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Effects of Chronic Stress on Immune Function and Health in the Elderly

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THE RELEVANCE OF AGE IN STUDIES OF STRESS AND IMMUNE FUNCTION

There is ample evidence that various stressors can alter immune function (Glaser & Kiecolt-Glaser, 1994a; Herbert & Cohen, 1993b). There is also clear evidence that immune function declines with age (reviewed in Solomon & Benton, 1994). Because immunosenescence occurs in persons with increasing age and is "indistinguishable from immunodeficiency secondary to underlying disease, malnutrition, toxic exposure, or genetic disorder" (Solomon & Benton, 1994, p. 341), older adults may be especially susceptible to the potentially negative effects of stress on immune function.

There are relatively few studies exploring the effects of stress on immune function among older adults. In a recent meta-analysis of the literature on stress-related immunological changes in human beings, Herbert and Cohen (1993b) were limited in their ability to explore age differences because most published studies had used younger subjects (i.e., mean age under 30 years). Older adults appear to show greater immunological impairments associated with clinical depression than do younger adults (Schleifer, Keller, Bond,

Cohen, & Stein, 1989), and a meta-analytic review of the depression and immunity literature similarly suggested that clinical depression had a more negative effect on immune measures among older adults than young adults (Herbert & Cohen, 1993a). Although it seems plausible that stress-related immune changes may become more pronounced with age among nonclinically depressed adults, further research is clearly needed.

THE RELEVANCE OF STRESSOR DURATION

It is particularly important to explore the effect of chronic stress on older adults in view of the glucocorticoid cascade hypothesis, which suggests that chronic stress may have persistent negative effects on immune function in older adults and may actually accelerate immunosenescence (Sapolsky, Krey, & McEwen, 1986). This hypothesis was generated from animal studies that found that aged rats were impaired in their ability to terminate glucocorticoid secretion at the end of a stressor relative to young rats. By analogy, because glucocorticoids down-regulate immune function, chronic stressors may have persistent and severe consequences for immune function in the elderly.

Although most studies have examined the immunological consequences of acute rather than chronic stressors, there are exceptions. Baum and his colleagues conducted an elegant series of studies using people who lived near the Three Mile Island (TMI) nuclear power plant (Baum, 1990; McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989). They compared psychological stress, endocrine function, and immune function in people living near TMI after the nuclear power plant sustained damage with a demographically comparable control group. TMI-area residents and controls had comparable blood pressure in the years before the TMI accident as reflected in records obtained from their physicians; in contrast, blood pressure data collected by the research team several years after the accident showed higher blood pressure in TMI residents as compared to controls (Baum, 1990). Chronic stress was implicated as a factor in enhanced cardiovascular reactivity as well as in higher levels of urinary catecholamines (Fleming, Baum, Davidson, Reitan, & McArdle, 1987; McKinnon et al., 1989). TMI residents had more neutrophils and fewer B lymphocytes, T suppressor/cytotoxic lymphocytes, NK cells, and higher antibody titers to latent herpes simplex virus (HSV) than did controls.

Higher antibody titers to latent HSV are thought to reflect poorer control of the latent virus by the cellular arm of the immune system (Glaser & Jones, 1994). Herpesviruses are different from many other viruses in that they remain in a latent state in the body after the primary infection subsides. The competence of the cellular immune response is a critical factor in the control of herpesvirus latency. When cellular immunity is compromised, the immune system's control over latent herpesvirus replication is impaired, and there are characteristic elevated herpesvirus antibody titers (Glaser & Kiecolt-Glaser, 1994b).

In addition to the studies on the long-term effects of living near TMI, several investigators have examined the consequences of caregiving for a relative with a progressive dementia (e.g., Irwin et al., 1991; Kiecolt-Glaser et al., 1987; McCann, 1991; Reese, Gross, Smalley, & Messer, 1994). These studies have provided data on the immunological consequences of a persistent stressor in older adults.

