Spousal Caregivers of Dementia Victims: Longitudinal Changes in Immunity and Health

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Providing long-term care for a demented relative profoundly affects caregivers' lives. We assessed changes in depression, immune function, and health in 69 spousal caregivers who had already been caregiving for an average of five years and 69 sociodemographically matched control subjects. Between the initial sample ("intake") and the follow-up data collected an average of 13 months later, caregivers showed decrements relative to controls on three measures of cellular immunity. Caregivers also reported significantly more days of infectious illness, primarily upper respiratory tract infections. Caregivers had a much greater incidence of depressive disorders than controls, with 25% of caregivers meeting syndromal criteria at intake and 32% at follow-up, compared with no cases among controls at intake and 6% at follow-up. 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.

INTRODUCTION

Providing care for a relative with Senile Dementia of the Alzheimer's Type (SDAT) or any of the other progressive dementias has profound effects on caregivers' daily lives. Caregivers have described the process as a kind of living bereavement, as they watch the disintegration of the personality and intellect of their relative (1). Long-term care of demented family members involves coping with severe behavioral problems including wandering, inability to communicate or recognize familiar people, and incontinence. The model survival time after SDAT onset is eight years, and thus caregiving has been conceptualized as a chronic stressor (2). Convergent data from several laboratories demonstrate that the stresses of dementia caregiving put family members at high risk for the development of depressive disorders, with 14% to 81% of caregivers meeting syndromal criteria in various studies (2–4).

In the first year of this longitudinal study, we assessed current and lifetime rates of psychiatric disorders in 86 spousal caregivers and 86 sociodemographically matched control subjects (5). Caregivers and controls did not differ in either the frequencies of depressive disorders in the years prior to caregiving or in first-degree relatives' incidence of psychiatric disorder, the most reliable predictors of sub-

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sequent depressive disorders (2). However, during the years they had been providing care, 30% of these spousal caregivers had experienced a depressive disorder, compared with only 1% that their matched controls experienced in the same time period. Only two caregivers who were depressed during caregiving had met criteria for a depressive disorder prior to caregiving, and family history was not even weakly related to the identification of at-risk caregivers. Thus, caregiving was linked to the onset of depressive disorders in older adults who had no prior evidence of vulnerability.

In addition to the greatly increased vulnerability to depressive disorders, the chronic stresses of dementia caregiving may have physiological consequences as well. For example, Pomara et al. (6) found that spouses of Alzheimer patients had significantly higher concentrations of γ-aminobutyric acid (GABA) in cerebral spinal fluid than control subjects. Moreover, in a cross-sectional study, we found that 34 spousal and offspring dementia caregivers had poorer immune function than 34 well-matched control subjects (7).

While dementia caregiving is clearly an extraordinarily long-term, unpredictable, and uncontrollable stressor, caregivers show considerable variability in their responses (1). Strong supportive social ties appear to be a key mediator of caregivers' vulnerability to depression (1, 2). The present study addressed the extent to which supportive personal relationships might also be an important mediator of caregivers' physical health; data from large, well-controlled epidemiological studies suggest that the evidence for social relationships as a major risk factor for morbidity and mortality rivals that of such well-established health risk factors as smoking, blood pressure, blood lipids, obesity, and physical activity (8).

Research with diverse populations has shown an association between cellular immune function and the quality of personal relationships, providing one possible physiological pathway linking social relationships and health. Lonelier medical students had poorer immune function than their less lonely contemporaries (9–10). Marital disruption, either through bereavement (11) or divorce (12) has been associated with decrements in immunity, while marital strife was associated with poorer immune function in intact marriages (12). Baron et al. (13) found that women whose husbands were being treated for urologic cancer who had higher levels of social support had better immune function than women who reported less support. In general, qualitative of functional aspects of immunity appear to be much more responsive to psychosocial influences in these studies than quantitative or enumerative aspects of immunity, e.g., percentages of total T-lymphocytes (12).

Links between social relationships and immunity could have a greater impact on older adults, since immune function declines with age, particularly the functional aspects of the cellular immune response (14, 15). 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 (16). Moreover, older adults show greater immunological impairments related to depression than younger adults (11).

There are two major competing hypotheses regarding long-term changes in

response to the chronic stresses of caregiving (17). The wear-and-tear hypothesis suggests that there will be progressive deterioration in caregivers' functioning as the dementia progresses. In contrast, the adaptation hypothesis posits that caregivers will eventually adapt to the demands of the situation and will either stabilize or improve. Limited longitudinal data showing stabilization in caregivers' levels of depressive symptomatology have supported the adaptation hypothesis (17, 18). However, physiological adaptation (or lack thereof) has not been assessed in longitudinal studies, and studies with rodents suggest that chronic stress could have prolonged adverse consequences for older adults: compared with young rats, aged male rats show impairments in their ability to terminate glucocorticoid secretion at the end of a stressor, consistent with some data from primates (19). Since glucocorticoids are known to be immune suppressive, the glucocorticoid cascade hypothesis (19) suggests that chronic stressors could have persistant and severe consequences for immune function in older adults, including acceleration of the aging of the immune response. The present study was designed to assess longitudinal changes in immunity, health, and depression secondary to a chronic stressor in spousal caregivers and controls, as well as the mediating role of social support.

