Major Life Changes, Chronic Stress, and Immunity

*Janice Kiecolt-Glaser and †Ronald Glaser

Departments of *Psychiatry and †Medical Microbiology and Immunology and †Comprehensive Cancer Center, The Ohio State University College of Medicine, Columbus, Ohio 43210

Data from human studies suggest that (a) psychiatric patients with a major depression diagnosis have poorer immune function than nondepressed comparison subjects; (b) poorer marital quality is associated with poorer performance on qualitative indices of immune function; (c) length of separation and degree of continued attachment to the (ex-)husband are significantly associated with immune function and distress in separated and divorced women; and (d) family caregivers of AD victims have poorer immune function than well-matched comparison subjects. Taken together, these data provide good evidence of more chronic distress-related alterations in immune function. Thus, in contrast to data obtained from studies with rodents, it appears that chronic stress in humans does not lead to immunological adaptation to the level of sociodemographically-matched peers.

A number of studies have shown a relationship between an accumulation of stressful life changes and subsequent health impairments (24). Unfortunately, the effect has generally been small, and correlations between life change scores and self-reported health are typically in the 0.30s or lower (31). In addition, the great majority of life events studies find organic disease in only a minority of subjects when objective assessment procedures are used, and the mechanisms whereby such effects might be produced have not been well understood.

We suggest that the increased distress that normally accompanies major life changes (or more enduring chronic stressors) also has adverse effects on immunity. Distress-related changes in immunity would theoretically have their greatest impact in individuals whose immune system functioning is already compromised to some extent, either by an immunosuppressive disease like AIDS or by a natural process such as aging. For these individuals, smaller decrements in immune function could have larger biological consequences, because they would exacerbate existing immunological deficits at the onset. Within this framework, we argue that psychosocial resources such as supportive interpersonal relationships that buffer or moderate
the distress associated with stressful life changes may also concurrently attenuate adverse immunological changes.

We are unaware of any relevant evidence from studies with AIDS patients linking greater distress with more rapid disease progression or mortality. However, there is some epidemiological evidence from the aging literature that is consistent with this framework. Within the first year after psychiatric admission, there are 50 times more deaths from pneumonia among elderly psychiatric patients than among their age-matched general-population contemporaries; the ratio drops to 20 times that of their age peers by the second year of hospitalization, suggesting that the transition may be a more important factor than the hospital environment (6). Although it is reasonable to assume that psychiatric patients are more distressed than the general population, it should also be noted that depression is the modal reason for psychiatric hospitalization in the elderly (29).

The immunological consequences of relatively commonplace stressful events such as academic examinations are reviewed elsewhere (see R. Glaser and J. K. Kiecolt-Glaser, this volume); in this chapter we focus on immunological and health-related consequences associated with major stressful life events as well as more chronic and enduring stressors.

CHRONIC STRESS AND IMMUNE FUNCTION IN RODENTS AND MONKEYS

Data from several studies with rodents suggest that the chronicity of a stressor may mediate tumor growth and certain immunological responses. For example, a single session of inescapable shock had adverse consequences for tumor size and survival in mice injected with a transplantable tumor (28). In contrast, mice that experienced 10 daily shock sessions had tumors that were significantly smaller than those of controls; survival times were quite similar to those of controls.

In related work, Monjan and Collector (19) operationalized the results of “chronic stress” in mice as the changes occurring over a 45-day period of exposure to daily high-intensity intermittent noise. The acute or short-term consequences of the stressor appeared to be immunosuppressive, with mitogen responsiveness falling below baseline levels. However, data from blastogenic assays began to show an increase above baseline levels between days 10 and 20 and were returning to baseline levels by the end of the study.

There are a number of problems in drawing parallels between the outcome of research with rodents and the expectation of similar processes in humans. Although both rodents and humans are mammals, the immune system in rodents is more sensitive to steroids, and there is evidence that both tumor induction and growth are mediated through somewhat different pathways (e.g., ref. 9). Moreover, the stressors that are used in research with rodents are normally physical stressors such as shock, noise, restraint, or rotation (1). It is not clear if adaptation to these physical stressors follows the same course as adaptation to the psychological stressors that are of primary interest in research with humans.

