Mechanisms of Psychological Influence on Physical Health

With Special Attention to the Elderly

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Interpersonal Relationships and Immune Function

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There is increasing evidence that the central nervous system can influence the functioning of the immune system, the body's defense against infectious and malignant disease (Ader, 1981). In this chapter we will review data linking the quality of interpersonal relationships with immunocompetence. We suggest that these data provide some insight into possible mechanisms through which interpersonal relationships might influence morbidity and mortality from infectious diseases, and possibly cancer.

It is important to highlight the conceptual framework that underlies our behavioral immunology research program, since this model provides the basis for the interpretation and discussion of the data presented in this chapter. We suggest that an increase in psychological distress, sustained over time, can lead to adverse immunological changes (Kiecolt-Glaser, Garner, Speicher,

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However, most individuals undergoing even major life changes do not become ill, or they only experience short illness episodes. Actual organically-based illness episodes are a function of differential exposure to pathogens, as well as the prior health of the individual (particularly in regard to immune system function). Thus, across individuals with equal exposure to an infectious agent like a virus, the probability of clinical illness and the intensity and duration of the illness episode are (at least in part) a product of the prior status of the individual’s immune system. Following this line of reasoning, the individuals who are presumably most likely to show health changes in response to stressors are those whose immune system function is already compromised to some extent, either by an immunosuppressive disease like AIDS, or by a natural process like aging that is associated with impaired immune function (Braveman, 1986). These individuals will most likely have poorer immunological defenses at the onset of a stressor, so that smaller stress-associated immunological decrements could have more important consequences.

In addition, individuals who are chronically distressed may also be at greater risk for infectious disease because of longer-term immunological changes. While there is some evidence that chronic physical stressors may produce immunological adaptation or even enhancement of immune function in rodents (Monjan & Collector, 1977), we find that more chronically stressed groups appear to have poorer immune function than well-matched comparison subjects. Thus, in contrast to rodent research, prolonged or chronic psychological stress in humans does not appear to lead to adaptation to the level of matched comparison subjects (Kiecolt-Glaser et al., 1987; Kiecolt-Glaser, Glaser, Strain, Stout, Tarr, Holliday, & Speicher, 1986; Schaeffer, McKinnon, Baum, Reynolds, Rikli, Davidson, & Fleming, 1985).

Thus, we are suggesting that behavioral influences on immunity are likely to have the most important health consequences in individuals who are already vulnerable, either because their immune function is already compromised by a natural process like aging, or through more chronic stress-related altera-

Pooer immune function has been associated with higher rates of mortality in individuals over 80 years of age (Roberts-Thomson, Whittingham, Youngchayud, & MacKay, 1974). Pneumonia and influenza constitute the fourth leading cause of death among the elderly (Yoshikawa, 1983). However, within the first year after psychiatric admission, there are fifty times more deaths from pneumonia among elderly psychiatric patients than found among their age-matched general population counterparts. The ratio drops to twenty times that of their age-matched counterparts by the second year of hospitalization, suggesting that the hospital environment per se may not be as important a factor as the transition (Craig & Lin, 1981). Moreover, while it is reasonable to assume that psychiatric inpatients are more distressed than community residents on the average, it should also be noted that depression is the modal reason for psychiatric hospitalization in the elderly (Solomon, 1981).

There are other epidemiological data consistent with higher rates of morbidity and mortality in more distressed populations. For example, the mortality rates among psychiatric patients are one and a half to two times as high as those among community residents, after removal of several obviously higher risk groups, including aged, chronically ill, and alcoholic patients (Babigian & Odoroff, 1969). Psychiatric patients also have a higher incidence of cancer (Fox, 1978).

If psychological resources like social support moderate distress and concurrently attenuate adverse immunological changes, then individuals with less interpersonal support should be at higher risk. In a longitudinal study of older adults, Blazer (1982) found that mortality was inversely related to three indices of social support (impaired roles and available attachments, perceived social support, and impaired frequency of social interaction). A longitudinal study of an inner-city elderly population found that social networks exerted a direct effect on subsequent self-reported physical symptoms, after controlling for initial symptom levels, with maximal buffering among those with greater numbers of life events (Cohen, Teresi, & Holmes, 1985). A number of other investigators have also found evidence of lower morbidity and mortality associated with greater support (Cohen and Syme, 1985).