METHOD

Caregivers of dementia patients were recruited from three local dementia evaluation centers in area hospitals, neurologists' referrals, the city's Alzheimer's Disease and Related Disorders Association (ADRDA) support groups, the monthly ADRDA newsletter, respite care programs, and governmental caregiver support programs. For study entry, caregivers had to be providing five or more hours of care per week. While most subjects were seen in our clinic, 26 caregivers were reluctant to leave their spouse unattended or bring them to the university despite free transportation, and they were interviewed at home.

Comparison subjects were recruited through newspaper advertisements, church groups, notices posted in senior citizen centers, and referrals from other participants; potential comparison subjects who reported any caregiving activities were excluded. Caregivers and comparison subjects were matched on sex, age, and education; we used education as a proxy for socioeconomic status because many of our caregivers were older women who had not worked outside of the home. Subjects were excluded if they had major immunologically related health problems such as cancer or recent surgeries. Subjects were paid $30 for participation in the study. All subjects gave written informed consent for participation after the experimental procedures were explained.

Subject Characteristics

There were 20 men and 49 women in each of the groups of 69 caregivers and 69 control subjects. The matching procedures were successful in producing groups that did not differ on age, education, or income, $Fs < 1$. The average age of caregivers was 67.26 (SEM = 0.98) compared with 67.75 (SEM = 0.93) for controls. The modal subject had completed several years of college and reported an annual family income between $20,000 and $30,000. The majority of subjects were caucasian, 95% of caregivers and 93% of controls. Most noncaregivers were married (68%); however, 19% were widowed, 12% were divorced, and one control subject had never married. While groups were not matched on marital status, the inclusion of divorced and widowed control subjects actually worked against confirmation of the experimental hypotheses, since intact marriages are associated with lower rates of psychopathology and less morbidity and mortality (8).

Caregivers had been providing care for an average of 5.20 years (SEM = 0.55) at intake. They reported spending an average of 8.26 hours per day caregiving (SEM = 0.68) at intake and 7.04 hours (SEM = 0.60) at follow-up. The majority of the caregivers lived at home with their spouse ($n = 45$), while 13 of the patients were institutionalized at intake, nine were moved from home to nursing home between sample points, and two spouses were moved back home

from a nursing home. All but one of the caregivers identified themselves as the primary caregiver at intake, regardless of their spouse's residence, consistent with other caregiver studies in which substantial numbers of spousal caregivers continue to describe themselves as a primary caregiver even after institutionalization of their spouse (1).

We lost subjects between intake and follow-up from our original group (5) of 86 caregivers and 86 controls for several reasons. Among the original 86 caregivers, 13 were no longer caregiving at follow-up because their impaired spouse had died. Of the remaining 73, two subjects moved, one subject died, and one was not reachable by phone or letter. Among controls, we lost five out of 86: one became a caregiver, two were not reachable by phone or letter, one refused further participation, and one died. After caregivers were assigned new matches among the remaining controls where necessary, the remaining unmatched controls ($n = 12$) were excluded from subsequent analyses.

The time between the intake and follow-up sample points ranged from 9 to 24 months, with a mean of 13.01 months (SEM = 0.35); 72.9% of the subjects were seen between 11 and 15 months. There were some stragglers due to difficulties in contacting and scheduling some subjects, while a few subjects, who had entered the study late in our first wave of data collection, were seen at a relatively shorter interval. However, it should be noted that control subjects had a *longer* interval between intake and follow-up 13.91 (SEM = 0.33), compared with caregivers, who had a mean of 13.01 months (SEM = 0.35). While this difference was not significant, $F(1,137) = 3.42$, $p < 0.07$, the difference is clearly in favor of controls, who had *more* time to change in a downward direction. In addition, as discussed shortly, change in immune measures was not correlated with interval between intake and follow-up.

Evaluation of Syndromal Depression and Depressive Symptoms

Intake interviews using the Structured Clinical Interview for DSM-III-R, nonpatient version (SCID-NP) (20) provided both current and lifetime prevalence, with the approximate date(s) of onset noted (5). The follow-up version of the SCID-NP, administered at the second visit, assessed development of symptoms in the intervening year. A postdoctoral fellow and advanced clinical psychology graduate students administered the interviews. Inter-rater reliability for SCID-NP diagnoses, calculated using randomly selected audiotaped interviews for 20% of the subjects, had a kappa coefficient of 0.80 for depressive disorders.

The Hamilton Depression Rating Scale (HDRS), a 24-item, interviewer-rated measure of depression, provided information of depressive symptomatology for the week prior to the interview (21). Inter-rater reliability, calculated for 10% of the sample, was $r = 0.83$.

Social Support Interview

The Social Support Interview (2, 22) asked subjects to "list the people in your life who are important to you, with whom you have contact, whether or not you like them," up to a total of 10. They subsequently made independent ratings of the degree to which they perceived each of the relationships to be helpful and upsetting/troubling (0 = not at all, 6 = extremely) with respect to both emotional support and tangible assistance. For each person named, subjects rated the frequency of contacts from daily 5, to less than monthly, 1. Closeness was rated from 0, not at all close, to 10, extremely close. While we previously averaged the network members' ratings (22), in this study we found that the number of people listed by caregivers and controls was significantly different; for this reason we summed the support ratings across all members of the network, since using averages would have overshadowed important differences in total support.

Status of the Dementia Patient

While most of the caregivers' spouses had a diagnosis of SDAT ($n = 46$), one was diagnosed as multi-infarct dementia, 16 as Parkinson's Disease with progressive dementia, two with Huntington's, one with Picks, and three with an unspecified dementia; research comparing SDAT caregivers with other progressive dementias suggests that dementia caregivers are similarly adversely affected (23). Seventy percent had received their diagnosis at one of three local neurology centers that used the National Institute of Neurological and Communicative Disorders and Stroke/ADRDA work-group standards for probable SDAT (24).

