adults vulnerable to feelings of loneliness, dysphoria, elevated and prolonged neuroendocrine stress responses, and ill health. Accordingly, social isolation predicts morbidity and mortality from broad-based causes in later life, even after controlling for health behaviors and biological risk factors (House, Landis, & Umberson, 1988).

Several demographic changes make it important to identify the underlying mechanisms by which social isolation might contribute to poor health. Chronic diseases (e.g., cancer, cardiovascular disease, affective disorders, drug or alcohol abuse, chronic obstructive pulmonary disease, sleep disorders, diabetes, and dementia) are the most frequent sources of complaints and the largest causes of morbidity and mortality in older adults. Life expectancy has increased in the US, increasing dramatically the number of older adults, individuals who are at risk for costly chronic diseases. The costs of medical care have also continued to rise more rapidly than inflation or the GNP, and a disproportionate amount of medical costs goes to the treatment of aging-related disorders. By the early 1990s, when approximately 11% of the population was over 65 years of age, 36% of all hospital stays and 48% of total days of

* Corresponding author.
E-mail addresses: Hawkley@uchicago.edu (L.C. Hawkley), Cacioppo@uchicago.edu (J.T. Cacioppo).

0889-1591/02/$ - see front matter © 2002 Elsevier Science (USA). All rights reserved.
PII: S0889-1591(02)00073-9

doctor care were for individuals aged 65 or over (Luskin & Newell, 1997).

The mechanisms by which the social world impacts on health have been elusive, in part because social isolation is associated with broad-based morbidity and mortality rather than with the etiology of a specific disease, in part because the term social isolation includes multi-farious aspects of the social world (e.g., marital status, membership in voluntary associations), in part because the effects of social relationships on long-term morbidity and mortality appear to unfold over years, and in part because mapping directly from the aggregate social epidemiological level of analysis to the modulation of regulated physiological processes within individuals ignores the complex processes that operate at intervening levels of organization.[1]

The health risk associated with *perceived* social isolation has been less well studied than that of actual social isolation but may help bridge the abyss between the extant epidemiological and biological levels of analysis.[2] Indeed, in a meta-analytic review, Uchino, Cacioppo, and Kiecolt-Glaser (1996) found that, if anything, perceived social connectedness or support was more strongly associated than was objective social support with lower levels of autonomic activity (e.g., lower resting blood pressure), better immunosurveillance (e.g., greater natural killer cell lysis), and lower basal levels of stress hormones (e.g., urinary catecholamines). Extending this work to health outcomes, low perceived social support and high hostility significantly increased the odds of carotid artery lesions among high risk women even after controlling for age, education, body mass index, smoking, drinking, and metabolic rate (Knox et al., 2000). In a study of 514 women requiring a breast biopsy after mammogram screening, those who had experienced a recent highly threatening life stressor and lacked intimate emotional social support were at nine times the risk of developing breast cancer (Price et al., 2001).

To date, only one prospective study has examined the health outcomes associated specifically with loneliness. Herlitz et al. (1998) reported that among 1290 patients who underwent coronary artery bypass surgery, ratings of the statement, "I feel lonely," predicted survival at 30 days and 5 years after surgery even after controlling statistically for preoperative factors known to increase mortality (see, also, Seeman, 2000). Cancer patients are particularly prone to feelings of loneliness (see Rokach, 2000), and loneliness is a major factor in the mental health of cancer survivors (Boer, Elving, & Seydel, 1998). Whether loneliness plays a role in physical health outcomes within this population is unclear. Suggestive evidence supporting a possible link between loneliness and cancer was provided by Fox, Harper, Hyner, and Lyle (1994), who found that loneliness measured prior to a mammogram screening was higher among women who later were diagnosed as having breast cancer relative to women who were proclaimed disease-free. Our purpose here is to review research that investigates loneliness as a social factor of potential importance in the link between stress and disease.

2. Predisease pathways

Health behaviors are a major determinant of long-term health, and stress can undermine a healthful lifestyle (Institute of Medicine Committee on Health & Behavior, 2001). Social relationships can indirectly affect health by influencing lifestyle variables, health behaviors, and appropriate and timely utilization of healthcare (i.e., "direct effects hypothesis," Cohen & Wills, 1985). Indeed, lacking supportive social ties, lonely individuals have been hypothesized to engage in fewer health-promoting behaviors and more health-compromising behaviors (cf. Seeman, 2000).

