

# HUMAN STRESS AND IMMUNITY

---

Edited by

**Ronald Glaser**

Department of Medical Microbiology and Immunology  
Ohio State University  
Columbus, Ohio

**Janice K. Kiecolt-Glaser**

Department of Psychiatry  
Ohio State University  
Columbus, Ohio



1994

**ACADEMIC PRESS**

San Diego New York Boston London Sydney Tokyo Toronto

## Stressful Personal Relationships: Immune and Endocrine Function

Janice K. Kiecolt-Glaser, William B. Malarkey, John T. Cacioppo, and  
Ronald Glaser

### I. OVERVIEW

Data from large, well-controlled epidemiological studies suggest that social isolation constitutes a major risk factor for morbidity and mortality, with statistical effect sized comparable to those of such well-established health risk factors as smoking, blood pressure, blood lipids, obesity, and physical activity (House, Landis, & Umberson, 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 (PNI; Kiecolt-Glaser & Glaser, 1992). For example, lonelier medical students had lower natural killer (NK) cell activity than fellow students who were not as lonely (Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984). Higher NK cell activity and stronger proliferative responses to mitogen stimulation were associated with higher social support in women whose husbands were being treated for urologic cancer than

among those with less support (Baron, Cutrona, Hicklin, Russell, & Lubartoff, 1990). Medical students who reported better social support mounted a stronger immune response to a hepatitis B vaccine than those with less social support (Glaser, Kiecolt-Glaser, Bonneau, Malarkey, & Hughes, 1992).

The support provided by certain key personal relationships is obviously more important than others: data from national surveys suggest that marital happiness contributes far more to overall ratings of happiness than any other variable, including satisfaction with work and friendships (Glenn & Weaver, 1981). Epidemiological studies demonstrate reliable mental and physical health differences between married and unmarried people (Verbrugge, 1979), and the loss of a spouse, either through bereavement (Irwin, Daniels, Smith, Bloom, & Weiner, 1987; Schleifer, Keller, & Camerino, 1983) or divorce (Kiecolt-Glaser, Fisher, Ogrocki, Stout, Speicher, & Glaser, 1987; Kiecolt-Glaser, Kennedy, Malkoff, Fisher, Speicher, & Glaser, 1988), has been linked to declines in cellular immunity.

Although loss of a spouse can provoke adverse mental and physical health changes, the simple presence of a spouse is not necessarily protective; a troubled marriage is itself a prime source of stress, while simultaneously limiting the partner's ability to seek support in other relationships (Coyle & DeLongis, 1986). Unmarried people are happier, on the average, than unhappily married people (Renne, 1971). In fact, depression is strongly associated with marital discord. Weissman (1987) found that unhappy marriages were a potent risk factor for major depressive disorder, associated with a 25-fold increase over untroubled marriages.

We will integrate data from several diverse lines of work in this chapter to argue that close personal relationships that are chronically abusive or stressful may provoke persistent physiological alterations. The endocrine system almost certainly serves as one important gateway between troubled personal relationships and health; stress can stimulate the release of pituitary and adrenal hormones that have multiple effects, including alterations in cardiovascular and immune function (Ader, Felten, & Cohen, 1991; Fredrikson, Tuomisto, & Bergman-Losman, 1991; Smith & Christensen, 1992). Interpersonal or social stressors can substantially elevate epinephrine (EPI), norepinephrine (NEPI), and cortisol (Dimsdale & Moss, 1980; Dimsdale, Young, Moore, & Strauss, 1987; Oleshansky & Meyerhoff, 1992). We speculate that heightened sympathetic nervous system (SNS) activity is one key mechanism fueling more persistent endocrine and immune alterations. Preliminary evidence suggests we can illuminate stressor effects by the addition of autonomic measures that provide a better understanding of individual variations in SNS activity (Sgoutas-Emch, et al., 1994).

We will also review the evidence for gender differences, with women showing greater psychological and physiological responsiveness than men to hostile or negative marital interactions (e.g., Ewart et al., 1991; Gaclick,

Bodenhausen, & Weyer, 1985); these data are consistent with epidemiological evidence that marriage appears to be more beneficial for men's health than women's (Burman & Margolin, 1992; House et al., 1988). Finally, we will argue that the links between marital discord and immunity could be stronger and could have more potent health consequences for older adults than younger adults.

## II. MARITAL INTERACTION

In two small cross-sectional studies, we found that lower marital satisfaction was associated with poorer immune function as well as greater depression and loneliness (Kiecolt-Glaser et al., 1987, 1988). While these data were provocative, the cross-sectional designs precluded inferences about the direction of causality, for example, people who were more depressed might have viewed their marriages as less supportive, and their depressive symptoms might have also potentiated the downregulation of immune function (Irwin, Brown, Patterson, Hauger, Mascovich, & Grant, 1992; Gotlib & Hooley, 1988). However, we speculated that the immunological differences we observed reflected endocrinological changes related to the heightened autonomic arousal associated with marital strife (Ewart et al., 1991; Levenson & Gottman, 1983; Morrell & Apple, 1990). We designed a prospective longitudinal study to test these hypotheses.

In order to make more definitive causal inferences about the relationships between marital discord and health, we selected 90 newlywed couples on the basis of extremely stringent mental and physical health criteria. We sent letters to demographically "appropriate" couples (first marriage, ages 20 to 40, no children) who had obtained marriage licenses 4 to 6 months previously. The first phase of the study was described as a phone survey of newlyweds' health and happiness, and subjects were told that they would be paid \$10 per couple for interviews concerning their physical and mental health if they returned an enclosed postcard; 2249 individuals were interviewed of 4758 who received letters, representing a 47% response rate. Eight percent of the couples who returned our original postcards were eventually admitted to the OSU Clinical Research Center (CRC), a hospital research unit, for 24 hr, where we assessed problem-solving behaviors and changes in autonomic, endocrine, and immune function.

We eliminated couples from further consideration after the initial phone interview if either spouse reported any acute or chronic health problems that might have immunological or endocrinological consequences, if they took any medications except birth control pills, if they drank more than 10 alcoholic drinks per week or used any street drugs, if they smoked, if they used caffeine excessively, or if they were not within 20% of their ideal weight for their height.

During a second set of phone interviews we collected both current and lifetimes psychiatric disorder data as well as a detailed medical history. We excluded subjects who had met DSM-III-R criteria for any psychotic diagnosis, any depressive or anxiety disorder other than simple phobia, or substance abuse. These criteria were designed to exclude previously impaired or vulnerable individuals whose psychopathology might produce marital discord (Gottlib & Hooley, 1988), as well as associated endocrinological or immunological alterations. We eliminated individuals with any history of major depression or dysthymia, since impairments in marital and other close relationships can persist for 4 years or more after an acute episode (Bothwell & Weissman, 1977).