Family members' ratings can provide reliable data on dementia patients' functioning (25). The Blessed

Dementia Scale (BDS) was developed to measure negative changes in a demented person's abilities across daily living, self-care, and personality domains. Higher scores on this 22-item scale denote greater decrements in ability, with a range of 0 to 28. BDS scores have been correlated with senile plaque count during postmortem histological examination, as well as impairments in neuropsychological testing and can be used to differentiate degree of dementia (26, 27).

The Memory and Behavior Problem Checklist (MBPC) (28) measures behavioral excesses and deficits in dementia patients, and the caregiver's reaction to those problems. The 29 items include some of the problems most distressing to caregivers, e.g., incontinence, inability to communicate, hiding things, and inability to recognize familiar people. The scale provides a measure of the frequency of problem behaviors as well as a measure of associated caregiver distress. The MBPC measures current symptoms and associated subjective caregiver distress, not impairment of the patient per se, as many behavior problems are most prevalent in the middle stages of dementia.

Health-Related Behaviors and Infectious Illness Assessments

Health-related behaviors, assessed at each interview, included medication use, caffeine intake, and alcohol intake. Subjects were asked to describe current status and any recent changes in amount of sleep in the last three days, and weight changes in the last two weeks.

To assess infectious illness episodes, we used the Health Review (29), a checklist of specific illness symptoms related to infectious disease (primarily upper respiratory illness). Validational evidence (29) showed that physicians' diagnoses were the same as those defined by a computer algorithm using Health Review symptom clusters in 77% of the cases examined. Moreover, all diagnostic differences were minor ones within the general category of acute respiratory illness.

We administered the Health Review as an interview. Subjects were read the symptom list and asked to indicate which symptoms occurred as part of an illness episode, as isolated symptoms, or as more chronic problems, with operational definitions provided for these categories. Subjects were also asked whether they saw a physician for the problem(s) and the number of days they were unable to perform their normal daily activities because of illness. At intake all subjects were asked about symptoms in the last six months, and then all subjects were called and reassessed every three months. In order to enhance subjects' recall of important events, we used a series of memory prompts from Bradburn et al. (30), e.g., reminding subjects of their data from the last phone call, highlighting important events that occurred in the time period such as major holidays, etc.

We were interested in the presence or absence of an infectious illness episode, not specific diagnoses. Data from each Health Review interview were reviewed by our project nurse who used pre-established International Classification of Disease-9 (ICD-9)-based criteria to decide whether a subject had an infectious illness. When necessary, follow-up telephone calls were made to collect additional information.

To help evaluate the validity of our infectious illness diagnoses, we got written consent from 30 subjects to contact their physician when they reported a visit related to Health Review symptoms. Of the 24 forms returned from physicians, 19 provided an infectious illness diagnosis when subjects had also met our criteria, and our evaluations also concurred with reports from three physicians who did not diagnose an infectious illness based on isolated symptoms. There was a disagreement in two cases in which subjects reported a physician visit but the physician reported no contact with the patient. Overall, these data strongly support the validity of the Health Review in this population.

We also assessed both test-retest and inter-rater reliability. The recall period for test-retest reliability was varied from several hours to one week. In each case we calculated kappas to examine agreement on presence or absence of each symptom, then ICD-9 criteria were applied, and Pearson correlations were calculated for number and length of illness episodes and physician visits. Our inter-rater reliability, calculated on 10% of the sample, showed an overall kappa of 0.93 for individual symptoms. When illness criteria were applied to symptom clusters, there was excellent agreement between symptom reports from raters who listened to the same interview, with correlations of 0.99 for total number of illnesses, illness duration, and associated physician visits, as well as good agreement when subjects were called back to assess test-retest reliability (correlation for total illnesses was $r = 0.79$; illness duration, $r = 0.81$; and physician visits, $r = 0.84$; all $p < 0.001$). In fact, our test-retest reliability also reflects inter-rater re-

liability, because the second call was always made by a second interviewer.

Immunological Studies

Blood for all subjects was drawn early in the morning, between 8:00 A.M. and 10:00 A.M. to control for diurnal variation. Interviews followed blood draws.

We bought laboratory supplies in quantity at the beginning of the study, and we used the same mitogen lots across the study. In addition, caregivers and controls were run in mixed groups across the year, so that we were always simultaneously collecting blood from both groups, so any immunological changes do not simply reflect differences in the timing for subject interviews.

Choice of Assays. We included assays to assess both quantitative and functional changes in cellular immunity. Functional assays included blastogenesis with two mitogens, concanavalin A (Con A) and phytohemagglutinin (PHA), as well as antibody titers to latent Epstein-Barr virus (EBV). The cellular immune response is thought to be important in controlling latent herpesviruses (31). Psychological stress has adverse effects on cellular immunity, and there is evidence that this interaction can modulate the control of latent herpesviruses (31). With compromised cellular immunity, reactivation of latent herpesviruses can occur, and there are characteristic elevations in herpesvirus antibody titers reflecting the antibody response to increased synthesis of the virus or viral proteins.

Immunofluorescence Assay. The indirect immunofluorescence (IF) assay was used to measure antibodies to EBV virus capsid antigen (VCA) IgG (10, 32). Antibody titers were assayed using smears of P3J HR-1 cells. Cells were fixed in acetone at room temperature for 10 minutes, adsorbed with two-fold 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 reabsorbed with goat antihuman IgG conjugated to fluorescein isothicyanate (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. Antibody titers were determined by the highest dilution of plasma still able to demonstrate IF positive cells. All slides were read blind coded.

