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Cellular Immune Responses to Acute Stress in Female Caregivers of Dementia Patients and Matched Controls

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This study investigated whether the stress of caregiving alters cellular immune responses to acute psychological stressors. Twenty-seven women caring for a spouse with a progressive dementia (high chronic stress) and 37 controls matched for age and family income performed a 12-min laboratory stressor. Cellular immune function was assessed by both functional and quantitative measures taken before (low acute stress), immediately after (high acute stress), and 30 min after (recovery from stress) exposure to the laboratory stressors. The laboratory challenges were associated with diminished proliferative responses but elevated natural killer (NK) cell cytotoxicity; however, subsequent analyses suggested that this elevated cytotoxicity was largely attributable to an increase in the number of NK cells in peripheral blood. The results suggest that although the stress of caregiving diminishes cellular immune function, caregiving appears to have little effect on cellular immune responses to or recovery from brief psychological challenges.

Key words: caregivers, chronic stress, cellular immunity, psychological stressors

Prior studies have compared the psychological and physiological responses of caregivers of relatives with Alzheimer's disease (AD) with those of age and sociometrically matched controls. Relatives who provide long-term care for a patient with AD report high levels of stress and dysphoria (e.g., George & Gwyther, 1986; Haley, Levine, Brown, Berry, & Hughes, 1987; Haley & Pardo, 1989) and clinical depression (Eisdorfer, Kennedy, Wisnieski, & Cohen, 1983; Kiecolt-Glaser, Malarkey, Cacioppo, & Glaser, 1994) as they attempt to cope with patients' difficult behavior.

Caring for a spouse with AD can be stressful for a number of reasons. Seeing the deterioration of a loved one, dealing with the patient's difficult behavior, and struggling with the financial burdens often posed by the patient's treatment may all contribute to the caregiver's perception of stress. Indeed, research has shown how multidimensional the process of caregiving for a loved one with AD can be. For instance, Walker, Pomeroy, McNeil, and Franklin (1994) discussed the "anticipatory grief" that is often present for caregivers, and the caregiving process is frequently described in terms of stages and themes that can include loss of the relationship, expectancy of death, and postdeath relief (Collins, Liken, King, & Kokinakis, 1993; Jones & Martinson, 1992).

The varied stages of caregiving suggest that the stress a caregiver experiences may change over time. For instance, many of the sources of stress are no longer present once the AD patient dies and the caregiver no longer needs to worry about the amount of time that caregiving takes or the patient's difficult behavior and suffering. The absence of these aspects of caregiving could result in fewer difficulties for bereaved caregivers. However, previous research focusing primarily on depression has shown that bereaved caregivers are often no better off than their active counterparts. For instance, Bodnar and Kiecolt-Glaser (1994) found that bereaved and active caregivers did not differ in terms of syndromal depression or depressive symptoms. Similarly, Collins et al. (1993) found no difference between the

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depression of active caregivers and that of bereaved caregivers. Thus, although the extant evidence supports the idea that there are many components that can contribute to the stress caregivers experience, it is not clear that the death of the AD patient has the effect of "lightening the load."

The chronic stress of caregiving for a relative with AD also has immunological consequences. Kiecolt-Glaser, Dura, Speicher, Trask, and Glaser (1991) found poorer proliferative responses of peripheral blood leukocytes (PBLs) to two mitogens in caregivers than controls; McCann (1991) found much poorer responses to delayed hypersensitivity skin testing in spousal caregivers of AD patients than in noncaregivers; and Esterling, Kiecolt-Glaser, Bodnar, and Glaser (1994) found a lower response of natural killer (NK) cells in PBLs to two cytokines that stimulate NK cell lysis, gamma-interferon and interleukin-2, in AD caregivers than in controls.

