CHAPTER 10

Social Support, Stress, and the Immune System

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Until recently, human studies that provided the physiological evidence linking psychological variables and susceptibility to infectious disease were extremely rare. However, the past several years have witnessed a sharp increase in research efforts to associate psychological variables with immunological changes. These studies, in the field of psychoimmunology, have begun to unravel and clarify the relationships among psychological, endocrinological, and immunological functions. To date, the literature suggests that distressing psychological responses may be a common denominator of the psychological events or other psychologically related variables that affect the body's ability to combat infection and disease through changes in the immune system.

BACKGROUND: IMMUNE FUNCTION

Measurements of immune function typically calculate the numbers and/or functional abilities of subgroups of lymphocytes (white blood cells). Lymphocyte subpopulations perform specialized functions, and so it is not possible to use a single immunological assay to determine global immunological competence. However, there is considerable interdependence among various immunological components, and adverse changes in one lymphocyte subpopulation can have multiple cascading consequences. Most of the immunological components discussed in this chapter take days or weeks to change significantly; whereas several days of heightened dysphoria can alter many immunological parameters. A bad afternoon is not a sufficient stimulus to produce important immunological changes.

The immune response has two arms: The cellular immune response is important to the defense against intracellular viruses such as the human immuno-
deficiency virus (HIV) responsible for AIDS, and cellular immunity refers to immunological activities that do not produce antibodies, particularly those that involve T-lymphocytes. T-lymphocytes, or lymphocytes that are derived from the thymus, have various subgroups with important activities. For example, some T-lymphocytes synthesize lymphokines, proteins such as gamma interferon, and the interleukins that function as communication links between immune and non-immune cells and thus are potent immunological mediators. Helper T-lymphocytes are so named because they stimulate a number of other immunological activities, particularly the B-lymphocytes' production of antibodies. Suppressor T-lymphocytes act in a feedback loop and shut off the activities of helper T-lymphocytes when a sufficient number of antibodies have been produced.

Blastogenesis is one of the most commonly used immunological assays in the psychoneuroimmunology literature. In this assay, mitogens (chemicals that mimic infectious agents such as bacteria or viruses) are used to stimulate the proliferation (replication) of lymphocytes. That is, lymphocyte proliferation in response to mitogen stimulation is thought to model the immune system's proliferative response when challenged by naturally occurring infectious agents. Poorer proliferative responses following mitogen exposure suggest that lymphocytes may be less efficient in their ability to respond to foreign invaders.

Natural killer (NK) cells are thought to provide an important defense against virus-infected cells and cancer cells (Herberman, 1982). Interferon, one of the lymphokines or chemical mediators, is a potent enhancer of a number of different immunological activities, including NK cell activity.

**BASIC RESEARCH: STRESS AND IMMUNE FUNCTION**

Before addressing the literature that is directly related to interpersonal relationships and immunity, we will briefly review some of the more general-behavioral immunology literature. It is a literature that is still quite small, and many of the studies have serious methodological flaws (Kicelt-Glaser & Glaser, in press-a). In addition, research published before the mid-1970s should be viewed with considerable caution. The field of immunology has undergone major changes since that time, and many of the earlier immunological laboratory procedures are not considered credible by contemporary immunologists.

Before 1980 there were only a few human studies in the literature, and their focus was the immunological sequelae of novel and intense events such as bereavement (Bartrop, Luckhurst, Lazarus, Kiloh, & Penny, 1977), the space flight of astronauts (Kimsey, 1975) or the consequences of 48 or 77 hours of noise and sleep deprivation (Palmblad, Bjorn, Wasserman, & Akerstedt, 1979).

One of the early psychoimmunology studies, however, still sets a standard for research in the field today. Kasl, Evans, and Niedermaier (1979) examined the relationship between psychosocial data and seroepidemiological data collected from West Point cadets. The cadets were part of a prospective study of the development of infectious mononucleosis, a disease whose etiologic agent is Epstein-Barr virus (EBV), one of the human herpesviruses. Those cadets who were EBV seronegative on arrival at West Point (i.e., had no prior exposure to the virus and thus were not latently infected) and who had a triad of psychological risk factors (high motivation for military career, poor academic performance, and a father who was an "overachiever") were more likely to become infected with EBV, and they spent longer periods in the campus infirmary. Moreover, antibody titers to the latent virus showed a similar relationship among those cadets who did not develop clinical symptoms. These data were the first to show concurrent and significant relationships among psychological stressors, immunological indices, and actual health outcomes.

