Chronic Stress and Immunity in Family Caregivers of Alzheimer's Disease Victims

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Although acute stress has been associated with transient immunosuppression, little is known about the immunologic consequences of chronic stress in humans. In order to investigate possible health-related consequences of a long-term stressor, we obtained blood samples for immunologic and nutritional analyses and psychologic data from 34 family caregivers of Alzheimer's disease (AD) victims and 34 sociodemographically matched comparison subjects. Family caregivers for AD victims were more distressed than comparison subjects without similar responsibilities. Greater impairment in the AD victim was associated with greater distress and loneliness in caregivers. Caregivers had significantly lower percentages of total T lymphocytes and helper T lymphocytes than did comparison subjects, as well as significantly lower helper–suppressor cell ratios; caregivers also had significantly higher antibody titers to Epstein–Barr virus than did comparison subjects, presumably reflecting poorer cellular immune system control of the latent virus in caregivers. The percentages of natural killer cells and suppressor T lymphocytes did not differ significantly. These data suggest that chronically stressed AD family caregivers do not show immunologic or psychologic adaptation to the level of their well-matched age peers.

There is good evidence that acute stressful events are associated with adverse immunologic changes in humans (1, 2). Even relatively commonplace events like academic examinations have been linked to transient changes in immunity; data from blood samples taken during examinations show poorer cellular immunity than those taken 1 month to 6 weeks earlier, when students were less distressed (3–7). In addition, individuals undergoing major novel stressful life changes such as marital separation and divorce have a poorer proliferative response than well-matched comparison subjects (8); bereaved spouses show poorer mitogen responsiveness after the death of a spouse than before (9).

There is some evidence from rodent studies suggesting that the chronicity of the stressor mediates both immunologic responses and tumor development. Data from one rodent study by Monjan and Collector (10) suggested that chronic stress might lead to an enhancement of immune function. Using daily high-intensity intermittent noise, they found that the acute or short-term consequence of the auditory stressor was immunosuppression, while more chronic stress appeared to result in enhanced mitogen responsiveness. Simi-

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larly, Sklar and Anisman (11) found that tumor size and survival were adversely affected by a single session of inescapable shock in mice injected with a tumor. However, mice that underwent ten daily shock sessions had tumor areas that were significantly less than those of controls, and survival times approximated those of the controls.

Although these data suggest that there may be adaptation or even enhancement of immunity in response to a more chronic stressor, there are problems in extrapolating from research with rodents to humans. In particular, adaptation may be different because the nature of the stressor is quite different; physical stressors like intermittent loud noise, rotational stress, or electric shock are used in rodent research, and adaptation to physical stressors could be quite different than adjustment to the cognitive stressors that are of primary interest in research with humans. Use of family caregivers for Alzheimer's disease (AD) victims provides an opportunity to examine the immunologic and psychologic consequences of a more chronic psychosocial stressor.

AD affects two million older adults in this country. The progressive cognitive impairments that are characteristic of AD lead to increasing needs for supportive care of afflicted individuals. Although 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 (12, 13). Since the modal survival time after onset is approximately 8 years (14), long-term care of these patients by family members may be conceptualized as a chronic stressor (15). The majority of AD patients live in the community, under the care of their relatives (13).

Cross-sectional data from several laboratories suggest that the stresses of AD caregiving leave family members at high risk for depression (16, 17). Moreover, there may be some progressive deterioration in caregivers' well-being over time related to the increasing impairment in the AD family member. George and Gwyther (18) found substantial deterioration in caregivers' well-being when measures were taken at 1-year intervals, including perceived decrements in health, decreased satisfaction with the amount of time available for social participation, decreased life satisfaction, and increased levels of stress-related psychiatric symptoms. These changes were particularly noteworthy because the baseline (time one) levels of well-being in these caregivers were already quite low in absolute terms.

Although limited evidence suggests that caregiving responsibilities may be associated with self-reported health impairments (19, 20), the health of AD caregivers has not been studied using objective physiologic measures. The relatively high incidence of depression among caregivers could have implications for their health, particularly in regard to immune function. Convergent data have linked depression with impaired immune function (9, 21, 22).