There is evidence from work with nonhuman primates that adaptation does not easily occur to a repeated psychosocial stressor. Research with unweaned squirrel monkeys showed that the characteristic behavioral response to repeated 1-hr separations from their mothers adapted over time. However, the monkeys still showed reliable elevations in plasma cortisol in response to repeated separations, even after 20 such separations had occurred. A related form of separation distress has also been associated with significant immunological alterations. Completely weaned squirrel monkeys that were separated from their mothers showed decrements in several indices of humoral immunity at 7 and 14 days after the separation compared to preseparation samples (5); those monkeys who were caged with others showed less immunosuppression than those who were caged alone.

In the remainder of this chapter we discuss related evidence from human studies that suggests that longer-term psychosocial stressors do not eventuate in immunological adaptation to the level of matched comparison subjects. We also briefly review evidence that suggests an association between distress and morbidity and mortality for infectious and malignant disease.

DEPRESSION AS A LONGER-TERM STRESSOR

If there were indeed simple parallelism between the observed enhancement of immunity in rodents following a stressor prolonged over several weeks (19), then one might expect that individuals who had been quite distressed for several weeks would show enhanced immune function or would not differ from their well-matched, nondistressed community counterparts. However, data from human studies stand in contrast to the results obtained with rodents. For example, the DSM-III diagnostic classification of major depression, the psychiatric patient subpopulation most closely studied to date, specifies that the essential symptoms must have been present for a period of at least 2 weeks; in fact, most of the patients with a major depression diagnosis in our psychiatric hospital retrospectively report that the salient depressive symptoms had been present for periods of several weeks to several months before they decided to seek treatment.

Work from several laboratories has suggested that patients with a major depression diagnosis have poorer immune function than nondepressed comparison subjects. Depressed patients have poorer blastogenic responsiveness (26) and lower percentages of helper T lymphocytes (16) than their nondepressed counterparts. Other data suggest that depressed patients may have lower percentages of peripheral T lymphocytes (27).

MARITAL DISRUPTION: SHORTER- AND LONGER-TERM EFFECTS

The disruption of a marriage, through either divorce or death, appears to be one of the most stressful of life experiences (4,12,22). Both bereavement and divorce are associated with high rates of physical and emotional disorders; marital disrup-
tion is the single most powerful sociodemographic predictor of physical and emotional illness (30). Separated adults have about 30% more acute illnesses and physician visits than married adults, and divorced people have six times more deaths from pneumonia than their married counterparts (18). Both bereaved and separated/divorced adults have a higher incidence of cancer than similar married individuals (7).

Research in behavioral immunology has shown an association between bereavement and impaired mitogen responsiveness in both cross-sectional and prospective work. Bartrop et al. (2) found that 26 bereaved spouses had an impaired proliferative response 2 to 6 weeks after their spouse’s death. In a prospective study of 15 men whose wives were dying of breast cancer, Schleifer et al. (25) collected blood samples before and after the wife’s death. The men showed poorer lymphocyte proliferation after the death than before.

Separation and divorce are consistently associated with greater morbidity and mortality than bereavement; in studies that provide separate data for separation and divorce, separation is reliably associated with greater health impairments than divorce (4,32). Summarizing the differences for separated and divorced women, Verbrugge (32) concluded:

Separated women are strongly disadvantaged, compared to married ones, for acute incidence, all short-term disability measures, major activity limitations, and partial work disability. . . . Divorced women are also strongly disadvantaged. . . . (p. 283).

Based on these epidemiological data, we designed a cross-sectional study to address the possibility that there were distress-related immunological differences between married and separated/divorced individuals.

We recruited 38 separated or divorced women and 38 sociodemographically matched married comparison women (13). The two groups were matched for age, education, number of years married, and socioeconomic status of the (ex-)husband. The shorter-term consequences of marital disruption were striking: the 16 women in the sample who had been separated 1 year or less had significantly poorer immune function on five of the six immunological assays than their 16 sociodemographically matched married counterparts. There were also longer-term differences as well; comparisons of the entire cohort of 38 separated/divorced women with the 38 married women showed significant differences on three of the six immunological assays, even though the women in the separated/divorced cohort had been separated from 1 month to 6 years, with an average separation time of about 2 years. Moreover, within the separated/divorced cohort, shorter separation periods and/or greater continued attachment to the (ex-)husband were associated with poorer immune function and greater depression.

It has been suggested that the differences in health between married and nonmarried individuals may largely be a function of differences in lifestyle, with nonmarried individuals engaging in behaviors that pose greater health risks. For example, nonmarried adults might have poorer nutrition or poorer sleep, and/or they might drink, smoke, or use drugs more than comparable married individuals (32).