Contemporary human psychoimmunology research during this decade has had several aims. Psychiatric investigators have examined the relationship between various immunological parameters and certain psychiatric syndromes, particularly major depression (Schleifer et al., 1984). A primary goal of many of these investigators has been the identification of biological markers for psychopathology. In general, research has shown that major depression is associated with poorer immune function when depressed patients are compared with well-matched nondepressed comparison subjects (e.g., Stein, Keller, & Schleifer, 1985). However, most of the immunological differences that have been demonstrated to date do not appear to be unique to psychiatric disorders.

A second line of research looked at the relationship among various psychosocial variables and secretory IgA, an immunoglobulin produced by B-lymphocytes. Most of these investigators did not control for flow rate and/or hydration, a process that requires more than simply timing saliva collection (Stone, Cox, Valdimarsdottir, & Neale, 1987). Thus, because of the virtual absence of reliable and valid immunological data using this method, we will not review these studies.

Another line of research has concentrated on immune function in nonhuman primates, particularly related to attachment and separation. Typically, these studies look at responses in animals separated from members of the same species. For example, altered responses of lymphocytes to mitogens were reported in macaque monkeys when separated from their peers (Reite, Harbeck, & Hoffman, 1981). In addition, antibody production to a challenge by an antigen was found to be significantly depressed in infant squirrel monkeys separated from their mothers (Coe, Wiener, Rosenberg, & Levine, 1985), but this immunosuppression could be ameliorated by the presence of peers (Coe et al., 1985).

**INTERPERSONAL RELATIONSHIPS AND HEALTH**

The beneficial effects of social companionship on immune function are particularly relevant to the social support literature concerning humans.

In the extensive social support literature, there is growing evidence that interpersonal support may affect health. For example, Blazer (1982) reported that three indices of social support (impaired roles and available attachments, per-
received social support, and impaired frequency of social interaction) predicted mortality in a sample of elderly persons. Another study with older adults suggested that social networks directly influenced subsequent self-reported physical symptoms, even after controlling for initial symptom levels (Cohen, Teresi, & Holmes, 1985). The physiological mechanisms underlying these health differences, however, are not well understood.

In the remainder of this chapter we will review recent studies that address the relationships among certain aspects of interpersonal relationships and immune function in several human populations. First we will examine the effects of acute stressors on the immune system and their relationship to loneliness. Then we will discuss studies that look at the adaptation to two longer-term stressors, marital disruption and caring for a relative afflicted with Alzheimer’s disease. An intervention study, considered next, suggests that self-disclosure of traumatic events may have immunological consequences. In the final section of the chapter, we will address health implications.

LONELINESS AND IMMUNE FUNCTION

For the last several years, our laboratory has been examining the immunological correlates of psychological distress in first- and second-year medical students during academic examinations. The paradigm compares data from blood samples drawn during an examination period with similar “baseline” data obtained four weeks before examinations (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985a; Glaser, Kiecolt-Glaser, Stout, Tarr, Speicher, & Holliday, 1985b).

In the first study, data from the examination blood samples showed lower activity by natural killer (NK) cells, compared with the lower-distress baseline samples. As noted earlier, NK cells are those cells that are thought to be involved in the surveillance and destruction of virus-infected cells and tumor cells (Herberman, 1982).

In addition, there were higher antibody titers (levels) to EBV relative to the levels found on the students’ return from summer vacation (Glaser et al., 1985a). Higher antibody titers to EBV and other herpesviruses indicate that the cellular immune response is less competent in controlling EBV latency. Once a person is infected with the virus, he or she will carry for life the virus in latently infected cells. It may be reactivated from these cells under a variety of circumstances, particularly if an individual is immunosuppressed. Reactivation of latent herpesviruses is thought to reflect poorer control of these viruses by the cellular immune response.