Caregivers of relatives with AD have also been characterized by an impaired immune response to influenza virus vaccination relative to matched controls (Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996). Specifically, caregivers were less likely to show a satisfactory increase in antibody titers 4 weeks after vaccination, they had lower in vitro interleukin-1β responses, and their PBLs produced less interleukin-2 in response to stimulation with influenza virus proteins. Because respiratory and viral infections remain a major cause of morbidity and mortality among older adults (McGlone & Arden, 1987), these differences in immune response to influenza virus vaccination may be significant. The health consequences of the stress also extend beyond infectious diseases; caregivers of relatives with AD have shown impaired wound healing relative to controls matched for age and family income (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995). Taken together, these studies offer substantial evidence of the deleterious effects of caregiving on overall psychological health and cellular immune functioning.

Acute stress has also been shown to have an impact on psychological state and cellular immune response. For instance, the cumulative evidence suggests that proliferative responses to mitogens are diminished but that NK cell cytotoxicity is enhanced in response to brief laboratory stressors (e.g., Cacioppo et al., 1995; Keast, Cameron, & Morton, 1988; Landmann et al., 1984; Manuck, Cohen, Rabin, Muldoon, & Bachen, 1991; Naliboff et al., 1991; Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Despite the plethora of research on the effects of caregiving stress and of brief psychological stressors, no prior study, to our knowledge, has investigated the combined effects of these two types of stress on cellular immune response.

In a possibly related study, Benschop et al. (1994) hypothesized that individuals experiencing high stress in their daily life would react differently to a new, acute stressful situation than individuals reporting low stress levels. Levels of chronic stress were operationalized in a study of male high school teachers (M age = 40.5 years) who reported experiencing either few (low chronic stress) or many (high chronic stress) daily hassles. Half of these individuals spent 30 min working on a partially insolvable three-dimensional puzzle and explaining their solution to a confederate (high acute stress), whereas half spent the same time reading popular magazines (low acute stress). Benschop et al. (1994) found no differences in endocrine or in the cellular immune measures studied in high and low stress groups at baseline, nor did the acute stressor have a differential effect on the autonomic responses, endocrine responses, or proliferative responses of PBLs to mitogens in these groups. Analyses of PBL subsets, however, revealed differences in the percentage of NK and T cells in PBLs obtained from the low and high chronic stress groups, with the former group showing larger increases in percentage of NK and T cells after exposure to the acute psychological stressor.

The present study was designed to investigate how caregiving might affect reactions to brief laboratory stressors reminiscent of those encountered in daily life. Specifically, the effects of brief laboratory stressors on quantitative and functional measures of cellular immunity, in caregivers and category-matched controls, were investigated in the present study to determine whether the chronic stress of caregiving altered cellular immune responses to acute stressors.

Method

Caregivers (n = 27) and noncaregiver controls (n = 37) served as participants (M age = 67.17 years, SEM = 1.03). Caregivers and controls did not differ in terms of age, income, height, weight, body mass index, or racial composition ($Fs < 1$). Twenty-one of the controls were married, 9 were widowed, and 7 were divorced or single. Eighteen of the caregivers were married, and the others were bereaved (mean time since bereavement: 32.2 months). Participants in the current study were a subset of those included in a long-term study of the effects of caregiving on health, in which multiple psychosocial questionnaires were administered. As a means of providing as representative a sample of primary caregivers as possible, spousal caregivers for the long-term study have been recruited from a variety of sources, including three local dementia evaluation centers in area hospitals, neurologists' referrals, the city's AD and Related Disorders Association support groups and the association's monthly newsletter, respite care programs, and governmental caregiver support programs. Because women are more likely than men to be caregivers for AD patients, all participants in the current study were women. To ensure that the physiological measures of interest were not obscured by physical conditions such as medication or diseases that compromise immune function, we specified the following inclusion criteria: (a) no history of chronic illness of an immunological or endocrinological nature; (b) no diabetes; (c) no history of cancer within the previous 5 years; (d) no use of beta blockers or calcium channel blockers; (e) less than 10 hr of exercise per week on average; (f) average consumption of fewer than 10 alcoholic beverages per week; and (g) no math, speech, or needle phobia. It was also required that participants be postmenopausal. Participants were asked to refrain from ingesting anti-inflammatory agents, antihistamines, or alcohol during the 24 hr preceding the test day.