As one consequence of our stringent inclusion criteria, our subjects were exceptional in their health habits, for example, their commitment to regular exercise. By admitting couples to the CRC for 24 hr, we were able to control such factors as physical activity, diet, and caffeine intake that can influence immune and endocrine function (Kiecolt-Glaser & Glaser, 1988), while simultaneously providing a uniform environment across couples. Moreover, all admissions were scheduled during the follicular phase of the woman's menstrual cycle. Thus, it seems reasonable to conclude that the behavior of the couples during their 24 hr together produced the observed endocrinological and immunological differences, rather than extraneous factors:

We asked couples to discuss areas of disagreement for 30 min early during their 24-hr admission. This "conflict" session was recorded on videotapes that were later scored for problem-solving behaviors using the Marital Interaction Coding System (MICS; Weiss & Summers, 1983). Across a large number of marital studies, distressed and nondistressed couples show reliable and stable behavioral differences during conflict: dissatisfied couples behave more negatively toward each other, and they are more likely to reciprocate their partner's negative behaviors (Sher & Weiss, 1991). Negative communication indices provide much more discriminative and predictive power than positive indices (Markman, 1991). Nondistressed couples are better able to set limits on negative communication and its reverberations than distressed couples (Markman, 1991; Margolin, Burman, & John, 1989). Thus, we expected that negative communication would be much more strongly related to physiological changes over 24 hr than positive aspects. We related these MICS-coded behavioral data to physiological data.

The endocrine samples collected immediately before, during, and 15 min after conflict provided a window on short-term reactivity: five of the six hormones we assayed changed during the 30-min problem discussion, and negative or hostile behavior produced greater and/or more persistent alterations. Specifically, hostile behavior during marital conflict was associated

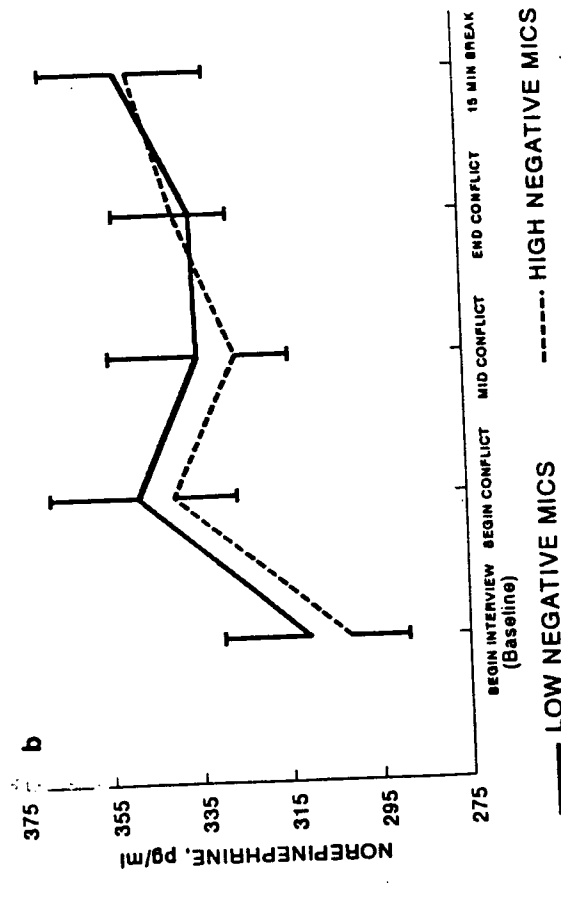
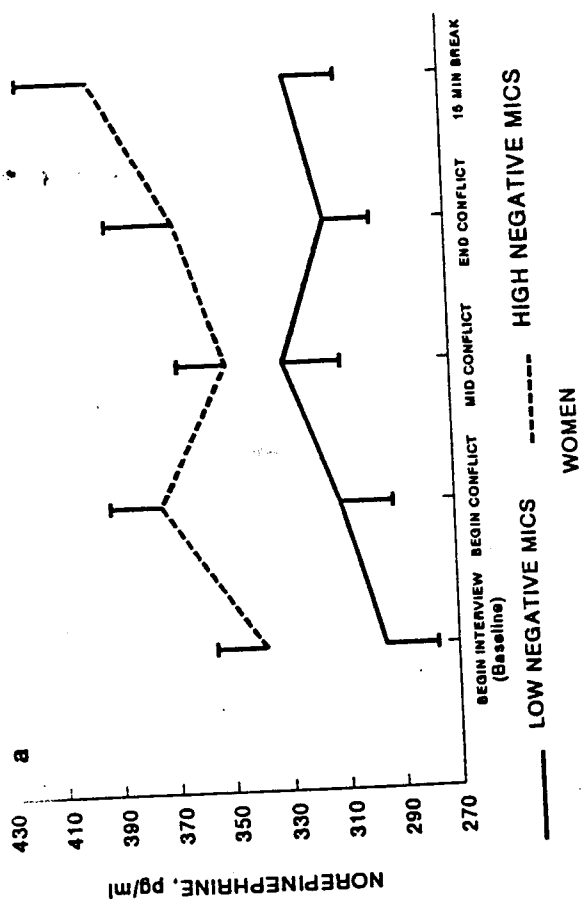
with decreased levels of prolactin (PRL) and increased levels of EPI, NEPI, growth hormone (GH), and ACTH.

Moreover, differences between high and low hostile behavior groups tended to be relatively larger for women than for men, particularly for the catecholamines (see Figures 1a, 1b, 2a, and 2b). NEPI levels remained elevated 15 min after the conflict, presumably reflecting persistence of sympathetic stimulation after termination of the stressor.