In order to better understand the health-related consequences of caregiving, we obtained psychologic data and blood samples for immunologic and nutritional analyses from AD caregivers and sociodemographically matched comparison subjects. We expected that caregivers would be more depressed and would have poorer immune status than comparison subjects. Moreover, greater impairment in AD pa-

tients was expected to be correlated with greater dysfunction in caregivers.

METHODS

The subjects were 34 caregivers and 34 matched comparison subjects. All subjects were interviewed and completed questionnaires at the time blood was drawn for the immunologic assays. All blood samples were drawn at the same time of day to control for diurnal variation.

The caregivers were recruited from the practices of an Ohio State neurologist and an internist ($n = 20$), and from local support groups affiliated with the Alzheimer's Disease and Related Disorders Association ($n = 14$). The comparison subjects were recruited from newspaper advertisements, notes placed on community bulletin boards, and personal contacts.

In our laboratory's behavioral immunology research with younger populations we normally limit participation to those individuals who are not taking any medication and who have no health problems with possible immunologic components. However, caregivers are primarily middle-aged or older, and the majority of older adults are likely to be taking some medications. Limiting the sample to those who are unmedicated would probably result in biased data, because only the very healthiest of the population would be eligible (23). An alternative strategy that we used successfully in other research with older adults (24) involved selecting as subjects those individuals who were not taking any immunosuppressive medication, and whose health problems did not have an immunologic component (e.g., excluding those individuals with cancer, recent surgeries, strokes, hormonal disorders, etc.). There is evidence that this approach results in reliable data: Goodwin and coworkers (25) examined various immunologic parameters in 279 healthy and 24 chronically ill individuals over 65, and in young controls. Although there were the expected differences between the young and old subjects on certain aspects of immune function, there were not differences between the two groups of older adults. They noted that the data supported age-related relationships in immune function, rather than age-associated diseases.

In addition, we matched subjects on the presence or absence of two kinds of medication—use of beta blockers for hypertension and estrogen supplements. Beta blockers are widely prescribed among the elderly, and data from in vitro studies suggest that they may have some consequences for blastogenesis (26). Although we are unaware of any comparable immunologic data for estrogen, there is good evidence for interactions between the immune system and the endocrine system (2). Rather than exclude all caregivers who might use these medications, we selectively recruited matched comparison subjects (described below) who were similarly medicated.

Subjects were also matched on three sociodemographic dimensions: age, sex, and education. Education was used as the socioeconomic status variable for matching purposes because occupation is of limited value in a sample that includes significant numbers of older women who may or may not have worked outside the home (27).

Self-Report Data

Depression, social contact, loneliness, self-reported physical health, and financial resources were assessed. The self-report measures we used have been used previously in studies with older adults.

Demographic and Health Data. Information on age, sex, years of education, current or former occupation, and household income were obtained. Health status data included medication usage, caffeine intake, and recent alcohol intake. Subjects were asked how many hours they had slept in the last 3 days compared to their usual needs, and whether they had experienced any recent weight changes, particularly during the previous week. Data on recent illnesses included the number of physician visits during the previous 6 months, and the number of days the subject was ill enough to be in bed during the same time period.

Depression. The short form of the Beck Depression Inventory (BDI) (28) was used because it appears to be more sensitive to mild to moderate levels of depression than other scales that are more biologically based (29); in addition, it has fewer somatically based items that may be characteristic of older nondepressed individuals. It has been used extensively in research, including several studies with caregivers (15). Population norms provide cutoffs for varying levels of depression.

Social Contact. We collected social contact information using selected questions from the Older Americans' Resources and Services Multidimen-

sional Functional Assessment Questionnaire (OARS), since there are good normative data for older adults, and its reliability and validity have been well-documented (30). The questions included information on the number of persons the subject knew well enough to visit in their homes, the number of times the subject talked to someone else in the past week, and the number of times they spent time with someone who did not live with them (and who was not their AD relative). They were also asked how often they find themselves feeling lonely.

AD Patient History and Current Functioning. Information on the estimated duration of the illness was provided by the family caregiver, as well as the time since a physician had made a tentative diagnosis of AD. Caregivers were also asked to estimate the amount of time they spent in caregiving activities during the previous week.

