Neuroimmunology of Normal Human Behavior

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INTRODUCTION

The publication of a volume entitled Neuroimmune Networks: Physiology and Diseases is a testament to the rapid expansion of literature in this relatively new field. The interactions among the nervous, endocrine, and immune systems are indeed becoming much better understood through the growing number of research papers in psychological, immunological, and neuroscience journals.

Complementing the recent findings on nervous system influences on immune function are several studies examining the effects of psychological distress on various aspects of the immune system. For example, some of the earliest of these studies examined lymphocyte responsiveness to mitogens in bereaved individuals (Bartrop et al., 1977). Blastogenesis was found to be significantly depressed in bereaved subjects, even when the death of the spouse was expected (Schleifer et al., 1983).

Our laboratory has examined immune function in several populations during acute psychological distress, as well as during periods of prolonged distress. This review focuses on recent findings and the significance of this research to the field of psychoneuroimmunology. The first section will review data from studies of acute psychological distress, and the second section will focus on chronic distress and immune function.

ACUTE PSYCHOLOGICAL DISTRESS AND IMMUNITY

Because of the prevalence of acute distress in our environment, we asked if such stressors had an impact on the immune system. Our model of acute distress consists of academic examinations in first- and second-year medical students (Kiecolt-Glaser et al., 1984; Glaser et al., 1985a,b). Written consent is obtained from each student, and feedback is provided as incentive. We typically administer a battery of psychological questionnaires to medical students 1 month prior to academic examinations (baseline) and then again during examination periods throughout the academic year. This paradigm allows us to examine data from three baseline-examination dyads in the same group of students. Questionnaires provide information on anxiety, depression, and loneliness, as well as on general health status. In addition to collecting psychological data from the students, we obtain blood samples at each sample point for immunological analyses. Plasma levels of albumin, a protein marker, are also analyzed for nutritional status at each sample point, since poor nutrition can have adverse effects on the immune system. For all of the studies discussed here, albumin levels were within normal ranges.

As an index of immune function, we use a battery of immunological assays; these include quantitative assays, such as T-lympho-
TABLE 1. Means (± S.D.) for the 16 Women Separated 1 Year or Less and 16 Matched Married Women

<table>
<thead>
<tr>
<th></th>
<th>S/D women</th>
<th>Married women</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV VCA*</td>
<td>520.50</td>
<td>147.12</td>
</tr>
<tr>
<td>(700.84)</td>
<td>(191.88)</td>
<td></td>
</tr>
<tr>
<td>Percentage of helper T-</td>
<td>26.43 (7.59)</td>
<td>32.91 (7.03)</td>
</tr>
<tr>
<td>lymphocytes*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of suppressor T-</td>
<td>20.01 (6.73)</td>
<td>22.66 (7.76)</td>
</tr>
<tr>
<td>lymphocytes*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Help-suppressor ratio</td>
<td>1.43 (0.66)</td>
<td>1.69 (1.47)</td>
</tr>
<tr>
<td>Percentage of N K cells*</td>
<td>7.50 (5.05)</td>
<td>12.79 (8.05)</td>
</tr>
</tbody>
</table>

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For< 0.005. Also significant: interaction between group and concentration of Con A, with S/D women having poorer responses to higher doses of Con A; and differences between groups in response to PHA, with S/D women having poorer proliferative responses to PHA.

Married women who reported greater satisfaction in their marriages (as measured by the Dyadic Adjustment Scale; Spanier, 1976) had better mitogenic responses to concanavalin A and phytohemagglutinin and had lower antibody titers to EBV VCA than did less happily married women. This latter result suggests better cellular immune control of virus latency in the former group.

In a follow-up study, blood samples and psychological data were obtained from 32 S/D men and 32 well-matched comparison men (Kiecolt-Glaser et al., 1988). S/D men reported more distress than did married subjects, as well as significantly more illness in the two months preceding the study. In addition to the psychological data, S/D men had EBV VCA antibody titers that were 2.5 times as great as titers in married subjects. Herpes simplex virus type 1 (HSV-1) titers were 10 times as great in the married cohort relative to the comparison subjects. These data are consistent with and support the conclusion that there is a down-regulation of cellular immunity and therefore poorer cellular immune control over latent virus in the S/D group.

These data on immune changes and marital disruption are consistent with those in the literature, reporting poorer health in S/D individuals. For example, there are more physician visits by S/D individuals than by married persons (Somers, 1979). In addition, there are more acute and chronic illness in S/D individuals as well (Verbrugge, 1979).

In another study we examined psychological and immunological data from caregivers of patients with Alzheimer's disease (AD; Kiecolt-Glaser et al., 1987b). Since AD is characterized by gradual cognitive and physical deterioration that often occurs over long periods of time (8–15 years; Heston et al., 1981), caregivers are often faced with significant changes in economic and social life styles, as well as with the stringent time demands of caregiving (George and Gwyther, 1984). In that study, AD caregivers reported more distress relative to a well-matched comparison group. Moreover, caregivers had significantly poorer immune function, including lower percentages of T-helper lymphocytes and higher antibody titers to EBV VCA relative to the comparison group.

Collectively, the data on marital disruption and caregivers provide evidence that, as with acute distress, more prolonged distress can impact negatively on certain aspects of immune function. Unlike the apparent adaptation that has been reported to occur in animals following chronic stress (Monjan and Collector, 1977), there does not seem to be similar adaptation in humans, despite the longer-term nature of the stressors.

CONCLUSIONS

Although there is still very little data in the literature, the relationships among psychological distress and immune function are becoming established. Future studies will more clearly define the mechanisms by which immunological changes occur during psychological distress. These mechanisms will involve actions of endocrine and CNS influences on the immune system; some of these interactions have already been established (Ader, 1981). Given the immunological consequences that have been documented thus far in populations experiencing acute and chronic distress, it is important to note that actual health outcomes following distress have not been extensively shown. Kiecolt-Glaser and Glaser (1988) have hypothesized that psychological stressors may have less important health consequences for young, healthy persons, but may be more significant for immunocompromised individuals, such as AIDS patients or the elderly. Long-term studies that follow such "at-risk" individuals longitudinally may provide data on the relationships between psychological distress, immune changes, and health outcome.

REFERENCES


CHRONIC DISTRESS AND IMMUNE FUNCTION

We examined the correlates on a longer-term stressor, adjustment to marital disruption, in women and in men, on several qualitative and quantitative immune measures. In the first study, psychological data and blood samples were obtained from 38 separated or divorced (S/D) women and 38 married comparison women matched for age, socioeconomic status, and educational level (Kiecolt-Glaser et al., 1987a).

Within the group of S/D women, those who were more attached to the (ex)spouse as measured by their responses to Kitson's (1982) Attachment Scale had a poorer lymphocyte proliferative response to mitogens and reported significantly more distress and loneliness than did S/D women who were not as attached to the former spouse. These data suggest that attachment to the former spouse may influence the immune response.

Because psychological distress subsequent to the break-up of a marriage is greatest within the first year following separation (Bloom et al., 1985), we examined data from 16 S/D women who had been separated 12 months or less and from 16 matched married comparison subjects. As shown in Table 1, S/D women had significantly higher antibody titers to EBV VCA and lower percentages of helper T-lymphocytes and NK cells relative to married women. In addition to these data, lymphocyte responses to two mitogens were poorer in the S/D group.