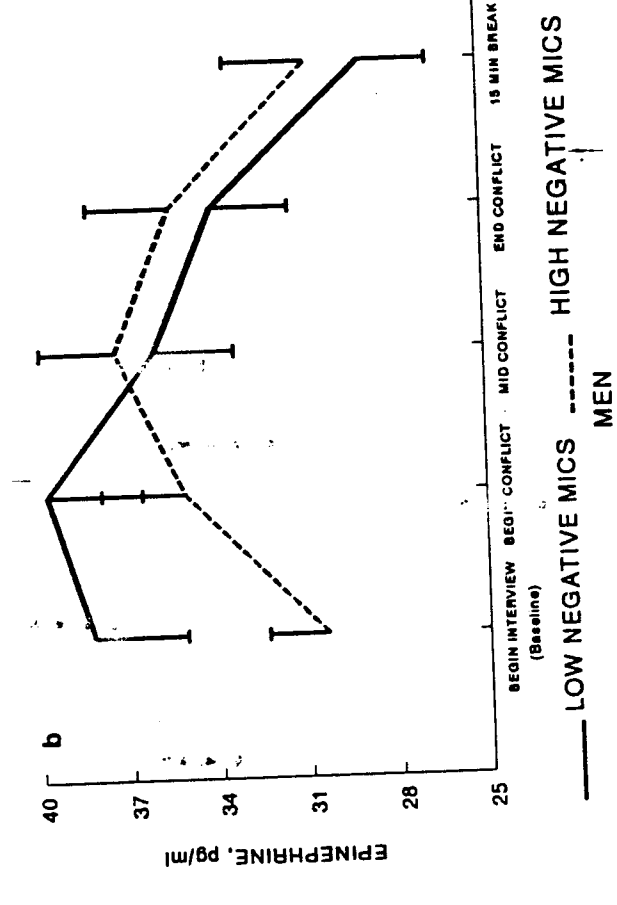
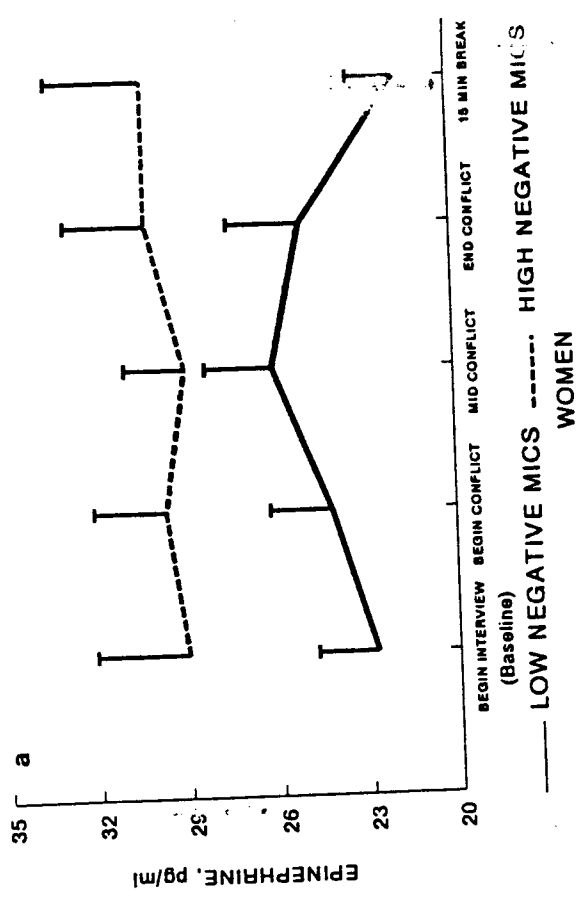
The pattern of group differences across the various hormones was noteworthy. For example, EPI and NEPI are generally associated with immunological downregulation (Rabir, Coher, Ganguli, Lysle, & Cunnick, 1989), and these levels were higher in the individuals who showed more hostile behaviors during conflict. In contrast, low hostile behavior individuals had higher PRL levels from the beginning of conflict through the 15-min recovery period. Since PRL is immune enhancing (Bernton, 1989), the combination of elevated catecholamines and depressed PRL levels could lead to diminished immune function in the group with more hostile behaviors.

We found that hostile behavior during marital conflict had immunological correlates as well. Blood samples drawn on entry and exit from the CRC for immunological analyses showed that high negative subjects demonstrated greater decrements over the 24 hr relative to low negative subjects on four functional immunological assays, NK cell lysis, the blastogenic response to two mitogens, and the proliferative response to a monoclonal antibody to the T3 receptor, as well as larger increases in the numbers of total T lymphocytes and helper T lymphocytes (Kiecolt-Glaser et al., 1993). The elevated plasma EPI levels in high negative subjects are the likely mediator for the increased numbers of T lymphocytes and T cell subsets (Kiecolt-Glaser et al., 1992; Sgoutas-Emch et al., 1994). High negative subjects also had higher antibody titers to latent Epstein-Barr virus, further suggesting downregulated cellular immune function (Glaser & Kiecolt-Glaser, 1994). In addition, subjects who exhibited more negative or hostile behaviors during their 30-min discussion of marital problems showed larger increases in blood pressure that remained elevated longer than low negative subjects. Positive or supportive problem-solving behaviors were not related to immunological or blood pressure changes. Consistent with the gender differences in endocrine change during conflict, women showed greater immunological decrements than men.

We also evaluated relationships between conflict behavior and more enduring endocrine alterations, because more persistent endocrine changes would be likely to have stronger consequences for both immune function (Ader et al., 1991) and cardiovascular function (Fredrikson et al., 1991; Smith & Christensen, 1992). Blood samples acquired hourly from 8:00 AM through 10:00 PM were pooled to provide composite daytime values for the



**FIGURE 2** (a) Changes in mean ( $\pm$  SEM) NEPI levels produced by the initial interview and marital conflict discussion. Note the continued persisted elevations in NEPI 15 min after completion of the conflict session in women.



**FIGURE 1** The figure shows mean ( $\pm$  SEM) values at each point in time for the two MICS groups, with women shown in the upper part of the figure (a) and men in the lower part (b). The responses to marital conflict produced greater differences in women related to negative behavior than men.

six hormones assessed during conflict. These composite daytime values allowed us to examine the extent to which certain interpersonal behaviors assessed during conflict may provoke more enduring endocrinological alterations.

We found stronger and more consistent links between behavior and endocrine function among women than men for the three classic stress hormones, EPI, NEPI, and cortisol. Women whose husbands were more likely to withdraw following the wife's negative behaviors during conflict were more likely to show elevated cortisol and NEPI levels; in contrast, this wife demand/husband withdraw sequence was not significantly related to husbands' endocrine data. The wife demand/husband withdraw interaction sequence appears to be a particularly destructive marital pattern, strongly associated with marital discord (Heavey, Layne, & Christensen, 1993). Consistent with the stronger endocrinological associations for wife demand/husband withdraw for women compared to men in this study, recent prospective work has linked this interactional pattern with longitudinal declines in wives' (but not husbands') marital satisfaction (Heavey et al., 1993).

These gender differences in our daytime endocrine data are consistent with other physiological data from this study in which relationships between physiological change and hostile or negative behaviors have been stronger for women than for men, and women's physiological changes following marital conflict have been more persistent than men's (Kiecolt-Glaser et al., 1993; Malarkey, Kiecolt-Glaser, Pearl, & Glaser, 1994). However, these data are not consistent with the escape-conditioning model (Gottman & Levenson, 1988), which predicts associations between husbands' physiological responses and their behavior, especially withdrawal.

It could be argued that our gender differences are not representative because we studied couples in the early stages of marriage who were generally quite happy, and/or our unusually stringent mental and physical health exclusion criteria produced a nonrepresentative sample. However, in data from a sample of hypertensive patients whose average age was 57, wives showed larger blood pressure increases during marital conflict than husbands, and women's blood pressure changes were specifically related to both hostile behaviors and marital quality; in contrast, only speech rate predicted men's blood pressure increases (Ewart et al., 1991). The fact that wives displayed larger blood pressure changes than husbands is particularly interesting because men typically show larger blood pressure and urinary EPI increases in response to acute stressors than women, although the "gender relevance" of a stressor may modulate responsivity (Stoney, Davis, & Matthews, 1987).