Of particular interest was the finding that those students who described themselves as lonelier (i.e., above the median on Russell’s UCLA Loneliness Scale, 1982) had lower NK activity and higher EBV antibody titers than did those students who described themselves as less lonely (Glaser et al., 1985a; Kiecolt-Glaser et al., 1984a). Loneliness is associated with unsatisfactory interpersonal relationships (Jones, Freemond, & Goswick, 1981) and is generally perceived by individuals as distressing (Peplau & Perlman, 1982).

In a related study, lonelier psychiatric inpatients had poorer NK cell function and higher urinary cortisol levels (a stress-responsive hormone) than did patients who reported less loneliness (Kiecolt-Glaser et al., 1984b). In addition, lonelier patients had a poorer lymphocyte proliferative response to the mitogen phytohemagglutinin (PHA). Collectively, these data suggest that loneliness is associated with poorer immune function.

MARITAL DISRUPTION AND IMMUNE FUNCTION

Marital disruption is associated with high rates of psychological and physical dysfunction. Two studies addressed the possibility that the heightened distress associated with marital disruption in epidemiological studies might also have immunological consequences. On the average, separated individuals are generally highly distressed, especially immediately after separation (Bloom, Asher, & White, 1978); as a group, they show considerably higher rates of clinical and subclinical depression than do married persons (Blumenthal, 1967). Separated/ divorced (S/D) individuals represent a greater percentage of both inpatient and outpatient populations than do married individuals (Bloom et al., 1978), and these differences are thought to be related in part to the stressfulness of the experience for many individuals.

Health-related changes following marital disruption have also been documented extensively. S/D individuals suffer from more acute and chronic illnesses than do married or single individuals (Verbrugge, 1979), and they visit physicians significantly more often than married persons do (Somers, 1979).

Psychological adjustment following marital separation typically occurs over a period of several years (Wallenstein & Kelly, 1980; Weiss, 1975), and so possible distress-related immunological changes might make S/D individuals more susceptible to illness during the first several years following separation. Therefore, certain immunological data from the S/D individuals were contrasted with data from married comparison subjects who were matched for age, sex, and socioeconomic status. Because distress following marital disruption is more pronounced within the first year after separation (Bloom, Hodges, Kern, & McFadden, 1985), psychological and immunological data from 16 women who had been separated for 12 months or less were compared with 16 married comparison women. Table 10.1 shows the immunological data for the S/D and married women. The S/D women had significantly higher levels of antibodies to EBV VCA (viral capsid antigen) relative to those for married women, suggesting poorer cellular immune system control over the latent virus in the former group. In addition, the S/D women had significantly lower percentages of NK cells than did the married comparison subjects. Lymphocytes from S/D women had a lower proliferative response to the mitogens concanavalin A (Con A) and PHA, indicating a potential deficit in the cells’ ability to respond to antigens (Kiecolt-Glaser et al., 1987a).

In addition, all the women’s plasma albumin levels were assessed, because nutritional deficits can negatively affect the immune system. In all of the studies
reported by Kiecolt-Glaser et al. (1987a), plasma albumin levels were within normal ranges for all subjects.

Marital satisfaction is critical to psychological well-being (Glenn & Weaver, 1981), but the simple presence of a spouse is not synonymous with a supportive relationship. In fact, a troubled marital relationship may actually place an individual at greater risk than would the absence of a partner; that is, the marital relationship may simultaneously be a source of stress and limit a person's ability to seek support in other relationships (Coyne & DeLongis, 1986). The relationship between immunological data and marital quality was examined using the Dyadic Adjustment Scale (DAS; Spanier, 1976).

Those women in the study who were more satisfied with their marital relationships had lower antibody titer to EBV VCA, as well as better proliferative responses of lymphocytes to Con A and PHA. These data therefore suggest that better marital quality is associated with better immune function.

It was also predicted that two variables would be related to poorer immune function in the S/D group, shorter separation times and greater continued attachment to the ex-husband (i.e., greater preoccupation with the ex-husband). Consistent with these hypotheses, those S/D women who were still more attached had a poorer blastogenic response than did those S/D women who were less attached to their ex-husband. In addition, women who were more attached to their ex-husband reported significantly more distress and loneliness.