The ratings of family members can provide one source of reliable data on level of AD patient function (31). Family members responded to the Memory and Behavior Problem Checklist (MBPC) (32) by providing ratings of the frequency of relevant behaviors associated with AD, as well as separate reaction ratings for the degree of associated bother or upset. The sum of the cross products of these two ratings provides a measure of the impact of the behaviors (33).

Immunologic Assays

The five immunologic assays included assessment of the percentages of total T lymphocytes, helper T lymphocytes, suppressor T lymphocytes, and natural killer (NK) cells. We also measured antibody titers to the latent herpesvirus Epstein–Barr virus (EBV), the etiologic agent for infectious mononucleosis.

Monoclonal antibodies were used to provide data on certain quantitative aspects of immune function. Natural killer cell percentages were assessed because NK cells are thought to be an important antiviral and antitumor defense. Distress-related changes in NK cell percentages have been found previously in medical students (7). Reliable stress-related changes in a functional NK measure, NK cell lysis, have been shown with two different target cells (3, 4, 7).

Data on the relative percentages of helper and suppressor T lymphocytes were also collected. Helper T cells stimulate important immunologic activities, including the production of antibody by B lymphocytes, an important defense against bacterial infections. Suppressor T cells act to shut off the activity of helper cells when sufficient antibody has been produced. Low helper-to-suppressor cell ratios are associated with immunodeficiency (34). Alterations in the percentages of helper and suppressor cells have been associated with examination stress (4, 5).

We measured antibody to EBV because antibody titers to latent herpesviruses appear to provide an indirect measure of cellular immune system competency (6). For example, patients on immunosuppressive therapies like chemotherapy or patients with immunosuppressive diseases (e.g., AIDS) have characteristic elevated herpesvirus antibody titers; cessation of an immunosuppressive drug therapy is ultimately followed by a drop in antibody titers to latent herpes-viruses. The increased herpesvirus antibody production in immunosuppressive conditions is thought to reflect the humoral immune system's response to an increased load of viral antigens. We have previously shown large and reliable stress-related changes in antibody titers to EBV and herpes simplex virus using a type 1 antigen (HSV-1) in medical students (6) as well as decrements in HSV-1 antibody titers in elderly adults following a relaxation intervention (24).

It should be noted that there is some evidence for the genetic transmission of early-onset AD (35), and there is some suggestion that AD may have an etiology related to immune function. The early-onset form of AD probably accounts for a relatively small proportion of AD patients, and the types of immunologic assays we used have not been related to the presence or absence of AD in previous studies (36). Therefore, although we used offspring caregivers, we did not expect that their immunologic data would be different from other subjects without a family history of AD.

NK, T Lymphocyte, and T Lymphocyte Subset Assays. The percentages of total T lymphocytes, helper-to-inducer T cells, and suppressor-to-cytotoxic T cells were determined using the monoclonal antibodies OKT-3, OKT-4, and OKT-8, respectively (Ortho), as previously described (5). The Leu-11 monoclonal antibody (Becton-Dickerson) was used to measure the percentage of NK cells.

Briefly, lymphocytes isolated on Hypaque–Ficoll gradients were washed with trypsin diluent and then resuspended in complete RPMI 1640 medium supplemented with 20% fetal bovine serum. Monocytes were removed by placing the cell suspensions in plastic tissue culture flasks and incubating at 37°C in a CO_2 incubator for 2 hours. The nonadherent cells were washed off and used to determine percentage of T-cell subsets. Lymphocytes (10^6) were incubated

in 0.01 ml of Leu-11, OKT-3, OKT-4, or OKT-8 monoclonal antibody for 30 minutes on ice. Cells were washed with cold RPMI 1640/PBS (1:1), resuspended in goat antimouse IgG conjugated to fluorescein isothiocyanate (Cappel Laboratories), and incubated for an additional 30 minutes on ice. The cells were washed and assayed, using an Ortho System 50 fluorescence activated cell sorter (FACS).

Immunofluorescence Assay. The indirect immunofluorescence (IF) assay was used to measure antibodies to EBV virus capsid antigen (VCA) (6). Antibody titers were assayed using smears of HR-1 cells. Cells were fixed in acetone at room temperature for 10 minutes, adsorbed with twofold dilutions of plasma prepared in phosphate-buffered saline (PBS), pH 7.4, for 30 minutes at 37°C. The cells were washed with PBS and readsorbed with goat antihuman IgG conjugated to fluorescein isothiocyanate (FITC) for 30 minutes at 37°C. The cells were washed with PBS, counterstained with Evans blue, mounted in Protex, and examined with a Zeiss UV microscope. A background control for the FITC-labeled antibody was performed. Antibody titers were determined by the highest dilution of plasma still able to demonstrate IF positive cells. All slides were read blind coded.