Moreover, consistent with both our blood pressure data and those of Ewart et al. (1991), Morell and Apple (1990) found that active negative affect accounted for 20% of the variance in women's systolic blood pressure during a 10-min marital conflict discussion, and 53% of the variance in self-

reported marital distress. While Morrell and Apple (1990) did not collect cardiovascular data from husbands, negative affect and marital distress were unrelated for men. Finally, limited longitudinal data suggest that wives' physiological responses to conflict may have greater predictive power for assessing risk for marital dissolution than husbands' data in couples married an average of 5 years (Gottman & Levenson, 1992). Thus, the gender differences in this study are compatible with physiological data from studies of longer-term marriages in which couples were not selected on such stringent health criteria.

It is not surprising to find that women show greater correspondence between marital conflict and more persistent physiological changes when one considers other evidence: wives demonstrate more detailed and vivid memories of marital disagreements than their husbands (Ross & Holmberg, 1990). Wives also report that they reminisce more frequently about important relationship events and spend more time thinking about their marital relationships than their husbands (Burnett, 1987; Ross & Holmberg, 1990). Since memories of stressful experiences can themselves continue to evoke stress-related physiological changes (e.g., Baum, Cohen, & Hall, 1993), women's stronger and more enduring memories may help sustain their physiological arousal. Indeed, increased sympathetic nervous system activity has been reliably associated with intrusive thoughts about past stressors in both clinical and nonclinical samples; importantly, NEPI is elevated as well (Baum et al., 1993; Southwick et al., 1993). Perhaps unresolved conflicts that follow wife demand/husband withdraw interactions may be more likely to fuel wives' continued reminiscence about the disagreements than similarly intense conflicts that were resolved, and/or unresolved conflicts may be more likely to resurface in subsequent interactions.

Floyd and Markman (1983) suggest that wives function as the "barometers" of distressed marriages, in part because women are more sensitive to negative marital interactions than men. Wives are better at decoding their spouse's emotional messages than husbands (Noller & Fitzpatrick, 1990); distressed wives can more accurately decode their husbands' negative messages than the reverse (Notarius, Benson, Sloane, Vanzerri, & Hornyak, 1989). Moreover, women may be more adversely affected by overt expressions of hostility in marital interactions than men (Gaelick et al., 1985). Wives' greater sensitivity to marital distress and their associated physiological arousal may be tied to their greater propensity to mend or end their marriages. Wives are more likely to voice their discontent with their marriages, and to do so earlier than their husbands (Hagestad & Smyer, 1982; Harvey, Wells, & Alvarez, 1978). Only one-quarter to one-third of marital separations are directly prompted by the husband's decision (Kitson, 1982). Wives' greater cognitive and emotional sensitivity to negative aspects of marital interactions (Huston & Ashmore, 1986) may also subject them to greater physiological consequences. As noted earlier, epidemiological evi-

ence shows that marriage appears to be more beneficial for men's health than for women's (Burman & Margolin, 1992; House et al., 1988).

These data provided a window on the pathways through which close personal relationships could affect physiological functioning and health. However, these data might underestimate the actual physiological impact of marital discord, since we deliberately selected individuals who were presumably the least vulnerable and the intensity of marital conflict is typically lower in the early years of marriage (Storaasli & Markman, 1990). Moreover, convergent evidence from psychosocial and immunological domains suggests that the links between marital discord and immunity could be stronger and could have more potent health consequences for older adults than younger adults; the number of relationships diminishes as people age, and the quality of close relationships becomes more salient (Carstensen, 1992). Thus, troubled marital relationships could have a greater impact on older adults because of their smaller social networks (Levenson, Carstensen, & Gottman, 1993). In addition, immune function declines with age, particularly functional aspects of the cellular immune response (Murasko, Weiner & Kaye, 1988; Wayne, Rhyne, Garry, & Goodwin, 1990). Finally, age and stress may interact to promote immune downregulation: older adults show greater immunological impairments related to depression than young adults (Schleifer, Keller, Bond, Cohen, & Stein, 1989). Accordingly, the increased depression and distress that are reliably associated with chronically abusive marital relationships (Bothwell & Weissman, 1977; Gotlib & Hooley, 1988) could have a greater physiological impact in older adults. In the next section we review evidence that the severe and lengthy marital changes produced by a spouse's progressive dementia can have important psychological and physiological consequences.

## II. SPOUSAL CAREGIVERS OF ALZHEIMER'S DISEASE PATIENTS

The process of providing care for a spouse with a severe, long-term debilitating illness such as Alzheimer's disease (AD) has been conceptualized as a chronic stressor (Light & Lebowitz, 1989). AD progresses at a unpredictable and uncontrollable rate; the only certainty is that progressive impairments will lead to increasing needs for supportive care. While mild memory impairments may be the only obvious problem in the early stages, the irreversible deterioration of brain tissue eventually culminates in profound cognitive and behavioral changes including disorientation, incontinence, and an inability to provide any self-care. Since the modal survival time after onset ranges from 8 to 20 years, long-term care of AD patients may be conceptualized as a chronic stressor (Fiore et al., 1983).

We assessed changes in depression, immunity, and health in 69 spousal

caregivers who had already been providing care for an average of 5 years and 69 sociodemographically matched control subjects (Kiecolt-Glaser et al., 1991). During the 13-month interval between the initial sample and the follow-up sample, caregivers showed decrements on three measures of cellular immunity relative to controls. Spousal caregivers who reported lower levels of social support at intake and who were most distressed by dementia-related behaviors showed the greatest and most uniformly negative changes in immune function at follow-up (Kiecolt-Glaser et al., 1991). Caregivers also reported that they had experienced more days of infectious illness, primarily upper respiratory tract infections. Caregivers had a substantially greater incidence of depressive disorders than the control subjects, with 25% of caregivers meeting syndromal criteria at baseline compared to no cases among controls, and 32% of caregivers meeting criteria at follow-up, 13 months later, compared to 6% of controls. Caregivers reported fewer important personal relationships than controls, they saw members of their network less frequently, and both closeness and helplessness ratings of the relationships were lower in the former (Kiecolt-Glaser et al., 1991). Those caregivers who reported the lowest levels of social support at baseline and who were most distressed by dementia-related behaviors showed the greatest and most uniformly negative changes in immune function at follow-up.

Other researchers have reported additional immunological differences between spousal caregivers and noncaregivers. McCann (1991) showed that the response to delayed hypersensitivity skin testing was markedly poorer in 34 spousal caregivers than 33 comparable noncaregivers. In fact, compared to normal age and gender standards, 50% of her caregivers were totally or relatively anergic, compared to only 12% of noncaregivers, and these differences were not attributable to health behaviors. Thus, her caregivers differed immunologically not only from the comparison sample, but from age-based norms as well.