A second putative predisease pathway is repeated or excessive catabolic action in response to stressors. Physiological activation in response to stressors is beneficial up to a point, but excessive activation may have hidden costs (Lithgow & Kirkwood, 1996). Because the metabolic requirements of psychological stressors are often minimal, the metabolic support provided by strong physiological reactivity may not be necessary for effective coping. Instead, disproportionate physiological responses may take a toll on homeostatic processes and physiological adaptive capacities and health across the lifespan. Supportive social relationships have the capacity to moderate stress responses indirectly through, for example, the receipt of practical assistance in times of need (i.e., "stress-buffering hypothesis," Cohen & Wills, 1985). Again, deficiencies in perceived social ties mean that the physiological systems of lonely individuals may absorb more of the impact of stressors encountered in daily life.

[1] In discussing the challenges of multi-level integrative research of this kind, Cacioppo and Berntson (1992) described the corollary of proximity, which states that mapping relations across levels of organization becomes more complex as the number of intervening levels increases. This increased complexity reflects the fact that many mappings are many-to-many across proximal levels of organization. Consequently, the mapping across diverse levels of organization becomes more tractable when the mapping proceeds across proximate levels of organization (Cacioppo & Berntson, 1992).

[2] Perceived social isolation forms the dominant factor underlying the UCLA loneliness scale (Adams, Openshaw, Bennion, Mills, & Noble, 1988; Russell, Peplau, & Cutrona, 1980). As such, loneliness is not so much an objective deficit in social ties as it is a perceived discrepancy between desired and actual social relationships (Jylhä & Jokela, 1990; Peplau & Perlman, 1982).

A third putative predisease pathway we recently introduced concerns the effects of social relationships on physiological repair and maintenance processes, including anabolic physiological processes. The recuperative functions of sleep, for example, appear to be influenced by an individual's perceived social context: lonely individuals show evidence of poorer sleep efficiency and more time awake after sleep onset than do nonlonely individuals (Cacioppo et al., 2002b).The possibility that the salubrity of restorative behaviors could be diminished by loneliness may help explain why simple frequency of health behaviors has not accounted for social isolation-related differences in morbidity and mortality.

In the remainder of this paper, we review the evidence for and revisions of each of these potential predisease pathways.

2.1. Health behaviors

According to the US Public Health Service (1990), at least 7 of the 10 leading causes of death in this country could be substantially reduced if people at risk would change just 5 behaviors: compliance with medical treatment regimens, exercise, diet, smoking and use of alcohol and other drugs. Loneliness may indirectly threaten health, as when loneliness results in reduced medical compliance, obscured symptoms, and an increase in the delay, if not the likelihood, of seeking care. Loneliness might also result in an increase in behaviors such as smoking or alcohol use, behaviors that contribute to health risk.

In our survey of 2632 male and female young adults, we found that loneliness, as measured with the R-UCLA Loneliness Scale (Russell et al., 1980) was not associated with poorer or less frequent health behaviors (Cacioppo et al., 2002a). For example, lonely and socially connected individuals (i.e., those low in loneliness) did not differ in number of weekly hours of exercise, number of caffeinated beverages consumed, nor number of cigarettes smoked. If anything, lonely college undergraduates were slightly less likely to consume alcohol than were socially connected individuals.

Results in a sample of 25 older adults (mean age = 65) followed a similar pattern (Cacioppo et al., 2002a). Although the sample was small, no differences were found in alcohol, caffeine, and tobacco use between lonely and socially connected individuals. In addition, self-reports of healthiness of diet, rate of seatbelt use, and compliance with medical regimens failed to reveal loneliness differences. This is not to suggest that health behaviors are unimportant in terms of their health outcomes—there is considerable evidence that the opposite is the case (Institute of Medicine Committee on Health & Behavior, 2001). However, these results are consistent with the epidemiological literature suggesting that the simple frequency in health behaviors can not explain differences in morbidity or mortality as a function of loneliness.