THE CHRONIC STRESS OF CAREGIVING

Caring for a family member with a progressive dementing illness is an extraordinarily long-term, unpredictable, and uncontrollable stressor. The progressive cognitive impairments characteristic of Alzheimer's disease (AD) lead to gradually increasing needs for care and assistance with daily living. The irreversible deterioration of brain tissue eventually progresses to the point at which the AD patient is unable to provide even the most basic self-care. Caregivers have described the process as a kind of living bereavement as they watch their relative's intellect and personality gradually disintegrate (Light & Lebowitz, 1989).

It is not possible to accurately predict or anticipate the time course of the disease. The modal survival time after onset is quite variable, ranging from 5 to 10 years (Hay & Ernst, 1987). Because of the long-term course of the disease, caregiving for a friend or relative with AD has been conceptualized as a chronic stressor (Fiore, Becker, & Coppel, 1983).

There is ample evidence that the stress of caring for a relative with AD adversely affects caregivers' mental health (Light & Lebowitz, 1989). The literature clearly shows greater self-reported psychiatric symptomatology among caregivers (Schulz, Visintainer, & Williamson, 1990) and suggests that caregiving places individuals at risk for

developing syndromal depressive disorders (Cohen & Eisdorfer, 1988; Dura, Stuckenberg, & Kiecolt-Glaser, 1990, 1991; Fiore et al., 1983; Gallagher, Wrabetz, Lovett, Del Maestro, & Rose, 1989).

Although the effects of caregiving on psychological health have been well documented, much less is known about the effects of caregiving stress on physical health. Most studies assessing physical health have relied on self-report measures. In their review of the literature, Schulz et al. (1990) noted that caregivers consistently report poorer self-rated health than do matched controls. Schulz et al. (1990) cautioned, however, that it is difficult to draw conclusions and causal inferences from such studies. Few researchers have used longitudinal designs to study the physiological consequences of caregiving stress. In the sections that follow, we review the results of a series of investigations addressing the effects of caregiving on health.

The Impact of Caregiving on Immune Function

Cross-Sectional Data. In the first study to assess the immunological consequences of AD caregiving, measures of psychological health, physical health, and immune function were collected from a group of 34 caregivers and a group of 34 matched noncaregivers (Kiecolt-Glaser et al., 1987). Participants were generally well educated, with a mean age of 60 years. The caregivers had been providing care for their impaired family member for an average of 5.5 years; thus caregivers were facing a chronic, rather than an acute, life stressor. The majority were caring for a spouse; the remainder provided care for a parent or parent-in-law. Half the caregivers lived in the same residence as the relative for whom they were caring, but the caregivers' psychological well-being was unrelated to living arrangement. Consistent with previous studies demonstrating negative psychological consequences of family caregiving, these caregiving subjects reported significantly greater depressive symptomatology, poorer self-rated mental health, and lower levels of life satisfaction than did sociodemographically matched comparison subjects.

Comparisons of immunological data revealed significant differences between caregivers and control: caregivers had lower percentages of total T lymphocytes (CD3+) and helper T lymphocytes (CD4+) than did noncaregiving comparison subjects. Although the two groups did not differ in the relative percentages of suppressor T cells (CD8+ cells), caregivers had a significantly lower CD4+/CD8+ ratio. No differences were found in the percentages of NK cells.

In addition to the differences observed in relative percentages of lymphocytes, caregivers had significantly higher antibody titers to latent Epstein-Barr virus (EBV) than did comparison subjects. Taken together with the quantitative immune measures, elevated EBV antibody titers (similar to the discussion for HSV) suggest that caregivers had poorer cellular immune function than that of noncaregivers.

In contrast, Reese and her colleagues (1994) compared three groups: 25 AD caregivers, 25 caregivers of stroke patients, and 25 noncaregivers. Of the AD caregiver sample, 56% were caring for a parent, 36% were caring for a spouse, and the remainder were caring for some other friend or relation. AD caregivers were significantly younger (mean age of 56) than the subjects in the other two groups (means of 64 and 61), and AD caregivers were slightly better educated with higher incomes. Reese et al. (1994) found no differences among groups on a battery of quantitative immunological assays, even though the AD caregivers reported more distress than did the other two groups.