Males and females may react in different ways following the disruption of a marriage, owing to economic, social, or other reasons (Albrecht, 1980; Bloom et al., 1985). Thus, in another study, psychological and immunological data were obtained from 32 S/D males and 32 matched married comparison subjects (Kiecolt-Glaser et al., 1988). The S/D men were more distressed than were the married comparison subjects. The S/D men also reported significantly more infectious illness in the two months before the study. The two groups also differed significantly on two qualitative indices of immune function: Antibody titers to EBV VCA were two and one-half times as great for S/D men, and antibody levels to herpes simplex virus, Type-1 (HSV-1) were ten times as great in the S/D group. HSV-1, like EBV, is a herpes virus that remains latent in infected cells and may be reactivated under certain conditions; this herpes virus is the one that produces cold sores. Together, these data suggest that the cellular immune system was less competent in controlling herpes virus latency in the S/D group, compared with that in the married cohort.

The data on S/D individuals are consistent with earlier work on the immunological consequences of bereavement. For example, Bartrop and his colleagues (Bartrop et al., 1977) found impaired proliferative responses by lymphocytes to mitogens in men following the death of their wives. Similarly, Stein and his associates (Schleifer, Keller, Camerino, Thornton, & Stein, 1983) reported decreases in lymphocyte responsiveness to mitogens in men whose wives had died from an extended illness, even though they had anticipated the death. Thus, even in situations of long-term distress, there appear to be significant impairments in immune function, with no apparent adaptation over time.

The data from studies of divorce and bereavement suggest collectively that marital disruption may have negative consequences for the immune system. Although it is not yet clear whether the immunological changes associated with marital disruption are actually of a magnitude to make individuals more susceptible to certain illnesses or infectious diseases, it is possible.

Moreover, these data on marital disruption are important in another context. Some data indicate that the immune system in rodents may adapt following chronic stress (i.e., Monjan & Collector, 1977). However, the stressors used in these and similar studies usually were physical stressors (e.g., noise, shock, cold). The data from these studies and the research on caregiving that we will discuss next suggest that adaptation to the emotional stressors that are more characteristic of humans may not be the same as adaptation to physical stressors.

### CAREGIVING AND IMMUNE FUNCTION

Another study examined the immunological correlates of chronic distress associated with caring for a relative afflicted with Alzheimer’s disease (AD; Kiecolt-Glaser et al., 1987b). AD is a progressive degenerative disease of the nervous system, characterized by severe dementia, confusion, and the need for total care. The modal time of survival for AD patients is 8 to 15 years after onset (Heston, Mastri, Anderson, & White, 1981). Caring for an AD patient is a chronic stressor, because caregivers face a host of adjustments associated with the gradual cognitive and behavioral deterioration of the loved one. In addition to the direct stresses of caregiving, social interactions may be limited because of the time de-

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**Table 10.1. Means (+/- SDs) for the 16 Women Who Were Separated 1 Year or Less and for 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 (706.84)</td>
<td>147.12 (191.88)</td>
</tr>
<tr>
<td>Percentage of Helper</td>
<td>26.43 (7.59)</td>
<td>32.91 (7.03)</td>
</tr>
<tr>
<td>T-lymphocytes*</td>
<td>20.01 (6.70)</td>
<td>22.66 (7.76)</td>
</tr>
<tr>
<td>Percentage of Suppressor</td>
<td>1.49 (0.66)</td>
<td>1.69 (1.47)</td>
</tr>
<tr>
<td>T-lymphocytes</td>
<td>7.50 (5.05)</td>
<td>12.79 (8.05)</td>
</tr>
</tbody>
</table>

*p < .05

Note: Also significant at .05 level:

- Interaction between group and concentration of Con A, with S/D women having lower responses to the higher doses of Con A
- Differences between groups in response to PHA, with S/D women having a poorer proliferative response to PHA

mands of caregiving (George & Gwyther, 1984). Moreover, there may be financial changes associated with caring for the impaired relative.