2.2. Stress

The autonomic, neuroendocrine, and immune systems are orchestrated in part to preserve conditions compatible with life in what Claude Bernard called the *milieu interieur* (1878/1974)—a state Esther Sternberg (2000) has called "the balance within." Humans do not reside in an unchanging, nurturant ecological niche, but rather explore, accommodate, and tame hostile and hospitable environments alike. In the process, disturbing forces (e.g., stressors) operate on the *milieu interieur*. The resulting disequilibrium can trigger counteracting normalizing forces (Chrousos, 2000). Stress has been implicated as a contributing factor to various physical and psychological disorders, but research is accumulating to suggest that stress is not as homogeneous a concept as once thought (e.g., see Cacioppo & Berntson, 1992). Here we examine two aspects of stress that have often been conflated: differential stress exposure and differential stress reactivity.

2.2.1. Differential exposure to stressors

The situations people encounter during their lifetimes can vary dramatically, in part due to the environment in which they find themselves and in part due to situations into which people choose to enter. We sought first to determine whether lonely individuals have a more stressful life history. Our study of college undergraduates revealed no differences in the number of major life events, traumas, or intrusive events reported by lonely and nonlonely individuals (Cacioppo et al., 2000a). Furthermore, an experience sampling component of our study revealed that lonely and socially connected students did not differ in the frequency or type of daily activities in which they engaged during everyday life (Hawkley, Burleson, & Cacioppo, in press). Finally, even the amount of time spent alone did not differ between the loneliness groups, reinforcing the distinction between loneliness and objective social isolation.

The absence of objective differences in daily activities, however, does not rule out differences in how similar events are experienced by lonely and socially connected individuals. Psychological assessments revealed that lonely individuals reported higher levels of perceived stress, more frequent and more severe hassles, and less intense "uplifts" than nonlonely individuals (Cacioppo et al., 2000a). Momentary stress ratings over the course of a day—as assessed in our experience sampling study—mirrored these differences: relative to socially connected individuals, lonely individuals rated their daily circumstances as more stressful, threatening, and demanding, and themselves as less capable of meeting those demands

(Hawkley et al., in press). Given that the lonely were no more likely than the socially connected students to be alone when these ratings were made, the greater stress reported by the lonely group cannot be attributed to social isolation per se. On the other hand, when interacting with others, lonely students viewed their social exchanges more negatively (i.e., with greater caution, conflict, and distrust) than did nonlonely individuals (Hawkley et al., in press). Given these situations were objectively largely comparable, the elevated levels of stress found for lonely individuals suggest differences in stress reactivity (and diminished stress-buffering by social partners) rather than stress exposure per se.

2.2.2. Differential reactivity to stressors

Individuals do not respond in a uniform fashion to psychological stressors, and individual differences in the magnitude and form of reactions to stressors have been a topic of research for decades (e.g., see Cacioppo, 1994; Turner, 1989). The research covered above suggests that lonely, compared to nonlonely, individuals are more likely to *perceive* daily events as stressful. Survey measures of coping styles further indicated that lonely individuals were significantly less likely to actively cope, seek instrumental support from others, or seek emotional support from others, and they were more likely to behaviorally disengage than were nonlonely individuals (Cacioppo et al., 2000a). Are the differences in perceived stress and coping styles related to greater peripheral physiological stress reactivity in lonely individuals or are these psychological differences associated with tonic differences in physiological functioning? To examine these questions, participants in our study of young adults were subjected to psychological and orthostatic stressors (Cacioppo et al., 2002a).