Both our married and our separated/divorced samples were selected in part based on criteria that included limited alcohol intake and an absence of drug use; although we did not select subjects on the basis of nutritional or sleep criteria, we found no evidence of systematic differences of a magnitude that would account for the observed differences in immune function. Therefore, although it is certainly possible that lifestyle factors may contribute to the reliable differences in morbidity and mortality found in epidemiological studies, it is also possible that there are persistent stress-related changes in physiological functions such as immunity that might have some cumulative impact on health.

POORER MARITAL QUALITY AS A CHRONIC STRESSOR

In addition to the possible differences between separated and divorced individuals, we were interested in the possibility that there might also be a relationship between immune function and marital quality. On the average, unmarried individuals are less distressed than those in troubled marriages (10,21). Data from Renne (23) also suggested a relationship between marital quality and health; unhappily married people reported poorer health than either divorced or happily married individuals of the same age, sex, and race.

Using the data from the 38 married women described above, we found that marital quality was a significant predictor of depression and loneliness in hierarchical multiple-regression equations even after subject’s education, the husband’s socioeconomic status, and the number of negative life events were entered on previous steps. In addition, poorer marital quality was associated with a poorer response on the three qualitative measures of immune function.

Longitudinal data from Levinson and Gottman (17) provide evidence of one physiological pathway through which chronically abrasive relationships might mediate immune function. They found that greater autonomic arousal in interacting married couples was strongly predictive of subsequent declines in marital satisfaction 3 years later. In addition, poorer health ratings at follow-up were strongly correlated with greater declines in marital satisfaction. If the presence of a spouse in a disturbed relationship is associated with persistent physiological arousal, then there may be concurrent alterations in endocrine function (20) that could contribute to the observed relationship between marital quality and immunity.

IMMUNOLOGICAL CORRELATES OF CHRONIC STRESS IN FAMILY CAREGIVERS FOR ALZHEIMER’S DISEASE VICTIMS

Alzheimer’s disease (AD) is thought to affect two million older adults in this country. The characteristic progressive cognitive impairments associated with AD lead to increasing needs for supportive care of the victims. Although mild memory impairments may be the only obvious symptom in the early stages, the irreversible deterioration of brain tissue eventually results in profound behavioral and cognitive
changes including disorientation, incontinence, and an inability to provide any self-care (11). Since 8 years is the modal time for survival after onset, the long-term care of these patients by family members is conceptualized as a chronic stressor (8). Alzheimer’s disease family caregivers appear to be at high risk for depression (8).

In order to study health-related consequences of caregiving for a demented relative, we obtained psychological and immunological data from 34 AD family caregivers and 34 sociodemographically matched (age, sex, and education) comparison subjects (14). Family caregivers for AD victims were significantly more depressed than comparison subjects and had poorer immune function on most of the cellular immunological assays (i.e., percentages of total T lymphocytes and helper T cells, the helper/suppressor ratio, and antibody to Epstein-Barr virus). These data suggest that chronically stressed AD family caregivers do not show immunological or psychological adaptation to the level of their well-matched age peers.

IMPLICATIONS

We have presented data from human studies that suggest that (a) psychiatric patients with a major depression diagnosis have poorer immune function than non-depressed comparison subjects; (b) poorer marital quality is associated with poorer performance on qualitative indices of immune function; (c) length of separation and degree of continued attachment to the (ex-)husband are significantly associated with immune function and distress in separated and divorced women; and (d) family caregivers of AD victims have poorer immune function than well-matched comparison subjects. Taken together, these data provide good evidence of more chronic distress-related alterations in immune function. Thus, in contrast to data obtained from studies with rodents (19,28), it appears that chronic stress in humans does not lead to immunological adaptation to the level of sociodemographically matched peers.

At present little is known about the importance of psychological factors in the progression of AIDS, especially in terms of possible changes related to HTLV-III/LAV latency (see R. Glaser and J. K. Kiecolt-Glaser, this volume). The well-publicized growth in the incidence of AIDS and its fatal consequences have led to increased depression and fear in groups at greater risk for the disease (3). Learning that one has AIDS is often followed by social ostracism at the very time when increased interpersonal support is needed and desired (3). Further research is needed to understand better the possible consequences of these and other acute and chronic psychosocial stressors for health and well-being in AIDS patients and those individuals who are at risk for AIDS.

ACKNOWLEDGMENTS

Work on this chapter was supported in part by grant No. 1 RO1 MH40787 from the National Institute of Mental Health.

REFERENCES