Blastogenesis. Mononuclear cells from 50 cc of blood treated with heparin were separated using Hypaque-Ficoll density gradients, washed 2 times with Mg- and Ca-free buffer, counted in a Coulter Counter, then used as described. Mitogens were used at a final concentration of 2.5, 5.0, 10.0, and 20.0 μg/ml in complete RPMI 1640 media supplemented with 5% fetal bovine serum (FBS) for both Con A and PHA, with assays performed in triplicate. Complete medium was used for background controls. One-tenth milliliter of mitogen was added to 1×10^5 lymphocytes (in 0.1 ml complete medium) in 96 well plates, and incubated at 37°C in 5% CO_2 for 60 hours. Fifty microliters of tritiated thymidine (10 μCi/ml, specific activity 83 Ci/mM) were added to each well and the plates incubated at 37°C in 5% CO_2 for 4 hours. Cells were harvested onto GF/A filters. Radioactivity was measured using a Beckman LS7000 scintillation counter. The data are presented as counts per minute (cpm) in the stimulated samples minus the cpm of the unstimulated samples (delta cpm). A base 10 logarithmic transformation was performed on the resulting values.

Monoclonal Antibody (MAb) Panel. To prepare peripheral blood leukocytes (PBLs) for reaction with the MAbs, mononuclear cells were obtained and then resuspended in RPMI 1640 media supplemented with 5% heat-inactivated FBS. Approximately 0.5 to 1.0×10^6 cells were aliquoted to 10 × 75 mm snap-cap tube(s) for reaction with the MAbs. The MAbs were conjugated with either FITC or phycoerythrin (PE) fluorochromes and paired for dual color analysis, with reagents and isotype controls from Coulter.

Nutritional Status

Plasma albumin levels provided objective information on the nutritional status of subjects using the methodology previously described (7). 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.

Data Analyses

We used several repeated measures multivariate analyses of variance (MANOVAs) to assess differences between caregivers and controls, change from intake to follow-up, and the interaction of these variables for correlated clusters of measure (e.g.,

social support dimensions, Health Review variables), followed by ANOVAs when there were significant effects found on the MANOVA. Hierarchical regression analyses were used to assess the contributions of social support and depression to changes in immunity. All correlations reported are Pearson correlations.

Throughout our data, we found virtually no significant gender differences. There were not significant sex differences in depressive symptoms, social support, immune function, or health-related behaviors. Thus, while sex was included as a variable in earlier analyses, sex differences will not be reported.

RESULTS

Depression

There were substantially higher rates of syndromal depressive disorders in caregivers at both intake and follow-up. At intake, four caregivers met criteria for major depression, seven caregivers met criteria for dysthymia, and six caregivers met criteria for depressive disorder not otherwise specified (NOS), for a total of 17 who met criteria; no control subject met criteria at intake, $\chi^2(1, N = 138) = 17.17$, $p < 0.001$, Yates corrected. At follow-up, 32% of caregivers met criteria for an affective disorder (seven for major depression, seven for dysthymia, and eight for depressive disorder NOS) compared with 6% (one case of dysthymia and three cases of depressive disorder NOS) among controls, $\chi^2(1, N = 138) = 13.70$, $p < 0.001$, Yates corrected.

Caregivers' interviewer-rated depression on the HDRS was significantly higher than found in the comparison subjects, $F(1,136) = 42.55$, $p < 0.0001$. Slight decreases in caregivers' depressive symptoms at follow-up and small increases in controls produced a significant group by time interaction, $F(1,136) = 5.55$, $p < 0.05$, without significant change from intake to follow-up, $F < 1$. Caregivers' mean was 8.07 (SEM = 0.80) at intake and 6.73 (SEM = 0.77) at follow-up; corresponding means for noncaregivers were 1.93 (SEM = 0.30) and 3.12 (SEM = 0.48).

Most caregiving studies have not found significant relationships between caregivers' depressive symptoms and the years spent caregiving, the number of caregiving hours/day, or the extent of patient impairment (1, 22), and this was true in our data. Intake HDRS ratings and BDS scores were not significantly related at intake, $r = 0.18$, or at follow-up, $r = 0.10$. The relationship between the HDRS and years spent caregiving was negligible, $r = 0.05$, while average daily caregiving hours were not significantly related to the HDRS at intake, $r = 0.14$, or at follow-up, $r = -0.05$.

To evaluate the association between caregiver depression and patient residence, an ANOVA included three groups (caregivers whose demented spouse lived at home at both times, in a nursing home at both times, or moved from home to nursing home); we found no differences in HDRS scores, with $Fs < 1$ for group membership, change over time, and the interaction of these two variables. At-home caregivers spent an average of 9.32 hours/day in caregiving, while caregivers whose patient was in a nursing home spent 3.55 hours/day, $F(1,67) = 15.16$, $p < 0.001$. The former had spent an average of 4.51 years (SEM = 0.56) years in caregiving, compared with 8.12 (SEM = 1.54) in the latter, $F(1,67) = 6.96$, $p < 0.01$.

Personal Relationships

Differences between caregivers and controls were assessed in a MANOVA that included the number of people in the

network, total helpful ratings, total upset ratings, frequency, and closeness. Caregivers reported less support than controls, $F(5,126) = 2.27$, $p < 0.05$, and support declined for both groups from intake to follow-up, $F(5,126) = 6.93$, $p < 0.001$. The results of subsequent ANOVAs, shown in Table 1, indicated that controls fared significantly better than caregivers on all dimensions except upsetting support.