Results revealed that lonely and nonlonely individuals showed different patterns of cardiovascular activation when confronted with a series of acute psychological stressors (e.g., mental arithmetic, public speaking). These tasks elicited comparable pressor responses and smaller cardiac responses (i.e., smaller increases in heart rate and cardiac output, smaller decreases in pre-ejection period) in lonely than nonlonely individuals (Cacioppo et al., 2002a). More striking, however, were loneliness differences in chronic levels of cardiovascular functioning. Comparable blood pressure was attributable to different sources in lonely and nonlonely individuals, with lonely individuals characterized by greater peripheral resistance (TPR) and lower cardiac output (CO) than nonlonely individuals. These differences were found at baseline and during the performance of psychological tasks, as well as during the orthostatic stress test (Cacioppo et al., 2002a). The stressfulness of the clinical setting in which these participants were tested did not appear to account for this pattern of cardiovascular activity, either. Ambulatory blood pressure and impedance cardiography was obtained from these participants during a normal day. Results again showed that blood pressure did not differ between loneliness groups, but lonely, compared to nonlonely, individuals were characterized by chronically elevated peripheral resistance and diminished cardiac output (Hawkley et al., in press). Importantly, when levels of depressed mood were held constant, the effects of loneliness on peripheral resistance were *enhanced*. Nor did negative affect account for loneliness differences in peripheral resistance, suggesting that loneliness operates through a unique mechanism that distinguishes it from related negative psychosocial states.

We speculated that chronically higher TPR and lower CO could contribute, over the years, to impaired cardiovascular functioning. Consistent with this possibility, we observed age-related increases in blood pressure among lonely, but not nonlonely, elderly adults (Cacioppo et al., 2002a). Whether loneliness predicts higher levels of TPR across the lifespan is not yet known, but a recent cross-sectional study of mid-aged African-American adults supports this possibility. Using a single item measure of loneliness derived from the CES-D (depression) scale, peripheral resistance was positively correlated ($r = .50$) with loneliness (J. Thayer, personal communication, March, 2002).

The cardiovascular profile differentiating lonely and socially connected individuals evokes the distinction between cardiovascular responses to passive and active coping tasks (Sherwood, Dolan, & Light, 1990), and to threat and challenge appraisals of active coping tasks (Blascovich & Tomaka, 1996). However, loneliness differences were evident in chronic cardiovascular functioning, including that which is shown during a normal day, not in cardiovascular reactivity to acute stressors (Cacioppo et al., 2002a). Whether lonely individuals chronically adopt a more passive coping style with everyday life or are characterized chronically by threat appraisals of everyday life, and whether such differences in world view account for the cardiovascular differences, remain to be determined.

Although work in this area has focused primarily on autonomic functioning (see review by Uchino et al., 1996), Seeman and McEwen (1996) have proposed that life stressors can impair health by elevating hypothalamic-pituitary-adrenocortical (HPA) activation, which over time enhances the wear-and-tear on the organism. Evidence for a loneliness difference in HPA activity was first reported by Kiecolt-Glaser et al. 1984a, 1984b, who observed that lonely nonpsychotic psychiatric inpatients excreted significantly greater amounts of urinary cortisol than did nonlonely inpatients.

In our study of young adults, we measured catecholamines, ACTH, and cortisol in blood samples collected in the morning and again in the late afternoon. Analyses revealed only morning levels of ACTH were

significantly higher among lonely than nonlonely students (Cacioppo et al., 2000a). Repeated measurements of salivary cortisol at nine random timepoints across the day uncovered the typical diurnal rhythm in cortisol, but we found no loneliness differences in the diurnal pattern of cortisol secretion or in mean daily levels of salivary cortisol, nor did we find differences in HPA reactivity to acute stressors in lonely and nonlonely individuals (Cacioppo et al., 2002a). Similarly, we found no loneliness group differences in mean levels of salivary cortisol or in diurnal cortisol variations in a sample of older adults (Cacioppo et al., 2002a). HPA-stimulated release of cortisol has a pulsatile nature, with major secretory episodes appearing during the early morning (Van Cauter, 1990). Together, these results suggest that urinary cortisol collected over an extended period (e.g., overnight, 24-h period) may be required to detect group differences in HPA activation. Physiological stress reactivity, however, may not be significantly greater in lonely than nonlonely individuals given the event is perceived as comparably stressful; instead, lonely individuals do appear more likely to perceive events in their daily life as stressful events.