There is also evidence of significantly higher mortality among bereaved, separated, and divorced individuals. Bereavement has been linked to greater
morbidity and mortality in epidemiological studies (e.g., Jacobs & Osifeld, 1977; Rees & Lutkins, 1967), although many of the studies in this genre have methodological limitations (Minkler, 1985). Bereaved individuals have a higher incidence of cancer than similar nonbereaved adults (Ernster, Sacks, Selvin, & Petrakis, 1979).

Other data suggest that separated and divorced individuals are a risk for both mental and physical illness; in fact, on an actuarial basis, there are greater health risks associated with separation and divorce than with bereavement (Bloom, Asher, & White, 1978; Verbrugge, 1979). Summarizing epidemiological evidence for differences in health, Verbrugge (1979) concluded that separated and divorced women had more acute and chronic illnesses than their age-matched married counterparts. Separated and divorced individuals also have reliably higher rates of clinical depression (Bloom, Asher, & White, 1978).

There is evidence of greater risk from some infectious diseases among separated and divorced women; separated/divorced adults have six times as many deaths from pneumonia as married adults (Lynch, 1977). In addition, separated women have 30 percent more acute illnesses and physician visits than married women (Somers, 1979).

These data provide evidence of health impairments in more distressed populations, in individuals whose marital relationship has been disrupted through divorce or death, and in older adults whose interpersonal relationships are less satisfactory and/or less numerous. Unfortunately, with a few exceptions, the studies described above do not specifically examine differences in infectious and malignant disease.

Research on the relationships between the immune system and the neuroendocrine system provides evidence of physiological pathways through which distress may modulate immune function (O’Dorisio, Wood, & O’Dorisio, 1985). There is evidence that alterations in at least certain aspects of endocrine function can have an effect on immune function, and the responsiveness of the endocrine system to psychological states is well known. There are also other pathways through which the central nervous system may influence immune function (Ader, 1981).

Measuring Immune Function

There is no single, global measure of immune system function. However, given the interdependence of the various components of the immune system, adverse changes in one aspect of immune function can have multiple repercussions.

There are a large number of different kinds of immunological assays, and those that will be discussed in this chapter can be roughly divided into two classes: qualitative assays and quantitative assays. Qualitative assays provide information on functional aspects of immunity, i.e., information about relative efficacy under certain conditions. Quantitative assays provide information on the relative percentages of certain cell types. In general, the literature on age-related alterations in immune function shows larger and more reliable differences on qualitative assays, with very mixed evidence for age-related differences in quantitative assays. The immunological assays mentioned in this chapter are described briefly below.

Blastogenesis is a qualitative assay in which the variable of interest is the amount of cells proliferate or replicate when cultured in the presence of a mitogen, a substance that stimulates lymphocyte replication. Blastogenesis is thought to provide information on the proliferative response of lymphocytes when exposed to an infectious agent such as a bacteria or virus. There are several different mitogens that are frequently used. Both phytohemagglutinin (PHA) and concanavalin A (Con A) stimulate the proliferation of certain subgroups of T-lymphocytes (thymus-derived lymphocytes). Among other activities, Con A stimulates both helper and suppressor T-cells. PHA stimulates proliferation of helper cells, but shows a somewhat diminished response in stimulating suppressor T-lymphocyte proliferation (Reinhartz and Schlossman, 1980). Pokeweed mitogen stimulates proliferation of both B-lymphocytes (cells responsible for the production of antibody) and T-lymphocytes.

Both helper and suppressor T-lymphocytes have critical regulatory functions. Helper cells facilitate a number of other immunological activities. One particularly important activity is the role helper T-lymphocytes play in stimulating B-lymphocytes to produce immunoglobulins (antibodies).Suppressor cells act in a feedback loop to shut off the activity of helper cells when sufficient antibody has been produced. If helper cell functioning is disrupted, immunodeficiency can result. The helper/suppressor ratio is sometimes used as one general index of immune function for certain populations, e.g., it is low in AIDS patients. The relative percentages of helper and suppressor T-lymphocytes are assessed with monoclonal antibodies, which identify particular markers on the cell’s surface (e.g., a marker identifying the cell as a helper T-lymphocyte).
Natural killer (NK) cell activity is thought to be an important antiviral and antitumor defense (Herberman, Orvaldo, Riccardi, Timonen, Schmidt, Maluish, & Djur, 1982). The NK cell activity or lysis assay is a functional assay that provides information on the ability of NK cells to lyse or destroy certain target cells. The assay is thought to provide an analog measure of the destruction of virus-infected cells or tumor cells in the body. The relative percentages of NK cells are often assessed in a quantitative assay using monoclonal antibodies.