All participants were tested at approximately the same time in the morning. A 20 gauge in-dwelling catheter was inserted into an antecubital vein. To allow adaptation to the lab, participants were placed in a supine position, given an innocuous set of questionnaires on which to work for approximately 20 min, and subse-

quently asked to relax for 10 min. After this adaptation period, participants were seated and instructed to relax for 6 min. After this prestress period, participants were exposed to a pair of experimental stressors that required active coping (math and speech, order counterbalanced), as described in Cacioppo et al. (1995). Each stressor lasted 6 min and was designed to bring about feelings of anxiety, nervousness, and frustration. These brief stressors were designed to be representative of the acute psychological stressors individuals encounter in their daily lives. As has been shown in our previous research, preliminary analyses of the current data revealed that responses did not vary as a function of type of stressor. Therefore, subsequent analyses collapsed across stressors to increase reliability (see review by Cacioppo, 1994).

A blood sample was collected at the beginning of the baseline period (after a 30-min habituation period; prestress period), a second blood sample was collected immediately after exposure to the stressors (poststress period), and a third sample was collected 30 min later (recovery period) for immune assays. Complete blood counts and differentials were conducted on each blood sample by the Clinical Immunology Laboratory at Ohio State University Hospital. Mononuclear cells were obtained from 30-ml heparinized blood on Histopaque-1077 (Sigma Chemical Co., St. Louis, MO) density gradients, washed twice with magnesium-free and calcium-free phosphate-buffered saline, and counted. The percentages of T lymphocytes (CD3+), two subsets of T lymphocytes (CD4+ and CD8+), and NK cells (CD56+) were determined via monoclonal antibodies (Coulter) and fluorescence activated cell sorter (FACS) analyses according to routine procedures (Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986).

NK cell cytotoxicity was measured by incubation of various concentrations of PBLs with ^{51}Cr-labeled K-562 target cells, as previously described (Glaser et al., 1986). Briefly, mononuclear cells were prepared at 75:1, 37.5:1, and 18.75:1 effector-to-target (E:T) cell ratios and were seeded in triplicate in 96-well microtiter plates (Costar Corp., Pleasanton, CA). Additional wells that contained only labeled target cells (K-562) in medium or target cells in medium that contained 5% sodium dodecyl sulfate were used to determine spontaneous and maximal release of radioactivity, respectively. Plates were incubated for 5 hr in a 5% CO_2 atmosphere at 37 °C, and supernatants were harvested. Activity was determined by the release of ^{51}Cr into the supernatant, which was measured with a Beckman 9000 gamma counter. NK cell cytotoxicity responses were largest at the 75:1 E:T cell ratio, so analyses were performed on this ratio. (Analyses of the 37.5:1 and 18.75:1 E:T ratios produced responses that were consistent but muted relative to the responses to the 75:1 E:T ratio.)

Mitogen-stimulated PBL activity was assessed via the Cell Titer 96 aqueous nonradioactive cell proliferation assay (Promega), which determines the number of viable proliferating cells by colorimetry and results in data comparable with those obtained through radioactive isotope incorporation procedures (Gieni, Li, & HayGlass, 1995; Shobitz, 1994). The assay is based on the conversion of the tetrazolium salt 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxphenyl)-2-(4-sulforphenyl)-2H-tetrazolium (MTS) into a formazan that is soluble in tissue culture medium. MTS is converted into the aqueous soluble formazan by dehydrogenase enzymes found in metabolically active cells. The quantity of formazan product—and thus the amount of 490 nm absorbance—is directly proportional to the number of living cells in culture. Optical density (OD) is measured at 490 nm directly from a 96-well plate without additional processing.