2.3. Maintenance and repair

In a healthy state, regulatory processes (e.g., homeostasis) buffer organisms from the effects of internal and external changes, and restorative processes (e.g., wound healing, humoral immunity) operate to refresh, buttress, and repair various forms of cellular damage (Cacioppo & Berntson, in press). Regulatory devices work only within certain limits of perturbation in buffering the organism from changes in the internal milieu, however, and restorative devices work only within certain limits to return the organism to an earlier condition. If the disturbance is too great or enduring, the very parameters around which these regulatory devices operate (e.g., basal levels of functioning or set points) can be affected (Cacioppo et al., 2000b; McEwen, 1998). The current zeitgeist of focusing on stress and stress reactivity has left the restorative side of the story understudied. Our research on loneliness suggests this may be an important oversight.

Consider the study by Marucha, Kiecolt-Glaser, and Favagehi (1998) on the effects of stress on wound healing. Two punch biopsy wounds were placed on the hard palate of 11 dental students. The first was performed during summer vacation, and the second was made on the contralateral side three days prior to their first major examination of the term. Wound size was measured at regular intervals to monitor days until healing was complete. The wounds took longer to heal in all eleven participants during high stress than low stress periods. Moreover, the time required to heal the wound during low stress periods, and the additional time it took for the wound to heal during exam stress were found to be uncorrelated, suggesting that the mechanisms responsible for basal levels of tissue maintenance may differ from those responsible for tissue repair. Six months after the completion of this study, we were able to locate eight of these individuals and administer the UCLA loneliness scale. Although preliminary, our results revealed that loneliness was significantly correlated both with wound healing time during the summer and with the additional time needed to wound heal during periods of stress.

Evidence that loneliness may play a role in maintaining health is provided by studies of cellular immunity. Natural killer cells (NKCs) are one of the first in a line of defense against cancer (Black, 1993). That loneliness may compromise this safeguard was suggested by research showing that levels of NKC activity were significantly lower among high than low lonely first-year medical students (Kiecolt-Glaser et al., 1984a, 1984b). Further evidence for the inadequacy of cellular immunity in lonely individuals is suggested by higher levels of antibodies to latent Epstein–Barr virus (EBV) among high versus low lonely medical students (Glaser, Kiecolt-Glaser, Speicher, & Holiday, 1985). In addition, among high relative to low lonely students, more virus was necessary to induce transformation of B lymphocytes into cells capable of holding the EBV DNA in a latent state (Kiecolt-Glaser, Speicher, Holliday, & Glaser, 1984c).

Additional evidence that social factors may play a role in maintenance and reparative processes is provided by the relationship between loneliness and the cytokines, interleukin-1β (IL-1β) and tumor necrosis factor (TNF). IL-1β is a signal transduction molecule involved in communicating with neural tissue and in producing energy to fight infection at its first appearance. Accordingly, IL-1β and TNF are early acting pro-inflammatory cytokines that serve to marshal an immune response at the site of a challenge. Using whole blood assays, Marucha et al. (1998) found lower levels of LPS-induced IL-1β and TNF during exam week than during summer vacation. When these assays were conducted contrasting the pro-inflammatory cytokine response to LPS-stimulated lymphocytes from lonely and nonlonely young adults, we found diminished responses for lonely, compared to nonlonely, individuals.

Could it be that loneliness diminishes the salubrity of restorative processes? To provide a more rigorous test of this hypothesis, we examined the efficacy of the quintessential restorative behavior—sleep.

Sleep deprivation has dramatic effects on metabolic, neural, and hormonal regulation—effects that mimic those of aging (Spiegel, Leproult, & Van Cauter, 1999). Young adults who participated in our study spent one night in the Clinical Research Center of the university hospital. In a double-blind procedure, the Nightcap was used to record sleep during their night in the hospital

and during several subsequent nights in their residence. Results from both sites revealed that sleep efficiency was lower and wake time after sleep onset was higher for lonely than nonlonely participants (Cacioppo et al., 2002b). Importantly, the Nightcap recordings revealed that total time asleep did not differ across the groups. The restorative act of sleep simply appeared more efficient and effective in nonlonely than lonely individuals.

Further evidence for this effect was found using the Pittsburgh Sleep Quality Inventory (PSQI). The PSQI is a self-report measure of sleep quality. Results from the PSQI revealed that lonely young adults reported poorer sleep quality, longer sleep latency, longer perceived sleep duration, and greater daytime dysfunction due to sleepiness than did nonlonely individuals—effects that were found in a study of older adults, as well (Cacioppo et al., 2002b). Thus, a pathway by which loneliness may affect health is via diminished restorative processes.