Nutritional Assays

Albumin and transferrin, two nutritional assays with relatively shorter and longer half-lives, were included to provide objective information on the nutritional status of subjects. There are well documented impairments in various aspects of immune function in undernourished individuals, and moderate to severe protein-caloric malnutrition is associated with increased frequency and severity of infection (37).

Protein assays provide better information on global nutritional status than those for carbohydrates and fats, since the former have varied nutritional building blocks, as well as very complex synthetic pathways. Different protein markers were used because of the differences in their half-lives; the half-life of albumin is 2–3 weeks, in comparison to 8 days for transferrin.

The procedure used to measure albumin is an adaptation of the bromcresol green dye-binding method of Rodkey (38), later modified by Doumas (39). This procedure is recognized as a particularly good procedure as compared to other dye-binding techniques because of its specificity and freedom from interference.

Transferrin is an iron-transporting protein. Concentration in plasma is affected by dietary intake of iron. Nutritionally deficient but calorie-rich diets are generally lacking in iron, and, as a result, plasma iron levels tend to be low and transferrin levels high. It has been shown that estimation of transferrin levels may be used to assess the effectiveness of total parenteral nutrition (40).

A rate nephelometry procedure using a Beckman human immunoglobulin reagent kit and a Beckman immunochemistry analyzer system was used to analyze transferrin levels. Antibody to human transferrin was used in the assay, in which the peak rate signal caused by the antigen–antibody complex is proportional to the increase in light scatter that is read by the instrument (41).

RESULTS

Sociodemographic Data

Sociodemographic data are shown in Table 1. Subjects ranged in age from 34 to 82. There were no reliable differences between caregivers and comparison subjects on the matching variables of age or education, or in subjects' total family income, $Fs < 1$. Six of the matched pairs were taking beta blocking medication, and five of the women in each cohort were taking an estrogen supplement.

The majority of the caregivers were spouses ($n = 20$), 13 were adult children, and 1 was an in-law. Half of the caregivers lived with their impaired relative ($n = 17$), 10 AD patients were in nursing homes, and 7 of the AD victims lived alone or with another relative but had additional care provided by our interviewees. The length of time reported since the caregiver reported that he or she had first noticed any AD symptoms ranged from 9 months to 16 years, with a mean of 5.45 years (SD = 3.82). The time that had elapsed since the initial physician's diagnosis of probable AD ranged from a new diagnosis to 11 years, with a mean and median of 2.83 years and 2.04 years, respectively.

TABLE 1. Subjects' Sociodemographic Characteristics

	AD caregivers	Comparison subjects
Sex		
Males	11	11
Females	23	23
Age	59.32 (12.98)	60.29 (13.27)
Marital status		
Married	32	29
Separated/divorced	1	4
Widowed	1	1
Number of children	2 90 (1.84)	2.44 (1.46)
Education		
Partial high school	1	—
High school graduate	5	7
Post high school business or trade school	2	4
1–3 years college	7	6
College graduate	11	7
Postgraduate college	8	10
Annual family income		
10,000–14,999	2	3
15,000–19,999	6	5
20,000–29,999	4	6
30,000–39,999	9	4
40,000 or more	11	15
Unanswered	2	1

TABLE 2. Means (SDs) for Psychologic Data from the BDI and the OARS

	AD caregivers	Comparison Subjects
Beck Depression Inventory short form)[a]	4.88 (6.18)	2 48 (2.58)
Current life satisfaction[a] (0 = poor, 2 = good)	1.62 (0.66)	1.91 (0.29)
Self-rated current mental health[a]	1 84 (0.87)	2.38 (0.65)
Self-rated mental health, compared to 5 years ago (0 = worse, 3 = better)[a]	1 57 (1.07)	2 03 (0.75)
Number of people known well enough to visit in their homes (0 = none, 3 = 5 or more)	2.90 (0.38)	2 85 (0 43)
Frequency of phone conversations with friends, relatives, or others in the past week (0 = none, 3 = daily or more)	2.42 (0.66)	2.35 (0.59)
Frequency of visits with someone not living with subject in the past week (0 = none, 3 = daily or more)	2.12 (0.74)	1.88 (0.84)
Feelings of loneliness (0 = quite often, 2 = almost never)	1.48 (0.61)	1.64 (0.59)

[a] $p < 0$ 05.
[b] $p < 0.01$.