Pomara, Deptula, Gallow, LeWirt, and Stanley (1989) found that spousal AD caregivers had higher cerebral spinal fluid GABA concentrations than controls. The authors noted that there is considerable literature suggesting a role for GABAergic systems in anxiety, with acute stressors in animals associated with alterations in GABA concentrations and in the activity of the GABA receptor-gated chloride channel in the brain. In another study of AD spousal caregivers, plasma levels of neuropeptide Y (NPY) were significantly elevated in caregivers compared to nondepressed control subjects, and NPY levels were inversely correlated with NK cell activity (Irwin et al., 1992). NPY is a sympathetic neurotransmitter that is released following emotional stress and may also modulate immunity during stress (Irwin et al., 1992). Thus, data from multiple laboratories show differences in endocrine and immune function between caregivers and controls.

While the stresses of active caregiving are well-documented (Light & Lebowitz, 1989), the end of caregiving does not signal a rapid return to

precaregiving psychological or immunological status. Our longitudinal data suggest that spousal caregivers continue to show higher rates of syndromal depressive disorders and poorer immune function than controls for as long as 3 years after bereavement. We examined changes in depression and social support in three groups: Continuing caregivers, who had been caregiving across a 4-year period ( $n = 98$ ), 49 bereaved caregivers, whose impaired relative died between Years 1 and 4, and 107 control subjects. Although an average of 19.8 months had elapsed since bereavement by Year 4, bereaved and continuing caregivers did not differ on syndromal depression or depressive symptoms; both groups were significantly more depressed than controls. The amount of time since bereavement was unrelated to depression or social support. Those caregivers who continued to ruminate more about caregiving after bereavement reported more depression, greater stress, and greater social isolation. Thus, our data suggest that the distress of family caregivers persists at least several years after the death of the patient.

While data are limited, immune function in bereaved spousal caregivers does not appear to differ from nonbereaved caregivers, while both differ from controls. We examined differences among continuing caregivers, bereaved caregivers and controls in the ability of their lymphokine activated killer (LAK)/NK cells to respond to two cytokines, interleukin-2 (IL-2) and interferon- $\gamma$  (IFN) (Esterling et al., in press). Consistent with caregiver data from Irwin et al. (1992), we found no differences among continuing caregivers, bereaved caregivers, and controls when we evaluated NK lysis without the addition of either cytokine. However, when we examined the response of NK cells to cytokines, we found clear group differences. We found that controls showed significantly greater enhancement in NK lysis than either of the caregiver groups following treatment with IFN- $\gamma$ , while bereaved and continuing caregivers did not differ from each other. Similarly, LAK activity in blood samples from continuing and bereaved caregivers did not differ following addition of IL-2, while controls showed greater enhancement of LAK activity than either of the caregiver groups. Thus, we find persistent immunological downregulation in bereaved caregivers consistent with their continued elevated risk for syndromal depression (& Kiecolt-Glaser, in press). In the final section we consider possible mechanism underlying the persistent physiological differences following chronic or longer-term stressors, and their importance for older adults.

#### IV. THE SEQUELAE OF CHRONIC STRESS: INTERACTIONS AMONG SYMPATHETIC NERVOUS SYSTEM ACTIVITY AND REACTIVITY, ENDOCRINE FUNCTION, AND IMMUNE FUNCTION

Recent studies of the immunological consequences of brief experimental stressors have provided preliminary evidence that individuals who exhibit the largest "sympathetically mediated" increases in cardiovascular reactivity also show the largest catecholaminergic increases and immune

changes (Kiecolt-Glaser et al., 1992; Manuck et al., 1991; Sgoutas-Emch et al., 1994). If sympathetic cardiac activation is a marker or determinant of longer-term changes in immune function, then the cardiovascular, endocrine, and immune changes evoked by brief experimental stressors may help to illuminate the nature of the interactions among these physiological systems. Importantly, preliminary evidence suggests that chronic stress may moderate cardiovascular reactivity, and thus it provides one possible mechanism through which chronic stress could modulate acute endocrine and immune change, as well as (speculatively) longer-term changes.

For example, we found that the chronic stresses of caregiving interacted with social support and age in modulating cardiovascular reactivity (Uchino, Kiecolt-Glaser, & Cacioppo, 1992). We used continuous noninvasive measures to monitor heart rate and blood pressure during a serial subtraction task and a structured interview. Caregivers low in social support displayed age-related increases in heart rate reactivity, while caregivers high in social support showed age-related decreases in heart rate reactivity. In contrast, control subjects who were either low or high in social support did not show comparable age-related heart rate reactivity. Similarly, low social support subjects were characterized by age-related increases in systolic and diastolic blood pressure, without a comparable trend for high social support subjects. As described previously, earlier data from our spousal caregivers in this sample showed that caregivers had poorer immune function than controls, and low social support was associated with greater declines in immune function over the course of a year (Kiecolt-Glaser et al., 1991).

Chronic stress has been implicated as a factor in enhanced cardiovascular reactivity as well as higher levels of urinary catecholamines in two studies from Baum's laboratory (Fleming, Baum, Davidson, Rectanus, & McArdle, 1987; McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989). In addition, cardiovascular measures took longer to return to baseline levels in chronically stressed subjects compared to those of unstressed subjects. In one of their longitudinal studies, Baum and colleagues (McKinnon et al., 1989) compared psychological stress, endocrine function, and immune function in people living near the damaged Three Mile Island (TMI) nuclear power plant with a demographically comparable control group. TMI-area residents and controls had comparable blood pressure in the years before the TMI accident as reflected in records obtained from their physicians. In contrast, blood pressure data collected by the research team several years after the accident showed higher blood pressure in TMI residents compared to controls (Baum, 1990). TMI residents also had more neutrophils and fewer B lymphocytes, T suppressor/cytotoxic lymphocytes, NK cells, and higher antibody titers to latent herpes simplex virus (HSV) than controls. Thus, consistent with the data from caregivers, other chronic stressors also appear to produce longer-term autonomic, immunologic, and endocrinologic alterations.

In further work from our own laboratory, we addressed the importance

of individual variations in SNS activity; we examined whether inter-individual variability on heart rate (HR) reactivity, assessed in a prescreening study, predicted individual differences in cardiovascular, endocrinological, and immunological response to a brief psychological stressor several weeks later. We found that the brief experimental stressor affected cardiovascular, neuroendocrine, and immune responses. Importantly, individuals pre-selected to be very high in HR reactivity (and thus likely differing in both SNS and parasympathetic responsiveness) showed magnified cortisol and NK cell cytotoxicity responses to the stressor (Sgoutas-Emch et al., 1994). Additional data from a second study showed a similar pattern of results, providing further evidence that brief stressors may activate the hypothalamic pituitary adrenocortical system to a greater extent in individuals who are higher in sympathetic cardiac activation (see Cacioppo, 1994). Thus, we can illuminate stressor effects by the addition of autonomic measures that provide a better understanding of individual variations in SNS activity.