The absence of significant immunological differences may be related to the exclusive use of quantitative assays by Reese et al. (1994). Meta-analyses have shown stronger and more consistent stress-related differences in qualitative or functional measures than have quantitative assays (Herbert & Cohen, 1993b). Indeed, although pilot work showed significant differences between caregivers and controls (Kiecolt-Glaser et al., 1987), a subsequent longitudinal study with a larger and more homogeneous sample did not yield significant differences in quantitative immunological data, but it did continue to demonstrate differences on functional assays (Kiecolt-Glaser et al., 1991).

Other researchers have also found differences on functional immunological assays between caregivers and controls. For example, McCann (1991) found that the response to delayed hypersensitivity skin testing was significantly poorer among older adult spousal caregivers than among noncaregivers. Whereas 12% of the control subjects in her study were categorized as totally or relatively anergic compared to normal age and gender standards, 50% of the caregivers were so categorized. Caregivers in this study not only showed immunologic deficits relative to a comparison sample, but demonstrated deficits compared to age-based norms as well.

Irwin et al. (1991) investigated the effects of AD caregiving stress on sympathetic nervous system activity and NK cytotoxicity. Plasma levels of neuropeptide Y (NPY) were significantly elevated in older spousal caregivers as compared to those of older controls, and NPY was nega-

tively correlated with NK cell activity among caregivers. NK activity itself, however, was not significantly different between spousal caregivers and controls. In summary, data from several cross-sectional studies suggest that individuals facing the chronic stress of caring for a relative with AD do not show physiological adaptation (i.e., caregivers do not appear to return to the level of well-matched controls).

Longitudinal Studies. In a longitudinal study of the immunological consequences of caregiving stress, 69 spousal caregivers and 69 matched controls were examined on two occasions an average of 13 months apart (Kiecolt-Glaser et al., 1991). The caregiver group consisted of all spousal caregivers who were continuing to provide care for their spouse and were available for follow-up assessment. Caregivers had been providing care for an average of 5 years prior to the initial assessment. Most caregivers were caring for their impaired spouse at home across both times of testing. The mean age was 67 years.

Between the two times of measurement, caregivers showed declines relative to controls on all three functional measures of cellular immunity included in the study: antibody titers to latent EBV, and the ability of lymphocytes to proliferate when exposed to the mitogens concanavalin A (Con A) and phytohemagglutinin (PHA). Caregivers showed increased antibody titers to EBV over time, whereas controls evidenced minimal change. Caregivers showed a decreased proliferative response to both Con A and PHA over time relative to controls, with differences most pronounced at the highest mitogen concentrations. In contrast, caregivers and controls did not differ significantly on quantitative immune measures. There were no group differences in CD3+, CD4+, or CD8+ cells at intake into the study, nor were there any significant differences in change over time on these measures.

Data on infectious illnesses showed differences between caregivers and controls. The Health Review (Jenkins, Kraeger, Rose, & Hurst, 1980), a checklist of specific illness symptoms related to infectious diseases, was administered every 3 months to assess illness episodes. Although caregivers did not report greater frequency of infectious illnesses, they reported illnesses of longer duration and were more likely to have visited their physician as a result of their illness.

Health behaviors were assessed in order to explore their contribution to the immunological differences observed between caregivers and controls. Similar to the results of the cross-sectional study, caregivers and controls did not differ on health behaviors (i.e., use of alcohol, tobacco, and caffeine), nor did they differ in nutritional status as assessed by

plasma albumin levels. Recent amount of sleep differed between the two groups, but sleep was not reliably related to any of the immunological data. Therefore, differences between groups in immune function and infectious illness could not be explained by recent health behaviors.

In an attempt to better understand factors contributing to observed immunological changes, participants were divided into those who showed overall down-regulation of cellular immunity (i.e., those showing decrements on the three functional immunological assays) and those who did not. Nearly one third of the caregivers were classified as "at risk" because of their uniform declines on functional immune measures. "At risk" caregivers did not differ from the remaining caregivers in the length of caregiving, amount of time per day spent caregiving, or extent of their spouses' cognitive impairment, but they were significantly more likely to have institutionalized their spouse between the initial assessment and follow-up than those not classified as "at risk." "At risk" caregivers also reported more distress in response to dementia-related behaviors and lower levels of helpful social support at the initial assessment. Although caregivers as a whole had substantially higher rates of syndromal depressive disorders than did controls at both times of assessment, negligible differences between depressed and nondepressed caregivers' immune data suggested that immunological down-regulation was not simply related to syndromal depression.