A number of other immunological parameters may be altered during stressful periods. Consistent with anecdotal speculation, changes in herpesvirus latency (as measured by changes in herpesvirus antibody levels) appear to be sensitive to various psychosocial stressors (Kiecolt-Glaser and Glaser, in press). There are five human herpesviruses. Once individuals are infected with any of these herpesviruses, they carry the virus in a latent state for life (Glaser & Gottlieb-Stematsky, 1982). When the immune system is comprised (e.g., by an immunosuppressive disease like AIDS, or by an immunosuppressive drug regimen such as those that precede most organ transplants) there are characteristic elevated herpesvirus antibody titers. These elevated titers are thought to reflect the increased production of antibody in response to enhanced viral replication; when immune system function improves, there is ultimately a drop in antibody titers to the latent herpesviruses (Glaser & Gottlieb-Stematsky, 1982).

The time course of immunological changes should be kept in mind: in contrast to the relatively rapid changes associated with autonomic or endocrine function, most components of the immune system change over days or weeks, not minutes or hours. Thus, while a bad afternoon is not sufficient to change most aspects of immunocompetence, several days of significantly increased distress (e.g., as seen in medical students before an examination) may lead to adverse immunological changes.

Loneliness and Immunity

Our earlier work addressed the relationships among immunity, relatively commonplace stressful events, and loneliness. Loneliness is associated with constricted and dissatisfying personal relationships (Jones, Freemon, & Goswick, 1981), and the experience of being lonely is generally distressing (Peplau & Perlman, 1982). While loneliness appears to result from perceived deficiencies in a person's social relationships, it is not synonymous with social isolation (Peplau & Perlman, 1982).

Using 75 medical students who volunteered for a research project on stress and immunity, we collected self-report data and blood samples a month before final examinations, on the first day of final examinations, and again after the students’ return from summer vacation (Kiecolt-Glaser et al., 1984a). There was a significant decrease in natural killer cell activity during examinations, when compared to baseline levels; we did not have NK data from the final sample point. Also, lonelier students (those scoring above the median on the UCLA Loneliness Scale developed by Russell, Peplau, & Cutrona, 1980) had significantly lower levels of NK cell activity than students who described themselves as less lonely.

We were also interested in possible changes in antibody titers to a latent herpesvirus, Epstein-Barr virus (EBV), the etiologic agent for infectious mononucleosis (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985). Evidence from seroepidemiological studies suggests that the mean antibody titer for EBV virus capsid antigen (VCA) in healthy adults is around 1:80 (Henle & Henle, 1982). In contrast, the EBV VCA geometric mean titer for our 49 EBV seropositive medical students was over 1:560 in both the blood samples obtained one month before final examinations as well as those taken during examinations. The geometric mean titer dropped to 1:93 after the students' return from summer vacation. Paralleling the pattern for the NK cell lysis data, lonelier students had significantly higher EBV VCA titers than their less lonely student colleagues, suggesting that cellular immune response in the former group was less competent in controlling herpesvirus latency. Similar stress-related changes occurred in antibody titers to two other herpesvirus, herpes simplex virus, the virus associated with cold sores, and cytomegalovirus a herpesvirus that produces a mononucleosis-like syndrome during the initial acute infection.

We also found that lonelier psychiatric patients had significantly lower levels of NK cell activity than less lonely patients (Kiecolt-Glaser et al., 1984b). Lonelier inpatients also showed a poorer proliferative response to the mitogen PHA, and had higher levels of stress-related urinary cortisol.

Psychosocial Enhancement of Immune Function

The data from medical students suggested that commonplace distress-producing events might be associated with significant alterations in immune function; moreover, both lonelier medical students and lonelier psychiatric inpatients had poorer immune function than their counterparts who were presumably more satisfied with their interpersonal relationships. Based on these data, we were interested in the possibility that psychosocial
interventions that reduced distress and/or loneliness might lead to an enhancement of immune function. We recruited 45 older adults from independent living facilities for an intervention study (Kiecolt-Glaser et al., 1985). Previous research had shown that increased attention was reliably associated with small but consistent improvements across a variety of mental and physical health indices in nursing home residents (Schulz, 1980; Rodin, 1980): such simple interventions as regular visits from college students have been associated with significant improvements in physician and self-ratings of physical and mental health, increased activity, and significant decreases in urinary cortisol.