Initial analyses of variance (ANOVAs) that included sex of subject revealed no differential sex effects for the major immunologic and self-report variables. Therefore, data were combined for subsequent analyses using ANOVAs with one variable, group membership.

Self-Report Data

Psychologic data are shown in Table 2. Caregivers had significantly higher scores on the short form of the BDI than comparison subjects, $F(1,66) = 4.02, p < 0.05$. Similarly, caregivers reported significantly lower general life satisfaction than comparison subjects, $F(1,66) = 5.34$, $p < 0.05$. Caregivers also rated their mental health as poorer than did comparison subjects on the OARS item, $F(1,66) = 8.11$, $p < 0.01$. Caregivers were significantly more likely than comparison subjects to say that there was a negative change in their mental health compared to 5 years ago, $F(1,66) = 4.79$, $p < 0.05$.

There were no significant differences between caregivers and comparison subjects on social support and loneliness questions from the OARS, as shown in Table 2. However, the pattern of correlations among AD impairment indices and social contact items shown in Table 3 suggests that caregivers with more impaired relatives had fewer social contacts with others and we were lonelier. In addition, the significant correlations between BDI scores and the three indices of impairment from the Memory and Behavior Problems Checklist suggest that greater impairment in the AD patient may be associated with greater distress in the caregiver.

Immunologic Data

Comparisons of immunologic data showed differences in the predicted direction, as seen in Table 4. The AD caregivers had significantly higher antibody titers to EBV VCA than comparison subjects, $F(1,65) = 4.65$, $p < 0.05$, presumably reflecting poorer cellular immune system control of herpesvirus latency in the for-

TABLE 3. Correlations Among Impaired Indices for the AD Victim and Depression and Social Contacts in Caregivers

	1.	2.	3.	4.	5.	6.	7.
1. MBPC frequency	1.00						
2. MBPC upset	0.62[a]	1.00					
3. MBPC cross-product of frequency and upset	0.61[a]	0.93[a]	1.00				
4. BDI depression score	0.28[b]	0.48[c]	0.60[a]	1.00			
5. Number of people known well enough to visit in their home	−0.25	−0.66[a]	−0.63[a]	−0.45[c]	1.00		
6. Frequency of phone conversations, past week	0.10	0.09	0.07	0.16	0.19	1.00	
7 Frequency of visits, past week	−0.23	−0.43[c]	−0.42[c]	−0.51[a]	0.48[c]	0.15	1.00
8. Feelings of loneliness	−0 44[c]	−0.41[c]	−0.46[c]	−0.50[a]	0.32[b]	0.02	0.35[b]

[a] $p < 0.001$.
[b] $p < 0.05$.
[c] $p < 0.01$.

TABLE 4. Means (SDs) for Immunologic and Nutritional Data

	AD Caregivers	Comparison subjects
Immunologic Assays		
EBV VAC[a,b]	640.70 (570.01)	376.72 (446.39)
Percentage of total T lymphocytes[b]	48.72 (13.97)	56.53 (14 15)
Percentage of helper T lymphocytes[c]	33.51 (10.86)	45.94 (12.05)
Percentage of suppressor T lymphocytes	18.30 (10 50)	21.02 (9.86)
Helper–suppressor ratio[d]	1.90 (0.97)	2.80 (1.86)
Percentage of NK cells	12.88 (6.92)	15.35 (9.53)
Nutritional Assays		
Albumin	4.23 (0.33)	4.14 (0.25)
Transferrin	296.78 (48.14)	284.79 (59.21)

[a]*Higher* antibody titers to a latent herpesvirus are thought to reflect *poorer* cellular immune system control over virus latency.
[b]$p < 0.05$.
[c]$p < 0.0001$.
[d]$p < 0.01$.

mer. Caregivers had significantly lower percentages of both total T lymphocytes, $F(1,62) = 4.87$, $p < 0.01$, and helper T lymphocytes than comparison subjects, $F(1,62) = 18.49$, $p < 0.0001$. Although the two groups did not differ in the relative percentages of suppressor T cells, $F(1,62) = 1.12$, there were significant differences in the helper-to-suppressor ratio, $F(1,62) = 5.77$, $p < 0.05$. There were no significant differences in the percentages of NK cells, $F(1,56) = 1.27$.