We used 96-well plates to set up samples in triplicate, with concanavalin A (Con A; Sigma) and phytohemagglutinin (PHA; Sigma) at final concentrations of 10.0 μg/ml, 5.0 μg/ml, and 2.5 μg/ml. Fifty microliters of sample cells from a stock solution of a concentration of 1×10^6 cells per milliliter, in RPMI-1640 medium supplemented with 5% fetal bovine serum, was added to 50 μl of each mitogen dilution and a media control. The plates were incubated in an atmosphere of 5% CO_2 at 37 °C, with humidity, for approximately 68 hr. After incubation, 20 ml of a 20:1 solution of MTS–phenazine methosulfate was added to the plates. The plates were then incubated for an additional 4 hr, after which OD was recorded via a Titertek Multiscan MCC plate reader. The background absorbance of the plate was removed by using a reference wavelength of 650 nm, per the manufacturer's suggestion. Analyses were performed on values averaged across concentration levels.

The degrees of freedom in all analyses were adjusted for measures in which technical problems resulted in incomplete data. The effects of the psychological stressors were evaluated via repeated measures analyses of variance (ANOVAs) with three levels for period (baseline, poststressor, and recovery) and two levels for group (caregiver and control). To avoid problems associated with possible violations of sphericity, we evaluated the statistical significance of the repeated measures F ratios based on degrees of freedom that were corrected according to the Huynh–Feldt epsilon.

Results

Three aspects of cellular immune function—blastogenic responses to Con A and PHA and NK cell cytotoxicity—were assessed in blood drawn before (low acute stress) and immediately after (high acute stress) exposure to the laboratory stressor. The chronic stress of caregiving was associated with a diminished proliferative response to Con A, $F(1, 61) = 5.91, p < .02$ (caregivers, M OD = 0.104; controls, M OD = 0.151), and a nonsignificantly diminished proliferative response to PHA, $F(1, 61) = 1.81$ (caregivers, M OD = 0.221; controls, M OD = 0.255). In addition, caregivers were characterized by a lower percentage of NK cell cytotoxicity, $F(1, 58) = 4.45$, $p < .04$ (caregivers, $M = 54.88\%$; controls, $M = 64.51\%$).

The brief psychological stressor had effects on the blastogenic responses, evident immediately and 30 min after exposure to the stressor, that were directionally similar to the chronic stress of caregiving (see Figure 1, top and middle panels). The laboratory stressor decreased the blastogenic responses to Con A, $F(2, 122) = 3.23, p < .05, \epsilon = .91$, and to PHA, $F(2, 122) = 3.51$, $p < .04$, $\epsilon = .97$. Pairwise comparisons further revealed that, relative to baseline, proliferative responses to Con A and to PHA were lower both immediately and 30 min after exposure to the brief laboratory stressor ($ps < .04$); poststress and recovery response levels did not differ from each other ($p > .5$).

The effects of the acute stressor on percentage of NK cell cytotoxicity differed in direction from the effects of the chronic stress of caregiving (see Figure 1, bottom panel). The brief psychological stressor increased percentage of NK cell cytotoxicity, $F(2, 116) = 7.87, p < .005, \epsilon = .58$, and pairwise comparisons revealed that, relative to baseline, percentage of NK cell cytotoxicity was elevated immediately after exposure to the stressor ($p < .006$) and returned to basal levels within 30 min ($p > .3$; see Table 1).

Differences in NK cell trafficking may help to explain the differential effects of chronic and acute stress on NK cell cytotoxicity. Analyses, for instance, revealed that the acute

psychological stressor altered the percentage of NK cells, $F(2, 116) = 19.58$, $p < .001$, $\epsilon = .87$, in peripheral blood (see Table 1). Pairwise comparisons confirmed that the percentage of NK cells was higher immediately after exposure to the stressor than at prestressor ($ps < .0003$) or recovery ($ps < .0001$). Percentage of NK cells at recovery dipped below prestress levels ($p < .05$). Absolute number of NK cells showed a pattern similar to that of the percentage of NK cells. Pairwise comparisons again revealed that the number of NK cells was higher immediately after exposure to the stressor than at prestressor ($ps < .0001$) or recovery ($ps < .0001$). In contrast to the percentage of NK cells, however, the number of NK cells at recovery was comparable to prestress levels.