TABLE 1. Changes in Social Support in Caregivers and Controls

	Caregivers	Controls
	Mean (SEM)	Mean (SEM)
Number of People Listed*		
Intake	7.49 (0.27)	8.43 (0.25)
Follow-up	6.40 (0.27)	6.91 (0.26)
Frequency of Support*		
Intake	2.17 (0.08)	2.39 (0.08)
Follow-up	1.82 (0.08)	2.03 (0.08)
Closeness of Support*		
Intake	55.80 (2.49)	64.93 (2.54)
Follow-up	51.89 (2.49)	53.85 (2.07)
Helpful Emotional Support**		
Intake	30.57 (1.22)	25.33 (1.26)
Follow-up	27.39 (.27)	29.46 (1.33)
Helpful Tangible Support***		
Intake	25.30 (1.31)	35.12 (1.49)
Follow-up	25.30 (1.41)	27.80 (1.45)
Upsetting Emotional Support[a]		
Intake	14.14 (0.91)	15.11 (1.05)
Follow-up	10.60 (0.60)	11.97 (0.69)
Upsetting Tangible Support[a]		
Intake	13.10 (0.85)	14.69 (0.93)
Follow-up	9.95 (0.63)	10.43 (0.84)

* Groups differ at $p < 0.05$.
** Groups differ at $p < 0.01$.
*** Groups differ at $p < 0.001$.
[a] No significant difference between caregivers and controls.

Moreover, most of the caregivers named their impaired spouses among their network members. Thus, while caregivers listed an average of one less person than controls at intake, the effective difference in network size may actually be closer to two.

While subjects provided separate ratings for both emotional and tangible dimensions of helpful and upsetting support, the correlation between emotional and tangible support was $r = 0.76$ at intake and $r = 0.84$ at follow-up, both $p < 0.001$. Thus, we summed the ratings for helpful emotional and tangible helpful support to produce a total score for use in regression analyses.

Health-Related Behaviors

Health-related behaviors did not distinguish between caregivers and controls. The great majority of both groups were nonsmokers, 86% of caregivers and 95% of controls. Similarly, 60% of subjects in both groups reported no alcohol use in the past week; amount of alcohol consumed did not differ between groups, $F < 1$. The average subject reported about three cups of coffee or tea per day, with no difference in intake between groups, $F < 1$. All subjects were within normal range on albumin using age-adjusted norms (33).

Amount of sleep in the last three days was the one area of health behavior that showed reliable group differences, $F(1,136) = 30.05$, $p < 0.001$, with negligible change from intake to follow-up, $F < 1$. Caregivers reported an average of 22.06 hours in the three days preceding the intake sample (SEM = 0.39), while control subjects reported an average of 23.93 hours (SEM = 0.13). However, correlations between sleep and the immunolog-

TABLE 2. Changes in EBV VCA IgG Antibody Titers Over 13 Months

	Mean	(SEM)	Uniformity of Changes	
Caregivers (n = 61)				
Intake	379.80	(74.51)	6 − Ranks	(year 1 > year 2)
Follow-up	903.08	(137.33)	47 + Ranks	(year 1 < year 2)
			8 Ties	(year 1 = year 2)
Controls (n = 63)				
Intake	526.00	(78.35)	25 − Ranks	(year 1 > year 2)
Follow-up	536.25	(82.99)	22 + Ranks	(year 1 < year 2)
			16 Ties	(year 1 = year 2)

ical data were small and unreliable, e.g., the largest correlation between sleep and immune data was between the peak Con A response and sleep at intake $r = 0.23$, $p < 0.01$, compared with $r = -0.11$ (not significant) at follow-up.

The majority of individuals over 65 years of age use some medication. Seven caregivers and nine controls reported use of estrogen, eight caregivers and six controls took beta blockers, 16 caregivers and 15 controls used prescription diuretics, eight caregivers and seven controls took thyroid medications, two caregivers and two controls used antianxiety drugs, and two caregivers and no controls reported use of prescription antidepressants. Because antidepressants have immunological consequences (11) and were not used in both groups, blood samples from the two caregivers who were using antidepressants were not collected. Blood samples were also omitted in four cases where subjects developed immunologically relevant medical problems. Analyses of immunological data showed no association between use of these medications and immune function. To assess the possibility that these medications might influence immune function and/or might have a differential influence in caregivers or controls, we conducted a series of analyses that included presence or absence of estrogen, beta blockers, and thyroid, along with a second grouping variable, caregivers vs. controls. While there were significant differences between caregivers and controls, as detailed below, in no case were there even marginally significant main effects related to the presence of any of these three drugs, nor were there any interactions between use of the medications and group membership.

Immunological Data

There were significant group differences on all three of the functional assays. Changes in antibody titers to EBV VCA are shown in Table 2. Eight of the subjects were EBV seronegative (i.e., not previously infected) and thus had no data for this assay. As shown by the dramatic increase in caregivers' mean titers, there was a significant interaction between group and change over time, $F(1,122) = 11.50$, $p < 0.001$. Similarly, there was a main effect for change over time, $F(1,122) = 12.43$, $p < 0.001$, clearly attributable to the changes in caregivers. Waller-Duncan post hoc analyses of the significant interaction showed that caregivers and controls did not differ at intake, but did differ significantly at follow-up, $p < 0.05$.