Nutritional Data

We used two nutritional markers, plasma albumin and transferrin levels, to assess the nutritional status of the subjects, since inadequate nutrition is associated with impairments in immunity. All subjects were within normal range for both markers. The two groups did not show even marginal differences on either albumin, $F(1,66) = 1.81$, or transferrin, $F < 1$. Thus, there is no evidence that the immunologic differences simply reflect underlying differences in nutrition.

Health-Related Data

The two groups did not differ reliably in the number of physician visits during the previous 6 months, or in the number of days they were ill in the same time period, $Fs < 1$. Similarly, there were not reliable differences in self-ratings of current health, or health as of 1 year ago, $Fs < 1$.

The two groups did not show differences in behavior that might have immunologic or other health-related consequences, including the number of smokers in the two groups, the number of packs smoked per week, the amount of alcohol consumed in the previous week, the average number of drinks normally consumed in a week, or in caffeine use, $Fs < 1$. There were no differences between the groups in recent weight change, $F(1,66) = 2.12$. There was a significant difference between the two groups in the amount of sleep subjects reported within the previous 3 days, $F(1,66) = 4.60$, $p < 0.05$, but the differences were not large. Caregivers reported an average of 23.07 (SD = 1.98) hours, whereas comparison

subjects reported a mean of 24.32 hours (SD = 2.83).

In order to help evaluate the possibility that any psychologic and immunologic differences between the two groups simply reflected diffences in the amount of sleep, correlations were computed between sleep and the immunologic parameters in caregivers. All of the correlations were negative, but none was significant. Sleep correlated −0.10 with BDI scores, whereas correlations between sleep and the immunologic measures ranged from −0.01 to −0.23.

Residence of AD Victim and Functioning of Caregiver

In order to evaluate possible differences among caregiver functioning as consequence of where their AD relative lived (with them, in an institution, or elsewhere), we compared demographic, self-report, immunologic, and nutritional data. The caregivers whose relative lived elsewhere were younger (mean age of 45.57, SD = 9.62) than those whose relative lived with them (mean = 62.06, SD = 10.00) or those whose relative was institutionalized (mean = 65.80, SD = 12.87), $F(2,31) = 7.42$, $p < 0.01$. There were no differences in the total time spent each day in caregiving activities, $F(2,31) = 2.20$, in part as a function of the very wide variability within each of the three groups: those living with their impaired relative reported spending an average of 9.87 hours a day (SD = 9.99), those whose relative was institutionalized reported a mean of 3.1 hours each day (SD = 2.33), and those whose relative lived elsewhere reported an average of 6.42 hours per day (SD = 7.93). Those caregivers whose relatives were institutionalized reported a significantly longer duration of illness, $F(2,31) = 12.18$, $p < 0.0001$. The two groups did not differ reliably on any of the three memory and behavior indices, $Fs < 1$.

There were no reliable differences on BDI scores, life satisfaction, or self-rated mental or physical health. There were significant immunologic differences only for percentages of NK cells, $F(2,27) = 6.49$, $p < 0.01$, with those whose relative was institutionalized having the highest values, with a mean of 19.26 (SD = 9.24), compared to those who lived with their AD relative (mean = 10.17, SD = 4.07), and those whose relative lived elsewhere (mean = 11.40, SD = 4.25). Nutritional comparisons showed no significant differences among these three groups.

Differences in AD Caregivers as a Function of Support Group Attendance

We compared the 14 caregivers who attended a support group with the 20 who did not. The two groups did not differ reliably on age, education, or family income. Support group members had been caregiving for substantially longer periods of time, $F(1,31) = 7.66$, $p < 0.01$. Support group members rated themselves as significantly less lonely, $F(1,31) = 6.11$, $p < 0.05$, and had significantly higher percentages of NK cells than nonmembers, $F(1,29) = 7.10$, $p < 0.01$. The differences on other psychologic or immunologic parameters were not significant.