When NK cell cytotoxicity was analyzed after equating for the number of NK cells in the PBL sample, the elevation

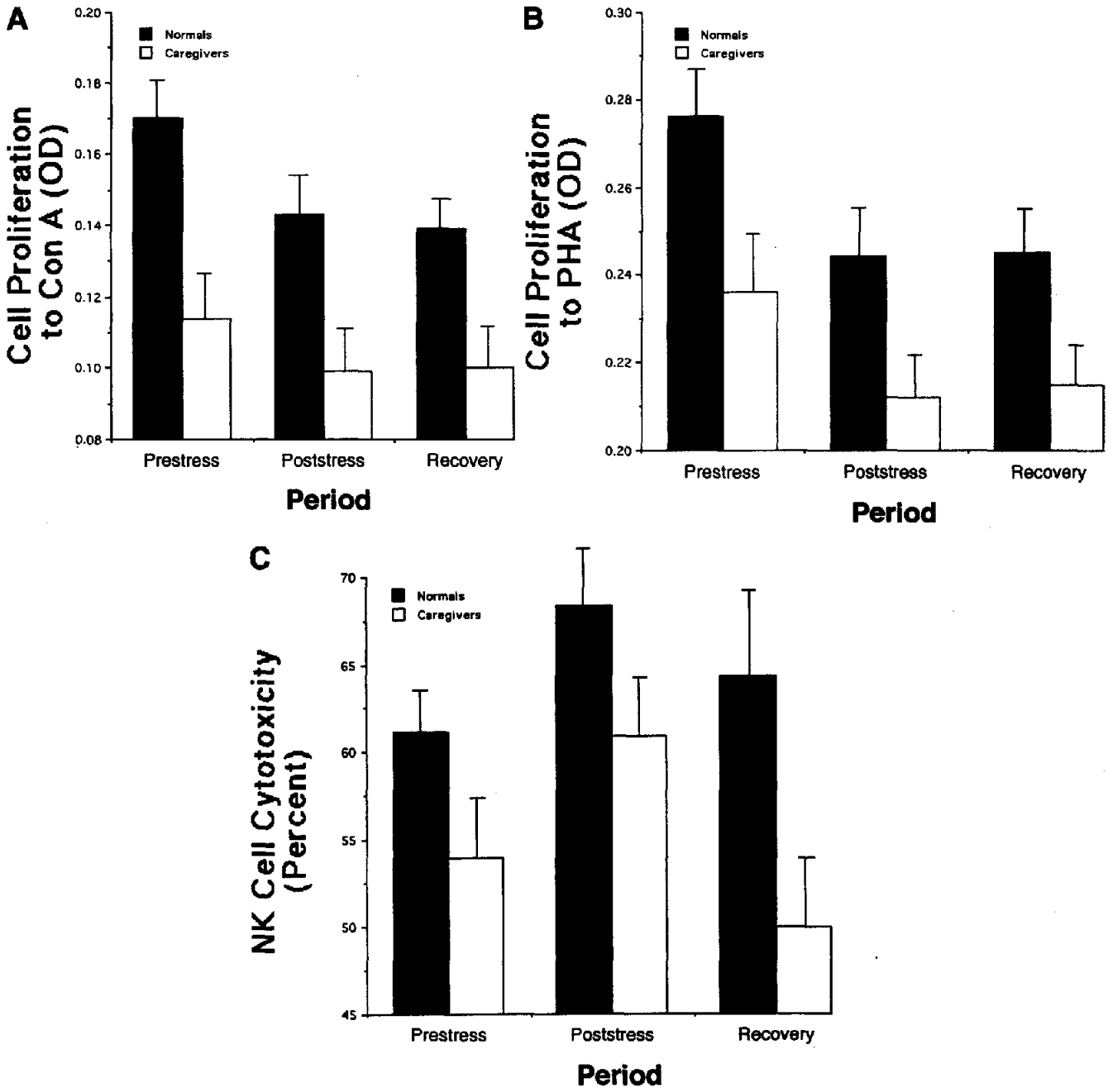

Figure 1. Mean responses as a function of caregiver status and brief psychological stressor. A: Cell proliferation to concanavalin A (Con A) at OD at 490 nm. B: Cell proliferation to phytohemagglutinin (PHA) at OD at 490 nm. C: Percentage of natural killer (NK) cell cytotoxicity. Bars represent standard errors. OD = optical density.