These data should not be taken to indicate that caregivers show continued declines in immune function related to years of caregiving. In fact, the best evidence is more consistent with the adaptation hypothesis, that is, that caregivers eventually stabilize in their responses to the stresses of caregiving (Townsend, Noelker, Deimling, & Bass, 1989). The "at risk" caregivers showed the largest declines, and the characteristics of this group are particularly important in this regard. As described previously, these individuals were more likely to have institutionalized their spouses in the intervening year. Caregivers who decided to place their spouses in a nursing home often made this decision because behavioral or other problems had become so severe that they could no longer cope. The decision to move the spouse was often a wrenching one, and caregivers frequently found themselves conflicted over nursing home placement, a condition that continued well after the initial move. Thus, rather than simply reflecting down-regulation related to chronicity, these caregivers appear to have been adapting to a new set of caregiving strains. Indeed, in the longitudinal data from this sample we have not observed continuous downward change in immune function, but rather stabilization at levels below those of control subjects.

Post-Stressor Functioning: Caregivers After Bereavement. Relatively few studies have explored the psychological recovery of caregivers after bereavement; even fewer have addressed the question of physiological recovery. Preliminary evidence on psychological recovery following bereavement suggests that, unlike the psychological rebound observed in "normal" bereavement (Harlow, Goldberg, & Comstock, 1991; Lund, Caserta, & Dimone, 1989; Thompson, Gallagher-Thompson, Futterman, Gilewski, & Peterson, 1991), caregivers' distress and depression are not substantially alleviated in the year following the death of their relative (Bass & Bowman, 1990; George & Gwyther, 1984). Recent research using structured psychiatric interviews to assess clinical depression revealed that former caregivers did not differ from continuing caregivers in their incidence of syndromal depression or in their level of depressive symptomatology an average of 2 years after the death of their impaired relative (Bodnar & Kiecolt-Glaser, 1994); both continuing and former caregivers were significantly more depressed than were noncaregivers.

The longer-term physiological consequences of caregiving were examined in a study that compared three groups of subjects: a group of 14 caregivers currently caring for an impaired relative, a group of 17 former caregivers, and a group of 31 noncaregiving control subjects (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994). Participants in the study were the first 62 subjects from the longitudinal project to receive their fifth annual appointment. Continuing caregivers were those who had been caring for a demented relative throughout all 5 years of the longitudinal study. At the time of the Year 5 assessment, they had been providing care for an average of 10 years. Approximately half of them continued to provide care for their family member at home. Former caregivers were those who had been caregiving when they initially joined the study but whose caregiving had ceased because of the death of their family member. The average length of time since the death of the family member was a little more than 2 years (26.57 months). The average age of the continuing caregiver, former caregiver, and noncaregiver groups was 68, 72, and 71, respectively.

The immunological question of interest was whether caregivers and controls differed on three NK cell assays: NK cell cytotoxicity and NK cell cytotoxicity after enhancement with two cytokines, recombinant interferon- γ (rIFN- γ) and recombinant interleukin-2 (rIL-2). These cytokines enhance NK cell cytotoxicity in vitro (Herberman & Ortaldo, 1981), and there is evidence that stress can modulate the synthesis of

these cytokines by nitrogen-treated peripheral blood leukocytes (Dobbin, Harth, McCain, Martin, & Cousin, 1991; Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986).

Consistent with the data from Irwin et al. (1991) discussed earlier, current caregivers, former caregivers, and noncaregivers did not differ in NK cell cytotoxicity. However, differences were observed in NK cell responses to rIFN- γ and rIL-2. Although current and former caregivers did not differ from each other in their response to these two cytokines, both groups demonstrated significantly poorer responses to these cytokines than did controls (Easterling et al., 1994).