DISCUSSION

Taken together, these data support the primary hypothesis of the investigation: caregivers appear more distressed and have

poorer immune function than their well-matched age peers. We found no evidence that the observed differences were a function of nutrition, alcohol use, or caffeine intake. Although the caregivers reported less sleep than comparison subjects, as would be expected from other studies (42), the amount of sleep was not reliably correlated with immune function or mood in caregivers.

The differences in immunity between the caregiving and comparison subject groups are particularly noteworthy, because these caregivers are less distressed than other caregiver samples described in the literature (15–17). These differences may be related to the fact that our caregivers were relatively well-educated, and income data suggest that they have more financial resources than described in other similar samples (33, 43). Given these relative advantages, it is reasonable to suggest that these data represent a "best case scenario" (44). The persistence of significant psychologic and physiologic differences between our two cohorts in spite of these relative advantages strongly supports the hypothesized negative impact of caregiving responsibilities.

In contrast to other studies (43, 45), we did not find that caregivers were more likely than individuals without comparable responsibilities to become isolated from their usual companions and social activities because of the time demands. However, we did find correlation evidence within the caregiver cohort that linked greater impairment in the AD victim with fewer social contacts and greater depression and loneliness. If caregivers experience increased social isolation as their relative's condition deteriorates, it could have important consequences; research with both older and younger adults suggests that social support may moderate stress-related depression or dysphoria and may also be related to morbidity and mortality (46, 47).

The immunologic data provide evidence of persistent alterations in cellular immunity associated with a chronic psychosocial stressor, in contrast to the longer-term adaptation or enhancement of immunity found in some studies with rodents (10, 11). Related evidence consistent with possible longer-term immunologic alterations in humans was provided in research on immune function, marital quality, and marital disruption (8); however, immunologic changes in these individuals were more closely tied to their adaptation to an acute stressor, marital disruption.

Although we did not find health differences between the two cohorts, the observed immunologic differences are consistent with the kinds of changes, (though of a much lesser magnitude) that are observed in immune-suppressed patients. For example, transplant patients and AIDS patients are good examples of immune suppression, although resulting from different processes; within both groups it is known that reactivation of latent virus occurs, including reactivation of EBV with associated increases in EBV antibody titers (49). There are higher EBV antibody titers among elderly than among younger adults (50), consistent with evidence that the former have relative deficits compared to their younger counterparts on some functional or qualitative immunologic assays (25, 51).

Data from other studies suggest there may be a number of other stress-related immunologic changes associated with acute stress, and such changes may have health consequences. For example, medical students followed over an academic year showed higher EBV antibody titers concomitant with a decrease in specific cell killing of EBV-infected cells during ex-

amination, compared with samples taken between examination periods (52). Other concurrent immunologic changes included markedly lower production of γ interferon by lymphocytes stimulated with Con A associated with examination stress. The activity of a lymphokine, leukocyte migration-inhibition factor, normally suppressed during recrudescence of herpes simplex virus type 2 infections, was altered during examination periods, and an increase in both plasma and intracellular levels of cyclic AMP was associated with examination stress as well. The medical students also reported more illness during examination periods.

Chronic distress-related immunosuppression may have its most important health consequences in groups with other, preexisting immunologic impairments, such as older adults with age-related decrements in immune function (48). Indirect evidence consistent with this premise is provided by the remarkably high mortality rates for elderly psychiatric patients from pneumonia: within the first year after psychiatric admission, there are fifty times more deaths from this infectious disease than found among age-matched general population counterparts. The ratio drops to twenty times that of their age-matched counterparts by the second year of institutionalization, suggesting that the hospital environment per se may be a less critical factor in mortality than the transition (53). In this context it should be noted that depression is the leading reason for psychiatric hospitalization in the elderly (54).

Since the modal age of onset for AD is 65–69 years (14), AD caregivers are themselves most often middle-aged or elderly (55). The significant functional immunologic decrements that accompany aging (25) are thought to be associated with the increased morbidity and mortality of infectious disease in the elderly (49, 52). Longitudinal studies with chronically stressed at-risk groups like caregivers may provide valuable information on the contribution of psychosocial variables to morbidity and mortality.

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