In this regard, earlier studies showed significant alterations in the mental health of AD caregivers. For instance, George and Gwyther (1984) found much higher levels of psychiatric symptoms and lower life satisfaction in caregivers than in their community age-mates. Moreover, a substantial percentage of AD caregivers meet the criteria for clinical depression (Drinka & Smith, 1983; Eisdorfer, Kennedy, Wisnieski, & Cohen, 1983). An important question raised by these studies is that in addition to mental health consequences, caregiving experiences might also be associated with chronic changes in immunological function (Kiecolt-Glaser et al., 1987b). To assess this hypothesis, psychological questionnaires were given to 34 AD caregivers and 34 sociodemographically matched comparison subjects. Blood samples for immunological and nutritional assays were also obtained.

AD caregivers had significantly poorer immune function than did their well-matched comparison subjects. Specifically, caregivers had lower percentages of helper T-lymphocytes, lower helper-suppressor ratios, and higher antibody titers to EBV VCA. In addition, caregivers were more distressed than were comparison subjects. There were no differences in nutrition.

The caregivers had been providing care for an average of two years. There were no significant relationships between the duration of caregiving and either the immunological or the psychological indices.

Together, the data on marital disruption and caregiving provide evidence that chronic psychological distress may have significant negative effects on both quantitative and qualitative aspects of immune function. There was no evidence of adaptation to distress in the AD caregivers, despite the long-term stress of caregiving.

**SELF-DISCLOSURE, IMMUNE FUNCTION, AND HEALTH**

The data from studies on loneliness, marital quality, and marital disruption are consistent with the growing evidence that interpersonal relationships may have health-related consequences. Data from recent studies suggest that one facet of interpersonal relationships, self-disclosure, may be particularly important to health. The self-disclosure literature indicates that there are psychological benefits associated with sharing personal secrets, including the increased affection that results between individuals, as well as reduced feelings of isolation and loneliness (Pennebaker, 1985).

In addition, health benefits may be associated with the disclosure of traumatic events. Pennebaker and O’Heeron (1984) made contact by mail with 19 spouses who had been bereaved within the last year because of suicide or accidents. The researchers found that an increase in the illness rate from before to after the death was negatively related to talking with friends about the death. Furthermore, the increase in health problems was positively associated with thinking about the spouse’s death, and the more the subjects talked with friends, the less they ruminated about their spouse’s death. These health correlations remained intact after controlling for the number of close friends before and after the spouse’s death. However, although these data show a correlational relationship, they do not provide evidence of the direction of the relationship. Therefore, Pennebaker and Beall (1986) designed a study to evaluate the direction of causality.

In that study, they had 46 undergraduates write for four consecutive days about either personally traumatic or trivial topics. The subjects in the “traumatic” group were asked to write about the emotions, the facts, or both the emotions and the facts associated with the traumatic event. Significantly fewer members of the group that wrote about both emotions and facts, compared with the other groups in the study, visited the health center during the several months following the study.

Based on these data, a later study investigated possible immunological correlates associated with the process of self-disclosure (Pennebaker, Kiecolt-Glaser, & Glaser, 1988). The subjects were 50 healthy undergraduates who were asked to write about either personal and traumatic events or trivial topics for four consecutive days, for 20 minutes a day. The topics that the trauma group discussed were personal and emotionally troubling, such as problems with homesickness on coming to college; loneliness; conflicts with members of the opposite sex; parental problems, including divorce, family quarrels, and family violence; death of a relative, friend, or pet; and serious injury or illness.

The immunological data were collected at the baseline (before the study began), at the end of the intervention four days later, at a six-week follow-up, and at a three-month follow-up. The immunological measures assessed the proliferative response of lymphocytes to Con A and PHA. Autonomic measures (blood pressure, heart rate, and skin conductance) were collected at the same intervals as the immunological measures.

There were no differences between the two randomly assigned groups at baseline, before the intervention began. However, significant differences began to emerge by the end of the intervention. Those subjects who wrote about traumatic events had a significantly higher mitogen response to PHA following the baseline than did those subjects who wrote about trivial events. Data from Con A, though not significant, were in the same direction as PHA. There were no differences in autonomic activity between the trauma and the trivial writing groups, and there were no changes in health-related behaviors (alcohol intake, caffeine intake, or exercise) over the course of the study.