When continuing and former caregivers were divided into low-cytokine responders (i.e., those responding below the median to both cytokines) and high-cytokine responders (i.e., those responding above the median to either or both cytokines), low responders reported less positive social support from their networks and described less closeness in their important relationships. High- and low-cytokine responders did not differ significantly in depressive symptomatology or health behaviors.

Consistent with data on psychological adaptation following long-term caregiving stress, these data suggest that former caregivers do not show physiological recovery in the years immediately following the cessation of caregiving. On a more positive note, there was some evidence indicating eventual adaptation and recovery. Relative to caregivers who were more recently bereaved, those who had been bereaved for longer periods had significantly higher levels of NK cell cytotoxicity after rIFN- γ stimulation and a similar trend after rIL-2 stimulation. Further study is required to determine the length of time required for recovery and whether or not a complete recovery of immune function is possible. A better understanding of what factors may assist and what factors may hinder the recovery process is also needed.

HEALTH IMPLICATIONS

It is often mistakenly believed that changes in immune function translate directly into changes in physical health. Although gross impairments in immune function such as those found in AIDS patients are clearly associated with increased morbidity and mortality, the effects of less extreme immune changes on physical health are largely unknown. Two recent studies, however, provide evidence that stress-related immune changes are relevant to protection against infectious illness.

In a carefully controlled prospective study, Cohen, Tyrrell, and Smith (1991) examined the relationship between stress and susceptibility to several different respiratory viruses. After completing measures of psychological stress, volunteers were inoculated with one of five viruses or a placebo. They were subsequently quarantined and monitored for the development of both respiratory infections and clinical colds (i.e., presence of cold symptoms in addition to the presence of infection). The researchers found that the incidence of respiratory infections and clinical colds increased in a dose-response manner with increases in psychological stress across all five viruses they studied.

Consistent with these results, Glaser, Kiecolt-Glaser, Bonneau, Malarkey, and Hughes (1992) found that stress interfered with the immune system's ability to generate an immune response to a primary antigen. Over 6 months, 48 medical students were given a series of 3 hepatitis B vaccine inoculations, each on the last day of a 3-day exam period. The 25% of the sample who seroconverted (i.e., produced a measurable antibody response to the vaccine) after the first inoculation were significantly less stressed and less anxious than those who did not seroconvert until after the second injection. In addition, students who reported greater social support demonstrated a stronger immune response to the vaccine at the time of the third inoculation, as measured by antibody titers to a hepatitis B surface antigen (HBsAg) and the blastogenic response to the viral peptide. These data suggest that the immunological response to vaccination can be modulated by a relatively mild, time-limited, commonplace stressor, a finding replicated in another population (Jabaaij et al., 1993). These studies demonstrated that the effects of stress on the immune system are significant enough to affect the ability of healthy young or middle aged adults to respond to an infectious pathogen.

However, susceptibility to an infectious agent is more relevant for older adults. Pneumonia and influenza together constitute the fourth leading cause of death among individuals over age 75 (Yoshikawa, 1983), and mortality from influenza infection is four times higher among those over age 60 than among those under 40 (Burns, Lum, Seigneuret, Giddings, & Goodwin, 1990). Immune senescence is thought to be associated (in part) with the greatly increased morbidity and mortality from infectious illness in the elderly and is thought to be related to the poor response of many older adults to vaccines (Phair, Kauffmann, Bjornson, Adams, & Linnemann, 1978). Older adults achieve lower peak antibody levels following vaccination and show more rapid decline of antibody levels over time (Burns et al., 1990). If chronic stress accelerates age-related declines

in immune function, as the glucocorticoid cascade hypothesis suggests, chronic stress could have serious health consequences for older adults, including increased risk and severity of infectious illness.

Potentially even more serious than an increased risk of infectious illness, Murasko, Weiner, and Kaye (1988) suggested that immunological changes may reflect changes in other systems as well and thus may provide a marker of physiological aging. They found that older adults who did not show lymphocyte proliferation in response to three mitogens were twice as likely to die over a 2-year period than were those showing a proliferative response. The major cause of death among their sample of older adults was sudden death or a diagnosable cardiovascular-related disease.