in NK cell cytotoxicity after exposure to the acute stressor was eliminated ($p > .15$). For instance, a repeated measures ANOVA on residualized scores for percentage of NK cell cytotoxicity (regressing on the number of NK cells from the corresponding period) indicated that the previously significant effect for period did not approach statistical significance, $F(2, 52) = 1.29, p > .25$.

Despite the significant impact of caregiving stress and acute stress on the assays, there was no evidence that caregiving altered responses to the acute psychological stressor. Indeed, none of the Group × Period interactions approached statistical significance ($ps > .10$). As can be seen in Figure 1, for instance, the effects of the acute stressor and recovery from the acute stressor appeared comparable for caregivers and controls.

Analyses of the quantitative measures of T cells yielded similar results regarding reactions to the laboratory stressor. As summarized in Table 1, the brief psychological stressor decreased total T-lymphocyte percentages (CD3+), $F(2, 118) = 44.05, p < .001, \epsilon = .83$; decreased helper–inducer T-cell percentages (CD4+), $F(2, 116) = 45.95, p < .001, \epsilon = .88$; increased suppressor–cytotoxic (CD8+) T cells, $F(2, 116) = 22.92, p < .001, \epsilon = .73$; and lowered the ratio of circulating helper to suppressor–cytotoxic T cells (CD4+/CD8+), $F(2, 116) = 27.55, p < .001, \epsilon = .82$. Neither any main effect for group nor any Group × Period interaction approached statistical significance, however. Furthermore, each of these percentages had returned to baseline levels by recovery, with the exception of NK cells (percentages were lower at recovery than baseline; see Table 1).

Analyses of some of the absolute numbers of T cells revealed patterns that were similar to the patterns of the percentages. Specifically, pairwise comparisons confirmed that the number of CD8+ cells was higher immediately after exposure to the stressor than at prestressor ($p < .0001$) or recovery ($ps < .0003$). The number of CD8+ cells had returned to prestress levels by the recovery period. Analyses of the absolute numbers of other T-cell subsets showed patterns that were somewhat different from the patterns shown by the percentage analyses. Although the percentage of CD3+ cells decreased after exposure to the stressor, the number of CD3+ cells increased in response to the stressor ($ps < .04$). Similarly, the percentage of CD4+ cells decreased in response to the stressor, whereas the number of CD4+ cells showed a nonsignificant increase ($ps > .18$).

Discussion

Consistent with prior research showing that long-term caregiving for a spouse with AD is associated with poorer proliferative responses to mitogens and diminished NK cell activity (cf. Glaser & Kiecolt-Glaser, 1994), caregivers in the present study were characterized by poorer proliferative responses to Con A and PHA relative to matched controls (see Figure 1, top and middle panels). Furthermore, the brief laboratory stressor used in the present study evoked significant changes in quantitative and functional measures of cellular immunity similar to those observed in prior research (see Table 1). Despite the apparent main effects of these factors on cellular immunity, no evidence was found to suggest that the chronic stress of caregiving altered the participants' responses to or recovery from the acute psychological stressors.