Of particular importance were the differences between the groups in health center visits. The information concerning the students’ health center visits was the average number of their visits in the preceding five months, data that were obtained from the health center with the students’ permission. Mental health visits, accidents, and routine checkups were excluded. The number of visits in the preceding five months were compared with the number of visits in the six weeks between the intervention and the six-week follow-up. The trauma subjects made fewer visits following the baseline than the control subjects did. These health data
replicate the earlier data from Pennebaker and Beall (1986) and thus suggest improvements in health associated with disclosing traumatic events. These health data followed much the same pattern as the immunological data did.

The data on the trauma group were analyzed further. High disclosers—those who reported that they had written about topics they had previously held back—were compared with low disclosers—those who reported that they had written about topics they had previously discussed with other individuals. High disclosers had a better mitogen response following the baseline than did low disclosers. In addition, from the beginning of the study to the follow-up, high disclosers showed a greater decline than did low disclosers in both systolic and diastolic blood pressure. Similar nonsignificant trends were noted for heart rate and skin conductance.

Thus, it appears that self-disclosure was associated with better immune function and health. Moreover, those individuals who reported that they had written about topics they had previously held back appeared to benefit the most.

**HEALTH IMPLICATIONS**

The studies that we described in this chapter suggest that close relationships have immunological correlates and that the quality of the relationship is important. For example, the data on marital quality demonstrate that the simple presence of a partner is not necessarily an asset. Similarly, Pennebaker’s research on self-disclosure highlights the importance of a confidant who will listen without judging or withdrawing love and support.

Although many of the physiological pathways are unclear, a prospective study by Levenson and Gottman (1985) provided evidence of a mechanism through which chronically abrasive relationships like poor marriages might affect immunity. In their longitudinal study, they showed that greater autonomic arousal in interacting married couples was a very strong predictor of subsequent declines in marital quality. In addition, poorer health ratings at a three-year follow-up were also strongly correlated with greater declines in marital satisfaction.

If a partner’s mere presence in a disturbed relationship is conducive to persistent physiological arousal, as can be inferred from Levenson and Gottman’s data, then there may be concurrent endocrinological alterations (Baum, Grunberg, & Singer, 1982) that could contribute to the relationships observed between marital quality and immunity. The endocrine system is quite responsive to a variety of emotional states (Baum et al., 1982), and there is convincing evidence of endocrinological and neuroendocrinological modulation of immune function (Ader, 1981).

Although we discussed a number of studies that relate distressing psychological responses and immunological changes, we should emphasize that the actual health consequences are not well established. Only a few studies showed a convergence among distressing psychological responses, immunological downregulation, and actual health changes (Glaser et al., 1987; Kasl et al., 1979; Kiecolt-Glaser et al., 1988; Pennebaker et al., 1988). It is likely that psychologically mediated immunological changes have a limited impact on healthy young individuals.

In theory, those individuals who are most likely to be at risk for organically based illness are already immunocompromised, such as AIDS patients, or are elderly, who have less efficient immune systems owing to the aging process (Kiecolt-Glaser & Glaser, in press-b).

One of the factors that has fueled interest in behavioral immunology in recent years is the AIDS epidemic (Kiecolt-Glaser & Glaser, in press-b). It is clear that there is very wide variability among individuals at all stages of HIV infection. Not all individuals who are exposed to HIV during high-risk activities will actually become infected with the virus; and of those who do become infected with HIV, many will remain latently infected with no clinical symptoms for years. It is known that poor nutrition, drug use, repeated HIV exposure, and other concurrent viral infections all can enhance HIV disease progression. There is still considerable variability, however, in addition to these factors. Several laboratories are currently addressing the possibility of psychological influence on HIV progression.

Clearly, longitudinal studies are needed that follow “at risk” populations over long periods of time. Such studies will provide a better understanding of the kinetics of distress-related immunological changes and the role of interpersonal relationships in mediating these changes.

**REFERENCES**