In order to asses the uniformity with

which caregivers and controls were changing on this assay, we examined the number of subjects within each group who showed an increase, decrease, or remained the same from intake to follow-up. As shown in Table 2, 77% of caregivers had higher EBV VCA titers in the follow-up sample compared with intake, while 35% of controls had higher titers and 40% had lower titers. Thus, changes in caregivers did not simply reflect changes in only a few outliers.

Data for Con A and PHA stimulated blastogenesis (Figure 1) were initially included in a single MANOVA that showed significantly higher values in controls than in caregivers, $F(2,124) = 5.34$, $p < 0.01$, as well as a number of significant interactions among group, time, and mitogen concentration, including an interaction between group and change from intake to follow-up, $F(2,124) = 3.35$, $p < 0.05$, with caregivers decreasing relative to controls. Group differences were larger at the highest concentration of mitogen. To better understand these effects, Con A and PHA data were analyzed in separate repeated measures ANOVAs that included one between-subjects variable (caregivers versus controls) and two within-subjects variables, change across the four concentrations for each mitogen, and change over time (from intake to follow-up).

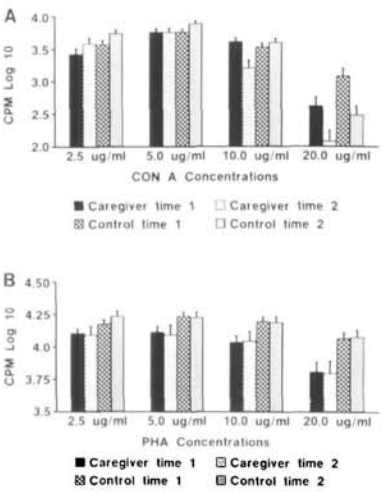

Fig. 1. Blastogenic response to (A) Con A and (B) PHA at intake and follow-up.

Con A data showed significantly lower proliferation among caregivers than controls, $F(1,125) = 8.05$, $p < 0.005$. As expected, the four concentrations of the mitogen differed significantly, $F(3,123) = 45.97$, $p < 0.001$, and there was a significant interaction between concentration and change over time, $F(3,123) = 142.36$, $p < 0.0001$, reflecting the increasing deficit shown in both caregivers and controls from intake to follow-up at higher mitogen concentrations. Finally, there was a three-way interaction among group, concentration, and change over time, $F(3,123) = 6.05$, $p < 0.001$: caregivers' mitogen responsiveness decreased relative to controls, and these differences were greatest at the highest mitogen concentrations.

A similar pattern was observed for PHA data. Caregivers had a poorer proliferative response than controls, $F(1,125) = 8.99$, $p < 0.01$, and caregivers decreased relative to controls as reflected in the group by time interaction, $F(1,125) = 6.28$, $p < 0.01$. These group differences were again most pronounced at the highest mitogen concentration, shown by the interaction between group and concentration, $F(3,123) = 3.22$, $p < 0.05$.

There was neither a significant group difference in a MANOVA that included

the three T cell quantitative immunological measures (percent T-lymphocytes, helper T-lymphocytes, and suppressor T-lymphocytes), $F(3,112) = 2.18$, nor a group by time interaction, $F < 1$. A second MANOVA with NK cells and B-lymphocytes showed neither a difference between groups, nor a group by time interaction, $Fs < 1$.

Syndromal Depression and Immune Function

A number of studies have suggested an association between syndromal depression and immune function (11). To assess the possibility that both the group differences as well as the changes in immune function were related to the presence or absence of syndromal depression, we compared caregivers who met DSM-III-R criteria with those who did not for both intake and follow-up blood samples. In each case, the differences between caregivers meeting syndromal criteria and those who did not were negligible, all $Fs < 1.60$. Thus, group differences in immunity were not simply a function of syndromal depression.

Health Data

The intake Health Review interview assessed illness symptoms in the prior six months. Subjects were called at three-month intervals after intake, and these data were combined with the data collected at the follow-up interview. Intake data were multiplied by two, while follow-up health data were divided by the number of intervening months and multiplied by 12, so all data in Table 3 reflect illness in the last 12 months.

TABLE 3. Infectious Illness in Spousal Caregivers and Controls over the Past 12 Months

	Caregivers	Controls
	Mean (SEM)	Mean (SEM)
Infectious illness episodes		
Intake	0.84 (0.16)	0.64 (0.11)
Follow-up	1.00 (0.13)	1.01 (0.11)
Days unable to perform normal activities*		
Intake	3.77 (1.29)	1.78 (0.57)
Follow-up	4.32 (0.88)	2.38 (0.46)
Physicians visits for these illness episodes**		
Intake	0.58 (0.16)	0.12 (0.07)
Follow-up	0.43 (0.08)	0.21 (0.06)

* Groups differ at $p < 0.05$.
** Groups differ at $p < 0.01$.

Inclusion of the three Health Review variables in a single MANOVA showed poorer health in caregivers than controls, $F(3,134) = 4.31$, $p < 0.01$. Subsequent ANOVAs for each of the three variables showed that total number of illnesses did not differ between groups. However, caregivers had longer illness episodes than controls, $F(1,136) = 4.30$, $p < 0.05$, as well as more physician visits for these episodes, $F(1,136) = 10.26$, $p < 0.01$. None of the three Health Review ANOVAs produced a significant interaction between group and change over time, all $Fs < 1.68$.