3. Implications for the onset and treatment of cancer

Each of the three broad predisease pathways described above—health behaviors, stress, and restorative processes—offers a point of entry through which social factors may influence health outcomes. Although our research has not dealt with cancer per se, social isolation is associated with increased risk of death from cancer as well as stroke and cardiovascular disease (e.g., Berkman & Syme, 1979; House et al., 1988). The diagnosis of cancer has also been associated with increased dysphoria, family problems, and feelings of loneliness and isolation (e.g., see Rokach, 2000). It would be wonderful to claim that decreasing loneliness could eradicate cancer, but such a possibility is not supported by our data. The physiological effects associated with loneliness that we documented, if in fact caused by loneliness, probably unfold over relatively long periods of time, possibly increasing vulnerability to cancer. Once the normal surveillance and maintenance processes have been disturbed by a sufficient amount that the disease of cancer takes hold, the major benefits of being socially connected probably do not operate through the salubrity of restorative behaviors but rather through effects with a shorter time course—such as tangible and appraisal support that fosters the patient securing optimal medical treatment and maximizing her or his medical compliance.

Consistent with the argument that the physiological effects of loneliness have a long time course, a prospective study of breast cancer survivors revealed that levels of social integration *before* breast cancer diagnosis predicted physical functioning and overall vitality during the four years following diagnosis (Michael, Berkman, Colditz, Holmes, & Kawachi, 2002). Moreover, consistent with the argument that the greatest health benefit to cancer patients is provided by the supportive aspects of social connectedness, the least socially integrated women prior to diagnosis also reported the greatest frequency of problems attaining informational, tangible, and appraisal support during the course of their disease. Indeed, interventions for cancer patients designed to improve their *feelings* of social support have not produced the dramatic health benefits that were originally envisioned (Spiegel, Bloom, Kraemer, & Gottheil, 1989; cf. Spiegel, 2001). Interventions of this sort may be more effective if greater attention is given to instrumental assistance that significant others can provide.

Acknowledgments

The research reported here was supported by a grant from the John D. and Catherine T. MacArthur Foundation (Mind-Body Integration Network) and by National Institutes of Health Grant No. PO1 AG18911.

References

Adams, G. R., Openshaw, D. K., Bennion, L., Mills, T., & Noble, S. (1988). Loneliness in late adolescence: A social skills training study. *Journal of Adolescent Research, 3*, 81–96.

Berkman, L. F., & Syme, S. L. (1979). Social networks, host resistance, and mortality: A 9-year follow-up study of Alameda County residents. *Am. J. Epidemiol., 109*, 186–204.

Black, J. G. (1993). *Microbiology: Principles and applications*. Englewood Cliffs, NJ: Prentice-Hall.

Blascovich, J., & Tomaka, J. (1996). The biopsychosocial model of arousal regulation. In M. P. Zanna (Ed.), *Advances in experimental social psychology* (Vol. 29, pp. 1–51). New York: Academic Press.

Boer, H., Elving, W., & Seydel, E. R. (1998). Psychosocial factors and mental health in cancer patients: Opportunities for health promotion. *Psychol. Health Med., 3*, 71–79.

Cacioppo, J. T. (1994). Social neuroscience: Autonomic, neuroendocrine, and immune responses to stress. *Psychophysiology, 31*, 113–128.

Cacioppo, J. T., & Berntson, G. G. (1992). Social psychological contributions to the decade of the brain: Doctrine of multilevel analysis. *Am. Psychol., 47*, 1019–1028.

Cacioppo, J. T., & Berntson, G. G. (in press). Balancing demands of the internal and external milieu. In H. S. Friedman, & R. Cohen Silver (Eds.), *Oxford handbook of health psychology*. New York: Oxford University Press.

Cacioppo, J. T., Burleson, M. H., Poehlmann, K. M., Malarkey, W. B., Kiecolt-Glaser, J. K., Berntson, G. G., Uchino, B. N., & Glaser, R. (2000b). Autonomic and neuroendocrine responses to mild psychological stressors: Effects of chronic stress on older women. *Annals of Behavioral Medicine, 22*, 140–148.