Stress-related changes in cardiovascular reactivity and the relationship between cardiovascular reactivity and endocrine and immune function may prove particularly important in older adults. In view of the evidence that SNS activity can inhibit antigen processing and presentation (Heilig, Irwin, Grewal, & Sercarz, 1993), these effects could be quite consequential for older adults.

Consistent with other evidence of immune senescence, many older adults do not respond to vaccines (or other "new" antigens) as efficiently as younger adults (Phair, Kauffmann, Bjornson, Adams, & Linnemann, 1978). Older adults attain lower peak antibody levels following vaccination, and they show more rapid or steeper rates of decline than younger adults (Burns et al., 1990). These age-related immunological decrements are thought to be associated with the greatly increased morbidity and mortality from infectious illness in the elderly. For example, among adults over 75 years of age, pneumonia and influenza together are the fourth leading cause of death (Yoshikawa, 1983). Mortality from influenza is four times greater among people over 60, compared to those younger than 40 (Burns et al., 1990).

Immunological changes may also predict increased morbidity or mortality in subsequent years. A 16-year longitudinal study of 105 healthy elderly men showed that declines in the absolute number of peripheral blood leukocytes (PBLs) were associated with subsequent mortality within 3 years of death when compared to those 5 or 10 years before death (Bender, Nagel, Adler, & Andres, 1986). There was not an association between the decrease in lymphocyte numbers and age at death, smoking status, or prior cardiac illness. Moreover, a 20-year longitudinal study of 273 health adults over 60 showed that poorer skin-test responses were associated with subsequent morbidity and mortality (Wayne et al., 1990). Evaluation of the blastogenic response in 403 older adults with a mean age of 86 showed that

the lymphocytes of 18% did not proliferate in response to three mitogens (Murasko et al., 1988). While the overall mortality of the population for a 2-year period was 15%, negative responders had twice the mortality of positive responders. The major cause of death in both groups was sudden death or a diagnosable cardiovascular-related disease. The authors suggest that decrements in cellular immunity may reflect changes in other systems as well, and may provide one marker of physiological aging.

Although epidemiological studies have established clear linkages between social factors and health (e.g., House et al., 1988), the pathways through which social factors produce these physiological outcomes are not known. We have presented evidence relating hostile marital interactions to alterations in blood pressure, endocrine function, and immune function in young and very healthy couples. We discussed how severe and long-lasting marital disruptions related to a spouse's progressive dementia can produce important psychological and physiological consequences. Recent data from studies of brief experimental stressors have provided preliminary evidence that individuals who exhibit the largest "sympathetically mediated" increase in cardiovascular reactivity also show the largest catecholaminergic actions and immune changes. Because chronic stress has been shown to affect cardiovascular reactivity (Fleming et al., 1987; McKinnon et al., 1989), individuals undergoing chronic stress may show particularly large sympathetic and immunological changes to daily hassles and stressors. Importantly, since infectious illness is the fourth leading cause of mortality among older adults (Yoshikawa, 1983), any further downregulation could have important consequences. Clearly, longitudinal studies that evaluate the relationships among personal relationships, SNS activity and reactivity, stress-related immune and endocrine changes, and longer-term changes in health are warranted to determine whether extrapolations from cross-sectional data on acute events to chronic and longitudinal effects are warranted.

ACKNOWLEDGMENTS

Funding for work reported in this paper was provided by two grants from NIMH (PO1 MH44660 and R37 MH42096), by the GCRC Grant MO1-RR00034 (National Center for Research Resources), and by The Ohio State University Comprehensive Cancer Center Grant CA-16058 from the National Cancer Institute.

REFERENCES

Ader, T., Felten, D. L., & Cohen, N. (Eds). (1991). *Psychoneuroimmunology*. New York: Academic Press.