Relationships among Social Support, Immune Function, and Health

In order to assess the contribution of social support and depression to immune function and health, we used hierarchical multiple regression analyses. The first equation evaluated the association between changes in immune function and

TABLE 4. Hierarchical Regression to Evaluate the Relationship Between Changes in Immune Function and Social Support

Independent variables	Cumulative				
	Beta	Multiple *r*	R^2	*t*	*df*
Step 1					
Intake EBV	−0.34			−4.08***	
Intake Con A	0.25			2.24*	
Intake PHA	0.10	0.45	0.21	0.97	(3,113)
Step 2					
Group	−0.70	0.48	0.23	2.53**	(4,112)
Step 3					
Age	0.13			−1.58	
Income	0.03	0.49	0.24	0.32	(6,110)
Step 4					
Intake social support	−0.41			−2.96**	
Follow-up social support	0.14	0.53	0.29	1.57	(8,108)
Step 5					
Intake social support × group interaction	0.69	0.55	0.31	2.14*	(9,107)

Dependent variable: Percent change on summary functional immunological measure.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

social support. In order to provide a summary change measure across the functional immunological assays, the intake peak Con A and PHA responses and EBV antibody titers were included in a principal components factor analysis. The analysis produced a single factor with an eigenvalue of 1.68 that accounted for 55.6% of the variance. Thus, the summary change dependent variable was obtained by calculating the percent change from intake for EBV VCA antibody titers and for the peak Con A and PHA responses; for both mitogens, we used the sum of log values for the 5.0- and 10.0-μg/ml concentrations. We normalized the percent change distributions by converting them to z-scores, and added the three z-scores together; for each of the three assays, higher values indicated greater negative change from intake. When a subject was missing a single value (e.g., for subjects who were EBV seronegative), the remaining two values were averaged to provide the total.

On the first step of the equation, intake values for EBV antibody titers and values for the peak Con A and PHA responses were entered. Group membership was entered on the second step, with caregivers coded as 0 and controls as 1. Age and income were entered on the third, controlling for sociodemographic influences; family income data were coded from 1, a family income of less than $3,000, to 16, over $60,000. Missing values for four subjects were assigned the median value of 10.

Both intake and follow-up ratings for helpful social support were entered on the fourth step. The final variable, entered on the last step, was the interaction between group membership and intake social support, since support might be differentially important between the groups.

As seen in Table 4, intake immune

function was (as expected) a strong and significant predictor of subsequent changes in immune function. In addition, as expected from the earlier analyses, caregivers showed significantly greater negative change at follow-up than controls. Neither age nor income made a significant contribution. However, both lower helpful social support at intake and the support by group membership interaction were significant predictors of negative changes in immune function, with the interaction reflecting the relatively greater importance of support for caregivers. The difference in sign between intake social support and follow-up social support reflected the fact that lower support at intake was associated with greater negative change in immune function, while decrements in support from intake to follow-up were nonsignificantly associated with greater negative change in immune function.

We used an identical equation with intake HDRS scores entered along with age and income on the third step to assess the possibility that the contributions of social support to immunity simply reflected prior differences in depression. Depression did not make even a marginal contribution to the variance, $t < 1$, and the contributions of intake social support and the group by support interaction were unchanged after controlling for depression.

Uniformity of Functional Immunological Down-Regulation

In addition to changes in specific aspects of immunity, we were interested in characteristics of individuals who showed decrements across all three functional assays. Such a pattern would suggest that these individuals were at particular risk, showing an overall down-regulation of cellular immunity. A total of 28 subjects of the 127 who had data available for at least two assays met this criterion; these represented 14% of controls and 32% of caregivers, $\chi^2(1, N = 127) = 6.23$, $p < 0.01$. We were particularly interested in differences between the one-third of the caregivers who showed decrements across assays ("at-risk") and the two-thirds of caregivers who did not. There were no differences between these two caregiver subgroups on age, education, income, health-related behaviors, or depression. However, there were differences between these caregiver subgroups in social support and responses to dementia behaviors, as well as a trend toward greater illness. A MANOVA that included the social support interview variables showed a significant interaction between caregiver subgroup and change from intake to follow-up, $F(4,53) = 2.85$, $p < 0.05$; subsequent ANOVAs showed that the at-risk caregivers reported lower helpful support at intake than the remaining caregivers, with the groups converging at follow-up. A MANOVA with the three Health Review variables showed a trend toward greater illness in at-risk caregivers, particularly at follow-up, in the group by year interaction, $F(3,56) = 2.34$, $p < 0.08$.

At-risk caregivers did not differ from the other two-thirds of caregivers in years of caregiving, hours per day, or BDS scores. However, the groups differed in their reaction to dementia-related behaviors, with at-risk caregivers reporting considerably more dementia-related distress. A MANOVA that included the two MBPC variables showed a significant group by year interaction, $F(2,54) = 3.18$, $p < 0.05$, as well as a near-significant difference between groups, $F(2,54) = 2.75$, $p < 0.07$, without a difference from year one to year

two, $F < 1$. Means on the MBPC reaction scale for at-risk caregivers were 28.44 (SEM = 4.50) at intake, compared with 24.78 (SEM = 5.42) at follow-up. Comparable values for the remaining caregivers were 18.28 (SEM = 1.66) and 17.85 (SEM = 1.98).

At-risk caregivers differed in one additional way from the remaining caregivers, they were significantly more likely to have institutionalized their spouse between intake and follow-up, $\chi^2(1, N = 62) = 4.45$, $p < 0.05$. In fact, when we compared caregivers whose relative had not moved during the year with those caregivers who had institutionalized their spouse, we found that the latter showed far greater negative changes on the composite immunological z-score discussed earlier, $F(1,63) = 7.81$, $p < 0.01$.