A 20-year longitudinal study of healthy older adults showed that poorer cell-mediated immunity was associated with subsequent morbidity and mortality (Wayne, Rhyne, Garry, & Goodwin, 1990), and a 16-year longitudinal study of healthy elderly men found that decreases in the absolute number of peripheral blood lymphocytes during the 3 years prior to death were related to subsequent mortality (Bender, Nagel, Adler, & Andres, 1986). These studies suggest that immunological decrements among older adults may be related to more than just increased infectious illness. Such suggestions heighten concern about the immune down-regulation observed among older adults experiencing the chronic stress of caregiving.

POTENTIAL DIRECTIONS FOR INTERVENTION

Psychological intervention studies that include measures of immune function are relatively rare (Kiecolt-Glaser & Glaser, 1991). One intervention study conducted with an older adult sample, however, did find positive changes in immune function following the intervention. Older adults living in retirement homes were randomly assigned to one of three conditions: a progressive relaxation training condition, a social contact condition, or a no contact control condition (Kiecolt-Glaser et al., 1985). Older adults in the relaxation and social contact conditions were visited by a student three times a week for one month. Participants were seen individually by the same student on each visit. Blood samples and self-report data were collected at baseline, at the end of the intervention, and at the 1-month follow-up.

Individuals in the relaxation condition showed significant increases in NK cell lysis at the end of the intervention (but not at follow-up) and a decrease in antibody titers to HSV both at the end of the intervention and

at the 1-month follow-up. Subjects in the social contact and no contact control conditions did not show significant changes on these measures.

Relaxation was also incorporated into a 6-week structured group intervention for patients with Stage I or II malignant melanoma (Fawzy et al., 1990). Although the mean age of the sample was 42 years, the sample included some older adults (age range 19 to 70 years). Fawzy et al.'s brief intervention (consisting of health education, enhancement of problem-solving skills regarding diagnosis, psychological support, and additional stress reduction techniques) produced beneficial psychological and immunological changes in treatment group members relative to controls. Despite the brevity of the intervention, intervention subjects showed increases in the percentage of large granular lymphocytes (NK cells), increases in NK cell cytotoxicity, and small decreases in the percentage of CD4+ T cells. These changes were not observed immediately after the intervention but became evident at the 6-month follow-up.

Although these studies demonstrate that immune function in older adults may be enhanced through psychosocial interventions, it remains to be seen whether interventions can counteract the toll that years of chronic stress takes on older caregivers' immune systems. An exploration of the ability of caregiver interventions to enhance immunity may have to wait until the efficacy of specific caregiver interventions has been better established. Given the recent findings that psychological and physiological impairments persist even after caregiving has ceased (Bodnar & Kiecolt-Glaser, 1994; Esterling et al., 1994), programs designed for recently bereaved caregivers may offer a more fruitful opportunity to evaluate the immune-enhancing capability of psychosocial interventions. Intervention programs designed for bereaved caregivers that are less likely to be fraught with the challenges of caregiver interventions (e.g., limited caregiver availability, profound daily stressors) may offer valuable insights into the plasticity of the long-term immunological down-regulation in older adults following chronic stress.

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7

Neuroimmune Interactions: Implications for Aging and Immunosenescence—Rodent Models

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One of the long-term objectives of research on aging must be to define the mechanisms underlying age and stress-related changes in immunocompetence and susceptibility to infection. For example, why do the elderly remain at risk for influenza infection despite years of intense research the efficacy of influenza viral vaccines? Similarly, how does behavior (stress) increase the occurrence of respiratory infections in the elderly, seen in such circumstances as caregiving to patients with Alzheimer's dementia? It is important to address both aging and stress in the same breath, as some of the underlying mechanisms are shared with regard to modulation of immunity. The rationale behind this connection derives from observations in experimental models that (a) stress-induced alterations in microbial pathogenesis and cellular immunity are caused by both adrenal-dependent (glucocorticoid) and -independent (sympathetic nervous system) mechanisms (Bonneau, Sheridan, Feng, & Glaser, 1993), (b) virus-infected, aged rodents have reduced virus-specific T cell responses and higher levels of morbidity and mortality, (c) aging is associated with altered glucocorticoid