- Baron, R. W., Currona, C. E., Hicklin, D., Russell, D. W., & Lubartoff, D. M. (1990). Social support and immune function among spouses of cancer patients. *Journal of Personality and Social Psychology*, 59, 344-352.
- Baum, A. (1990). Stress, intrusive imagery, and chronic distress. *Health Psychology*, 9, 653-675.
- Baum, A., Cohen, L., & Hall, M. (1993). Control and intrusive memories as possible determinants of chronic stress. *Psychosomatic Medicine*, 55, 274-286.
- Bender, B. S., Nagel, J. E., Adler, W. H., & Andres, R. (1986). Absolute peripheral blood lymphocyte count and subsequent mortality of elderly men. *Journal of the American Geriatric Society*, 34, 649-654.
- Bernson, E. W. (1989). Prolactin and immune host defenses. *Progress in Neuroendocrinology*, 2, 21-29.
- Bodnar, J., & Kiecolt-Glaser, J. K. Caregiver depression after bereavement: Chronic stress isn't over when it's over. *Psychology and Aging*. (in press).
- Bothwell, S., & Weissman, M. M. (1977). Social impairments four years after an acute depressive episode. *American Journal of Orthopsychiatry*, 47, 231-237.
- Burman, B., & Margolin, G. (1992). Analysis of the association between marital relationships and health problems: An interactional perspective. *Psychological Bulletin*, 112, 39-63.
- Burnett, R. (1987). Reflections in personal relationships. In R. Burnett, P. McGhee, & D. Clarke (Eds.), *Accounting for relationships: Explanation, representation, consciousness* (pp. 102-110). London: Methuen.
- Burns, E. A., Lum, L. G., Seigneuret, M. C., Giddings, B. R., & Goodwin, J. S. (1990). Decreased specific antibody synthesis in old adults: Decreased potency of antigen-specific B cells with aging. *Mechanisms of Ageing and Development*, 53, 229-241.
- Cacioppo, J. T. (1994). Autonomic, neuroendocrinologic and immunologic response to stress, with emphasis on social processes and interindividual variation. *Psychophysiology*, 31, 113-128.
- Carstensen, L. L. (1992). Social and emotional patterns in adulthood: Support for socioemotional selectivity theory. *Psychology of Aging*, 7, 331-338.
- Coyne, J. C., & DeLongis, A. (1986). The role of social relationships in adaptation. *Journal of Consulting Clinical Psychology*, 54, 454-460.
- Dimsdale, J. E., & Moss, J. (1980). Plasma catecholamines in stress and exercise. *Journal of the American Medical Association*, 242, 340-342.
- Dimsdale, J. E., Young, D., Moore, R., & Trauss, H. W. (1987). Do plasma norepinephrine levels reflect behavioral stress? *Psychosomatic Medicine*, 49, 375-382.
- Esterling, B., Kiecolt-Glaser, J., Bodnar, J., & Glaser, R. Chronic stress, social support and persistent alterations in the natural killer cell response to cytokines in older adults. *Health Psychology*. (in press).
- Ewart, C. K., Taylor, C. B., Kraemer, H. C., & Agras, W. S. (1991). High blood pressure and marital discord: Not being nasty matters more than being nice. *Health Psychology*, 10, 155-163.
- Fiore, J., Becker, J., & Coppel, D. B. (1983). Social network interactions: A buffer or a stress? *American Journal of Community Psychology*, 11, 423-439.
- Fleming, I., Baum, A., Davidson, L. M., Rectanus, E., & McArdle, S. (1987). Chronic stress as a factor in physiologic reactivity to challenge. *Health Psychology*, 6, 221-237.
- Floyd, F. J., & Markman, H. J. (1983). Observational biases in spousal observations: Toward a cognitive behavioral model of marriage. *Journal of Consulting and Clinical Psychology*, 51, 450-457.
- Fredrikson, M., Tuomisto, M., & Bergman-Losman, B. (1991). Neuroendocrine and cardiovascular stress reactivity in middle-age normotensive adults with parental history of cardiovascular disease. *Psychophysiology*, 28, 656-664.
- Gaelick, L., Bodenhausen, G. V., & Wyer, R. S. Jr. (1985). Emotional communication in close relationships. *Journal of Personality and Social Psychology*, 49, 1246-1265.
- Glaser, R., & Kiecolt-Glaser, J. K. (1994). Stress-associated immune modulation and its implications for reactivation of latent herpesviruses. In R. Glaser & J. Jones (Eds.), *Human herpesvirus infections*. (pp. 245-270). New York: Dekker.
- Glaser, R., Kiecolt-Glaser, J. K., Bonneau, R., Malarkey, W., & Hughes, J. (1992). Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. *Psychosomatic Medicine*, 54, 22-29.
- Glenn, N. D., & Weaver, C. N. (1981). The contribution of marital happiness to global happiness. *Journal of Marriage and Family*, 43, 161-168.
- Gotlib, I. H., & Hooley, J. M. (1988). Depression and marital functioning: Current status and future directions. In S. Duck (Ed.), *Handbook of personal relationships* (pp. 543-570). Chichester, England: Wiley.
- Gottman, J. M., & Levenson, R. W. (1988). The social psychophysiology of marriage. In P. Noller & M. A. Fitzpatrick (Eds.), *Perspectives on marital interaction* (pp. 182-199). Clevedon, England: Multilingual Matters.
- Gottman, J. M., & Levenson, R. W. (1992). Marital processes predictive of later dissolution: Behavior, physiology, and health. *Journal of Personality and Social Psychology*, 63, 221-233.
- Hagestad, G. O., & Smyer, M. A. (1982). Dissolving long-term relationships: Patterns of divorce in middle age. In S. Duck (Ed.), *Personal Relationships*, 4: *Dissolving relationships* (pp. 115-188). New York: Academic Press.
- Harvey, J. H., Wells, G. L., & Alvarez, M. D. (1978). Attribution in the context of conflict and separation in close relationships. *New directions in attribution research* Vol. 2. (pp. 235-260). Hillsdale, NJ: Erlbaum.
- Heavey, C. L., Layne, C., & Christensen, A. (1993). Gender and conflict structure in marital interaction: A replication and extension. *Journal of Consulting and Clinical Psychology*, 61, 16-27.
- Heilig, M., Irwin, M., Grewal, J., & Sercarz, E. (1993). Sympathetic regulation of t-helper cell function. *Brain, Behavior, and Immunity*, 7, 154-163.
- House, J. S., Landis, K. R., & Umberson, D. (1988). Social relationships and health. *Science*, 241, 540-545.
- Huston, T. L., & Ashmore, R. D. (1986). Women and men in personal relationships. In R. D. Ashmore & F. Del Boca (Eds.), *The social psychology of female-male relations* (pp. 167-210). New York: Academic Press.
- Irwin, M., Daniels, M., Smith, T. L., Bloom, E., & Weiner, H. (1987). Impaired natural killer cell activity during bereavement. *Brain, Behavior, and Immunity*, 1, 98-104.
- Irwin, M., Brown, M., Patterson, T., Hauger, R., Maslovich, A., & Grant, I. (1992). Neuro-peptide Y and natural killer cell activity: Findings in depression and Alzheimer caregiver stress. *FASEB Journal*, 5, 3100-3107.
- Kiecolt-Glaser, J. K., Cacioppo, J. T., Malarkey, W. B., & Glaser, R. (1992). Acute psychological stressors and short-term immune changes: What, why, for whom, and to what extent? *Psychosomatic Medicine*, 54, 680-685.
- Kiecolt-Glaser, J. K., Dura, J. R., Speicher, C. E., Trask, O. J., & Glaser, R. (1991). Spousal caregivers of dementia victims: Longitudinal changes in immunity and health. *Psychosomatic Medicine*, 53, 345-362.
- Kiecolt-Glaser, J. K., Fisher, L., Ogrocki, P., Stout, J. C., Speicher, C. E., & Glaser, R. (1987). Marital quality, marital disruption, and immune function. *Psychosomatic Medicine*, 49, 13-34.
- Kiecolt-Glaser, J. K., Dura, J. R., Speicher, C. E., Trask, O. J., & Glaser, R. (1991). Spousal caregivers of dementia victims: Longitudinal changes in immunity and health. *Psychosomatic Medicine*, 53, 345-362.
- Kiecolt-Glaser, J. K., Garner, W., Speicher, C. E., Penn, G., & Glaser, R. (1984). Psychosocial modifiers of immunocompetence in medical students. *Psychosomatic Medicine*, 46, 7-14.

Renne, K. S. (1971). Health and marital experience in an urban population. *Journal of Marriage and Family*, 23, 338-350.

Ross, M., & Holmberg, D. (1990). Recounting the past: Gender differences in the recall of events in the history of a close relationship. In J. M. Olson & M. P. Zanna (Eds.), *Self-influence processes* (pp. 135-152). Hillsdale, NJ: Erlbaum.

Sher, T. G., & Weiss, R. L. (1991). Negativity in marital communication: Where's the beef? *Behavioral Assessment*, 13, 1-5.

Schleifer, S. J., Keller, S. E., Bond, R. N., Cohen, J., & Stein, M. (1989). Depression and immunity: Role of age, sex, and severity. *Archives of General Psychiatry*, 46, 81-87.

Schleifer, S., Keller, S., & Camerino, M. (1983). Suppression of lymphocyte stimulation following bereavement. *Journal of the American Medical Association*, 250, 374-377.