DISCUSSION

This study provided data on longitudinal changes in certain aspects of immune function, health, and depression in chronically stressed spousal caregivers and well-matched control subjects. The average caregiver had been providing care for five years at intake, and thus might have been expected to show physiological adaptation. However, caregivers showed decrements relative to controls on all three of the functional measures of immunity assessed in this study. Caregivers also experienced significantly more days ill from infectious disease, primarily upper respiratory tract infections, and they visited physicians more often than controls. Although caregivers and controls did not differ significantly in number of illness episodes, there was evidence that exposure to pathogens was less frequent in caregivers. Caregivers' social support data indicated that they had fewer people in their networks as well as less frequent contacts with network members than controls; moreover, caregivers spent an average of eight hours a day in caregiving activities.

Consistent with other caregiver studies (1), caregivers had a much greater incidence of syndromal depressive disorders than controls, as well as higher levels of depressive symptoms. Neither severity of depressive symptoms nor presence of syndromal depression was reliably related to either intake levels or subsequent changes in immune function. As in Baron et al. (13), the association between social support and immune function was not mediated by depression.

Caregivers reported fewer important personal relationships than controls, they saw members of their network less frequently, and both closeness and helpfulness ratings of the relationships were lower. Lower levels of social support at intake were associated with poorer immune function at follow-up, and these effects were more pronounced for caregivers than for controls. These data provide evidence of one possible physiological mechanism through which personal relationships may affect health (8).

When PBLs obtained from the caregivers and matched controls were stimulated with Con A and PHA, the group differences were largest at the highest concentration of both mitogens at both time points. The data suggest that the PBLs from the AD caregivers were not able to respond as well as the PBLs from the control subjects to Con A and PHA at optimum concentrations, and that whatever the reason behind this deficit, e.g., IL-2 production, the inhibition was magnified at the highest concentration. It is

also possible that an increase in suppressor cell activity occurred in the AD caregivers as compared with the PBLs from the control group at the highest concentrations of Con A and PHA (34). If this is the case, the impact on the blastogenic response by the suppressor cells would have been due to an increase in activity of the cells, rather than in the percentage of suppressor cells, since we found no significant difference between groups in the percentage of suppressor ($CD8^+$) cells, as already discussed.

While caregivers showed decrements on all three of the functional immunological measures relative to controls, there were not significant differences in percentages of total T-lymphocytes, helper or suppressor cells, NK cells, or B-lymphocytes. Functional aspects of cellular immunity have been implicated in age-related immunological declines that are thought to be associated with the increase in the risk and severity of infectious disease and the increased risk for malignant disease (14–16). Most studies show that there is no significant age-related change in the percentages of lymphocyte subpopulations (34).

EBV VCA antibody titers showed the most dramatic changes. These changes are likely to reflect broader down-regulation of cellular immunity. The competence of the cellular immune response is the most critical factor in control of herpesvirus latency (35). With compromised cellular immunity (e.g., patients with immunosuppressive diseases like AIDS or in patients undergoing immunosuppressive therapies like chemotherapy), the immune system's control over latent herpesvirus replication is impaired. Characteristic elevations in herpesvirus antibody titers that occur in the absence of any other symptoms are thought to reflect the antibody response to increase synthesis of the virus or viral proteins. When the cellular immune system becomes more competent (such as cessation of immunosuppressive therapies), herpesvirus antibody titers normally decline. Moreover, elevations in herpesvirus antibody titers are associated with the down-regulation of cellular immunity that accompanies aging (36).

Our caregivers had been providing care for an average of five years and yet we found significant immunological changes. While SDAT has a variable course, several particularly disturbing symptoms often appear between four and six years into the course of the illness: incontinence, nighttime agitation, and wandering (1). These symptoms are often the very ones that caregivers find most disturbing and frequently serve as the final stimulus for institutionalization. In support of this interpretation, the largest negative immunological changes occurred among the 19% of caregivers who institutionalized their spouse between intake and follow-up.

These findings may have particular importance for older adults in the context of the glucocorticoid cascade hypothesis (19) discussed earlier. One of the hypothesized consequences of the glucocorticoid cascade is the acceleration of the process of immunosuppression associated with aging. In caregivers, especially those who are older, chronic stress could have longer term, potentially irreversible consequences.

Immunological changes may also reflect other physiological changes. Evaluation of the blastogenic response in 403 elderly adults showed that the lymphocytes of 18% did not proliferate in response to three mitogens (14). While the overall mortality of the population for a two-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. Similarly, a 20-year longitudinal study of 273 healthy adults over 60 showed that poorer cell-mediated immunity was associated with subsequent morbidity and mortality (15).

In summary, we did not find evidence of physiological adaptation. Chronically stressed caregivers showed negative immunological changes when compared with controls. Caregivers' mental and physical health was also poorer than controls. The caregivers who showed the greatest and most uniform immunological declines were those who reported lower levels of social support at intake and who were most distressed by dementia-elated behaviors.

These data may have implications for public policy. SDAT is the fourth leading cause of death in the United States, with recent epidemiological data showing a far greater incidence than previously suspected (37); SDAT caregivers have been called the "second victims" of the disease (38). When considering the human and economic costs of SDAT and other dementing illnesses and the need for research on etiology and treatment, the costs to caregivers' lives should clearly be considered as well.

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