Paralleling our observations, Benschop et al. (1994) found no reactivity differences in their low and high stress groups in terms of autonomic, neuroendocrine, or proliferative responses to acute stressors. There are also differences between the two studies, however. As in prior research (e.g.,

Table 1
Subpopulations of Leukocytes in Spousal Caregivers and Controls as a Function of Acute Psychological Stressor

Measure	Baseline	Poststressor	Recovery
NK cells***			
Mean % ± *SEM*	$15.47 \pm 1.52_a$	$19.84 \pm 1.46_b$	$13.04 \pm 0.99_c$
Mean cell no.[a] ± *SEM*	$239.07 \pm 21.28_a$	$388.01 \pm 31.22_b$	$248.05 \pm 21.28_a$
CD3+ T cells***			
Mean % ± *SEM*	$75.14 \pm 0.90_a$	$71.34 \pm 1.19_b$	$76.90 \pm 0.85_c$
Mean cell no.[a] ± *SEM*	$1{,}338.22 \pm 60.90_a$	$1{,}445.82 \pm 72.73_b$	$1{,}524.16 \pm 76.69_b$
CD4+ T cells***			
Mean % ± *SEM*	$55.59 \pm 1.23_a$	$51.31 \pm 1.31_b$	$56.71 \pm 1.16_a$
Mean cell no.[a] ± *SEM*	$990.38 \pm 45.60_a$	$1{,}040.43 \pm 53.01_a$	$1{,}132.59 \pm 59.45_b$
CD8+ T cells***			
Mean % ± *SEM*	$22.16 \pm 1.04_a$	$24.43 \pm 1.10_b$	$22.17 \pm 1.01_a$
Mean cell no.[a] ± *SEM*	$395.47 \pm 32.86_a$	$500.01 \pm 41.85_b$	$434.45 \pm 30.89_a$
Mean % CD4+/CD8+ T cells*** ± *SEM*	$2.96 \pm 0.19_a$	$2.46 \pm 0.15_b$	$2.97 \pm 0.18_a$
Mean Con A* ± *SEM*[b]	$0.15 \pm 0.012_a$	$0.12 \pm 0.01_b$	$0.12 \pm 0.01_b$
Mean PHA* ± *SEM*[b]	$0.26 \pm 0.014_a$	$0.23 \pm 0.012_b$	$0.23 \pm 0.01_b$
Mean % NK cytotoxicity** ± *SEM*	$57.99 \pm 2.12_a$	$65.01 \pm 2.10_b$	$58.01 \pm 3.42_a$

Note. Means with different subscripts are significantly different at $p < .05$ or less. NK = natural killer; Con A = concanavalin A; PHA = phytohemagglutinin.
[a]per ml. [b]Expressed as optical density at 490 nm.
*$p < .05$. **$p < .01$. ***$p < .001$.

Kiecolt-Glaser et al., 1991, 1994; Schulz et al., 1997), we found that caregivers were characterized by poorer cellular immunity than matched controls. In contrast, Benschop et al. (1994) found that teachers who reported relatively high versus low levels of daily hassles did not differ in their basal cellular immunity. Benschop et al. (1994) did find that teachers who reported relatively low levels of daily stressors showed larger NK and T-cell responses to the laboratory stressor, as indexed by cell numbers. The chronic stress of caregiving and the stress of frequent daily hassles, therefore, should not be treated as equivalent in terms of their impact on cellular immunity.

Effect sizes in the present study further indicated that the magnitude of immune changes associated with caregiving is similar to the magnitude of immune changes due to acute psychological stressors. The chronic stress of caregiving was associated with effect sizes (Cohen's *d*) of .49 for percentage of NK cell cytotoxicity, .32 for NK cell numbers, .48 for proliferation of PBLs to Con A, and .29 for proliferation of PBLs to PHA, whereas our brief laboratory stressor produced effect sizes of .43 for percentage of NK cell cytotoxicity, .47 for NK cell numbers, .23 for proliferation of PBLs to Con A, and .24 for proliferation of PBLs to PHA. Interestingly, although caregiving and acute stress had differential effects on NK cell cytotoxicity, the magnitude of these effects was comparable. This result should be considered tentative, however, because the use of different chronic or acute stressors may yield quite different effect sizes. Whether the similarity in effect sizes reflects the operation of negative feedback mechanisms in the body that constrain the magnitude of the responses to stressors or reflects the particular laboratory stressors used in this study is a matter for future research. Fortunately, the effect-size statistic allows comparisons of this sort to be made.