Cacioppo, J. T., Ernst, J. M., Burleson, M. H., McClintock, M. K., Malarkey, W. B., Hawkley, L. C., Kowalewski, R. B., Paulsen, A., Hobson, J. A., Hugdahl, K., Speigel, D., &

Berntson, G. G. (2000a). Lonely traits and concomitant physiological processes: The MacArthur Social Neuroscience Studies. *Int. J. Psychophysiol., 35*, 143–154.

Cacioppo, J. T., Hawkley, L. C., Berntson, G. G., Ernst, J. M., Gibbs, A. C., Stickgold, R., & Hobson, J. A. (2002b). Lonely days invade the night: Social modulation of sleep efficiency. *Psychol. Sci., 13*, 385–388.

Cacioppo, J. T., Hawkley, L. C., Crawford, E., Ernst, J. M., Burleson, M. H., Kowalewski, R. B., Malarkey, W. B., Van Cauter, E., & Berntson, G. G. (2002a). Loneliness and health: Potential mechanisms. *Psychosomat. Med., 64*, 407–417.

Cacioppo, J. T., Kiecolt-Glaser, J. K., Malarkey, W. B., Laskowski, B. F., Rozlog, L. A., Poehlmann, K. M., Burleson, M. H., & Glaser, R. (2002c). Autonomic and glucocorticoid associations with the steady state expression of latent Epstein–Barr virus. *Horm. Behav., 42*, 32–41.

Carstensen, L. L., Pasupathi, M., Mayr, U., & Nesselroade, J. (2000). Emotional experience in everyday life across the life span. *J. Pers. Soc. Psychol., 79*, 644–655.

Chrousos, G. P. (2000). The stress response and immune function: Clinical implications. The 1999 Novera H. Spector Lecture. *Ann. N. Y. Acad. Sci., 917*, 38–67.

Cohen, S., & Wills, T. A. (1985). Stress, social support, and the buffering hypothesis. *Psychol. Bull., 98*, 310–357.

Fox, C. M., Harper, A. P., Hyner, G. C., & Lyle, R. M. (1994). Loneliness, emotional repression, marital quality, and major life events in women who develop breast cancer. *J. Commun. Health, 19*, 467–482.

Fung, H. H., Carstensen, L. L., & Lang, F. R. (2001). Age-related patterns in social networks among European Americans and African Americans: Implications for socioemotional selectivity across the life span. *Int. J. Aging Hum. Dev., 52*, 185–206.

Glaser, R., Kiecolt-Glaser, J. K., Speicher, C. E., & Holliday, J. E. (1985). Stress, loneliness, and changes in herpesvirus latency. *Journal of Behavioral Medicine, 8*, 249–260.

Hawkley, L. C., Burleson, M. H., & Cacioppo, J. T. (in press). Loneliness in everyday life: Cardiovascular activity, psychosocial context, and health behaviors. *J. Pers. Soc. Psychol.*

Herlitz, J., Wiklund, I., Caidahl, K., Hartford, M., Haglid, M., Karlsson, B. W., Sjoland, H., & Karlsson, T. (1998). The feeling of loneliness prior to coronary artery bypass grafting might be a predictor of short- and long-term postoperative mortality. *Eur. J. Vasc. Endovasc. Surg., 16*, 120–125.

House, J. S., Landis, K. R., & Umberson, D. (1988). Social relationships and health. *Science, 241*, 540–545.

Institute of Medicine Committee on Health and Behavior (2001). *Health and behavior: The interplay of biological, behavioral, and societal influences*. Washington, D.C.: National Academy Press.

Jylhä, M., & Jokela, J. (1990). Individual experiences as cultural—A cross-cultural study on loneliness among the elderly. *Aging & Society, 10*, 295–315.

Kiecolt-Glaser, J. K., Garner, W., Speicher, C., Penn, G. M., Holliday, J., & Glaser, R. (1984a). Psychosocial modifiers of immunocompetence in medical students. *Psychosom. Med., 46*, 7–14.