Spoutas-Emch, S., Cacioppo, J. T., Uchino, B., Malarkey, W. B., Pearl, D., Kiecolt-Glaser, J. K., & Glaser, R. (1994). The effects of an acute psychological stressor on cardiovascular, endocrine, and cellular immune response: A prospective study of individuals high and low in heart rate reactivity. *Psychophysiology*, 31, 264-271.

Smith, T. W., & Christensen, A. J. (1992). Cardiovascular reactivity and interpersonal relations: Psychosomatic processes in social context. *Journal of Social and Clinical Psychology*, 11, 179-301.

Southwick, S. M., Krystal, J. H., Morgan, A., Johnson, D., Nagy, L. M., Nicolaou, A., Heninger, G. R., & Charney, D. S. (1993). Abnormal noradrenergic function in post-traumatic stress disorder. *Archives of General Psychiatry*, 50, 266-274.

Strongy, M. C., David, M. C., & Matthews, K. A. (1987). Sex differences in physiological responses to stress and in coronary heart disease: A causal link? *Psychophysiology*, 24, 127-131.

Storaasli, R. D., & Markman, H. J. (1990). Relational problems in the early stages of marriage: A longitudinal investigation. *Journal of Family Psychology*, 4, 80-98.

Uchino, B. N., Kiecolt-Glaser, J. K., & Cacioppo, J. T. (1992). Age and social support: Effects on cardiovascular functioning in caregivers of relatives with Alzheimer's Disease. *Journal of Personality and Social Psychology*, 63, 839-846.

Verbrugge, L. M. (1979). Marital status and health. *Journal of Marriage and Family*, 41, 267-285.

Wayne, S. J., Rhyme, R. L., Garry, P. J., & Goodwin, J. S. (1990). Cell mediated immunity as a predictor of morbidity and mortality in subjects over sixty. *Journal of Gerontology, Medical Sciences*, 45, M45-M48.

Weiss, R. L., & Summers, K. (1983). The marital interaction coding system III. In E. E. Filsinger (Ed.), *Marriage and family assessment* (pp. 85-115). Beverly Hills, CA: Sage.

Weissman, M. M. (1987). Advances in psychiatric epidemiology: Rates and risks for major depression. *American Journal of Public Health*, 77, 445-451.

Yoshikawa, T. T. (1983). Geriatric infectious diseases: An emerging problem. *Journal of the American Geriatrics Society*, 31, 34-39.

Kiecolt-Glaser, J. K., & Glaser, R. (1988). Methodological issues in behavioral immunology research with humans. *Brain, Behavior, and Immunity*, 2, 67-78.

Kiecolt-Glaser, J. K., & Glaser, R. (1992). Psychoneuroimmunology: Can psychological interventions modulate immunity? *Journal of Consulting and Clinical Psychology*, 60, 569-575.

Kiecolt-Glaser, J. K., Kennedy, S., Malkoff, S., Fisher, L., Speicher, C. E., & Glaser, R. (1988). Marital discord and immunity in males. *Psychosomatic Medicine*, 50, 213-229.

Kiecolt-Glaser, J. K., Malarkey, W. B., Chee, M., Newton, T., Cacioppo, J. T., Mao, H., & Glaser, R. (1993). Negative behavior during marital conflict is associated with immunological down-regulation. *Psychosomatic Medicine*, 55, 395-409.

Kitson, C. G. (1982). Attachment to the spouse in divorce: A scale and its application. *Journal of Marriage and Family*, 44, 379-393.

Levenson, R. W., Carstensen, L. L., & Gottman, J. M. (1993). Long-term marriage: Age, gender, and satisfaction. *Psychology and Aging*, 2, 301-313.

Levenson, R. W., & Gottman, J. M. (1983). Marital interaction: Physiological linkage and affective exchange. *Journal of Personality and Social Psychology*, 45, 587-597.

Light, E., & Lebowitz, B. D. (1989). *Alzheimer's Disease treatment and family stress: Directions for research*. Rockville, MD: National Institute of Mental Health.

Malarkey, W., Kiecolt-Glaser, J. K., Pearl, D., & Glaser, R. (1994). Hostile behavior during marital conflict alters pituitary and adrenal hormones. *Psychosomatic Medicine*, 56, 41-51.

Manuck, S. G., Cohen, S., Rabin, B. S., Muldoon, M. F., & Bachen, E. A. (1991). Individual differences in cellular immune response to stress. *Psychological Sciences*, 2, 111-115.

Margolin, G., Burman, B., & John, R. S. (1989). Home observations of married couples reenacting naturalistic conflicts. *Behavioral Assessment*, 11, 101-118.

Markman, H. J. (1991). Constructive marital conflict is NOT an oxymoron. *Behavioral Assessment*, 13, 83-96.

McCann, J. J. (1991). Effects of stress on spouse caregivers' psychological health and cellular immunity. Unpublished dissertation, Rush University College of Nursing, Chicago, IL.

McKinnon, W., Weisse, C. S., Reynolds, C. P., Bowles, C. A., & Baum, A. (1989). Chronic stress, leukocyte subpopulations, and humoral response to latent viruses. *Health Psychology*, 8, 389-402.

Morell, J. A., & Apple, R. F. (1990). Affect expression, marital satisfaction, and stress reactivity among premenopausal women during a conflictual marital discussion. *Psychology of Women Quarterly*, 14, 387-402.

Murasko, D. M., Weiner, P., & Kaye, D. (1988). Association of lack of mitogen-induced lymphocyte proliferation with increased mortality in the elderly. *Aging: Immunology and Infectious Disease*, 1, 1-6.

Noller, P., & Fitzpatrick, M. A. (1990). Marital communication in the eighties. *Journal of Marriage and Family*, 52, 832-843.

Notarius, C., Benson, S., Sloane, D., Vanzetti, N., & Hornyak, L. (1989). Exploring the interface between perception and behavior: An analysis of marital interaction in distressed and nondistressed couples. *Behavioral Assessment*, 11, 39-64.

Oleshansky, M. A., & Meyerhoff, J. L. (1992). Acute catecholaminergic responses to mental and physical stressors in man. *Stress Medicine*, 8, 175-179.

Phair, J., Kauffmann, C. A., Bjornson, A., Adams, L., & Linnemann, C. (1978). Failure to respond to influenza vaccine in the aged: Correlation with B-cell number and function. *Journal of Laboratory and Clinical Medicine*, 92, 822-828.

Pomara, N., Deptula, D., Galloway, M. P., LeWitt, P. A., & Stanley, M. (1989). CSF GABA in caregiver-spouses of Alzheimer's patients. *American Journal of Psychiatry*, 146, 787-788.

Rabin, B. S., Cohen, S., Ganguli, R., Lysle, D. T., & Cunnick, J. E. (1989). Bidirectional interaction between the central nervous system and the immune system. *Critical Reviews in Immunology*, 9, 279-312.