Differences in the temporal dynamics of immune responses to the chronic stress of caregiving and to the acute laboratory stressor were also evident on the immune measures. Lymphocyte proliferation in response to mitogens tended to be depressed by both chronic and acute stress, and this reduced functional capacity was still evident 30 min after the participants' exposure to the laboratory stressors. Percentage of NK cell cytotoxicity, in contrast, was uniformly depressed as a function of the chronic stress of caregiving but was transiently elevated after exposure to the laboratory stressor. Studies of the effects of physical exercise have also demonstrated increased NK cell numbers and activity followed by a decrease after exercise (e.g., Fiatarone et al., 1989; Nieman et al., 1991; Pedersen et al., 1988; Schedlowski et al., 1993). These and related studies suggest that one important mechanism underlying the effect of acute stressors on NK cell activity is the quick mobilization of NK cells from marginal pools in the spleen and lung (cf. Keast et al., 1988).

The caregivers and controls who participated in this study may not be entirely representative of the population of elderly women. We constituted as representative a sample as possible, establishing exclusionary criteria based only on factors that could bias the measures of interest. To the extent that caregivers tend to be less healthy as a group than controls (Schulz et al., 1997), the sample in this study may be healthier than the population of elderly women generally and caregivers of spouses with AD in particular. Therefore, it is important to use caution in generalizing these results to all caregivers or to all elderly people. To the extent that our sample is representative of caregivers and other chronically stressed individuals, however, the results of the current study may provide a bit of good news for caregivers. Although there are negative immunological consequences associated with the chronic stress of caregiving, caregivers' phasic cellular immune responses to the hassles and stresses they encounter during the course of daily life appear similar to those shown by noncaregivers.

The mean reactivity and temporal dynamics and recovery of cellular immune responses to an acute stressor also appeared to be similar for caregivers and controls. This result appears to be at odds with results reported by Pike et al. (1997), who examined physiological and psychological responses to an acute laboratory stressor as a function of chronic life stress. Pike et al. used a median split to compare the reactions of 11 men who reported low levels of life stress with the reactions of 12 men who reported relatively high levels of life stress. The acute stressor induced subjective distress; increases in circulating catecholamines, β-endorphin, adrenocorticotropic hormone (ACTH) and cortisol; and a selective redistribution of NK cells into the peripheral blood. More interestingly, results showed that the high-stress group showed greater subjective distress, higher peak levels of epinephrine, lower peak levels of β-endorphin and NK cell lysis, greater redistribution of NK cells, and a more protracted diminution of NK cell lysis in response to the acute stressor than the low-stress group.

Although these results are intriguing, several differences in the Pike et al. (1997) study and the present research warrant note. First, the sources of chronic stress were quite different in the two studies, with chronic stress in the present study stemming from caregiving for a spouse with dementia. Chronic stress in the Pike et al. study ranged from caregiving for an ill relative and executive job loss with complications to simple changes in finances and fleeting conflicts with roommates. Second, participants in neither study were assigned randomly to high and low chronic stress conditions, but personality processes (and attendant participant selection) may play a less important role in caregiving for a spouse who unexpectedly developed a dementia than in life stressors more generally. To what extent individual differences in neuroticism, hostility, or the like contributed to the results of these studies warrants consideration. Pike et al. also reported results from a sample that was less than half the size of ours. Furthermore, their study may have generalizability concerns. Of the 52 volunteers they recruited, 28 were excluded for various reasons such as medication use and medical status.

These differences should not mask the conceptual similarities in the outcomes of the two studies, however. In both studies, for instance, acute and chronic stressors were associated with changes in NK cell distribution and cytotox-

icity. These studies are in agreement, therefore, on the potential significance of psychological factors in research on immune function and point to the importance in future research of paying special attention to the nature of stressors and the possible role of individual differences.

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