Kiecolt-Glaser, J. K., Ricker, D., George, J., Messick, G., Speicher, C. E., Garner, W., & Glaser, R. (1984b). Urinary cortisol levels, cellular immunocompetency,and loneliness in psychiatric inpatients. *Psychosom. Med., 46*, 15–23.

Kiecolt-Glaser, J. K., Speicher, C. E., Holliday, J. E., & Glaser, R. (1984c). Stress and the transformation of lymphocytes by Epstein–Barr virus. *J. Behav. Med., 7*, 1–12.

Knox, S. S., Adelman, A., Ellison, C., Arnett, D. K., Siegmund, K., Weidner, G., & Province, M. A. (2000). Hostility, social support, and carotid artery atherosclerosis in The National Heart, Lung, and Blood Institute Family Heart Study. *Am. J. Cardiol., 86*, 1086–1089.

Lithgow, G. J., & Kirkwood, T. B. L. (1996). Mechanisms and evolution of aging. *Science, 273*, 80–81.

Luskin, F., & Newell, K. (1997). Mind-body approaches to successful aging. In A. Watkins (Ed.), *Mind-body medicine: A clinician's guide to psychoneuroimmunology* (pp. 251–268). New York: Churchill Livingstone.

Marucha, P. T., Kiecolt-Glaser, J. K., & Favagehi, M. (1998). Mucosal wound healing is impaired by examination stress. *Psychosom. Med., 60*, 362–365.

Michael, Y. L., Berkman, L. F., Colditz, G. A., Holmes, M. D., & Kawachi, I. (2002). Social networks and health-related quality of life in breast cancer survivors: A prospective study. *J. Psychosom. Res., 52*, 285–293.

Peplau, L. A., & Perlman, D. (1982). Perspective on loneliness. In L. A. Peplau & D. Perlman (Eds.), *Loneliness: A sourcebook of current theory, research and therapy* (pp. 1–20). New York: Wiley.

Price, M. A., Tennant, C. C., Butow, P. N., Smith, R. C., Kennedy, S. J., Kossoff, M. B., & Dunn, S. M. (2001). The role of psychosocial factors in the development of breast carcinoma: Part II. Life event stressors, social support, defense style, and emotional control and their interactions. *Cancer, 91*, 686–697.

Rokach, A. (2000). Correlates of loneliness as perceived by the terminally ill. *Curr. Psychol., 19*, 237–248.

Russell, D., Peplau, L. A., & Cutrona, C. E. (1980). The revised UCLA loneliness scale: Concurrent and discriminant validity evidence. *J. Pers. Soc. Psychol., 39*, 472–480.

Seeman, T. E. (2000). Health promoting effects of friends and family on health outcomes in older adults. *Am. J. Health Promotion, 14*, 362–370.

Seeman, T. E., & McEwen, B. D. (1996). Impact of social environment characteristics on neuroendocrine regulation. *Psychosom. Med., 58*, 459–471.

Sherwood, A., Dolan, C. A., & Light, K. C. (1990). Hemodynamics of blood pressure responses during active and passive coping. *Psychophysiology*, 27,656–668.

Spiegel, D. (2001). Mind matters—Group therapy and survival in breast cancer. *N. Engl. J. Med., 345*, 1767–1768.

Spiegel, D., Bloom, J. R., Kraemer, H. C., & Gottheil, E. (1989). Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet, 2*, 888–891.

Spiegel, K., Leproult, R., & Van Cauter, E. (1999). Impact of a sleep debt on metabolic and endocrine function. *Lancet, 354*, 1435–1439.

Sternberg, E. M. (2000). *The balance within*. New York: W.H. Freeman.

Turner, R. J. (1989). Individual differences in heart rate response during behavioral challenge. *Psychophysiology, 26*, 497–505.

Uchino, B. N., Cacioppo, J. T., & Kiecolt-Glaser, J. K. (1996). The relationship between social support and physiological processes: A review with emphasis on underlying mechanisms and implications for health. *Psychol. Bull., 119*, 488–531.

US Department of Health and Human Services (1990). *Healthy People 2000: National health promotion and disease prevention objectives*. Washington, DC: US Government Printing Office.

Van Cauter, E. (1990). Diurnal and ultradian rhythms in human endocrine function: A minireview. *Horm. Res., 34*, 45–53.