In order to evaluate the relative potency of relaxation and social contact, our 45 older adult subjects were randomly assigned to a relaxation condition, a social contact condition, or a no intervention condition. Subjects in the relaxation and social contact conditions were seen individually three times a week for a month, by the same student each time. Blood samples and self-report data were collected at baseline before the interventions began, at the end of the one-month intervention period, and at a one-month follow-up.

Post hoc analyses of significant interactions showed discrete changes in the relaxation cohort: relaxation subjects showed a significant increase in NK cell activity at the end of the intervention when compared to baseline, and a significant decrease in antibody titers to herpes simplex with a Type 1 antigen. Taken together, the increase NK activity and lower antibody titers are consistent with improved cellular immune system function at the end of the intervention. While NK cell activity did not differ significantly from baseline levels at the one-month follow-up, HSV antibody titers were still significantly lower than baseline levels at follow-up.

Self-report distress data from the Hopkins Symptom Checklist showed discrete changes only for the relaxation group; however, few subjects had reported much distress-related symptomatology at baseline, so there was little room for improvement. There were no significant changes in loneliness. Although relaxation was framed as a control-enhancing intervention, there were no significant changes in feelings of control.

Data from blastogenesis assays showed some general enhancement across the three experimental groups. There was a significant improvement in the self-rated quality of sleep across the three groups as well. Since the total sample was comprised of four cohorts from four different facilities and data were collected at four different times of year, these effects are unlikely to be the product of facility- or season-related changes, and may reflect some more general enhancement associated with experimental participation.

The changes in the immunological variables suggested that relaxation might have some positive consequences for immune function. While we did not find discrete differences associated with the social contact intervention as we had expected, our subjects were residents of independent living facilities, rather than nursing homes as in previous research (Rodin, 1980; Schulz, 1980). The latter's greater environmental restrictions may increase the potency of social contact as a mood altering intervention.

We are aware of only one other study published to date that has examined behavioral influences on immunity in older adults. Thomas, Goodwin, and Goodwin (1985) found low but statistically significant correlations between "satisfying confidant relationships" and two immunological indices, total lymphocyte count and mitogen response to one concentration of PHA, among a sample of 106 women between the ages of 61 and 89 years of age, after correcting for psychological distress and other variables; the correlations were not significant for the 91 men in the sample. If, however, distress and support are causally related, these limited data may underestimate the magnitude of the effects.

Marital Disruption and Marital Quality

The loneliness data suggested that more chronic changes in immunity might be associated with the quality of interpersonal relationships. Further studies on marital disruption have provided a way to examine acute changes in immune function in response to the loss of an important relationship, as well as subsequent adjustment. The marital quality data suggest that the simple presence of a spouse does not necessarily have positive psychological and physiological correlates.

Bartrop, Luckhurst, Lazarus, Kiloh, & Penny (1977), in one of the earlier human psychoimmunology studies, showed that bereaved spouses had a poorer proliferative response to mitogen stimulation two to six weeks after the spouse's death than nonbereaved controls. In a prospective study of bereavement, Schleifer, Keller, Camerino, Thornton & Stein (1983) followed 15 men whose wives were dying of breast cancer, with collection of blood samples before and after the wife's death. They found that these men had a poorer blastogenic response after the wife's death than they did before be-reavement, in spite of the fact that the death had been anticipated. Most of the men in
their sample were back to their prebereavement immunological levels within a year.

Our laboratory's interest in the immunological correlates of marital disruption was fueled by the epidemiological literature reviewed earlier. However, we were also interested in a possible relationship between marital quality and immune function, since unhappy marriages are associated with increased distress: on the average, unmarried individuals are less distressed than those in troubled marriages (Glenn & Weaver, 1981; Pearl & Lieberman, 1979). Furthermore, poorer marital quality has also been associated with poorer health; in a study by Renne (1971), unhappily married people reported poorer health than either divorced or happily married individuals of the same age, sex, and race.

Taken together, these studies suggest that both poorer marital quality and marital disruption are associated with greater distress and poorer health. We were interested in the possibility that there were also concomitant immunological alterations in certain more vulnerable individuals. In order to test these speculations, we recruited 38 separated or divorced women and 38 sociodemographically-matched married comparison women who completed questionnaires and allowed blood samples to be drawn (Kiecolt-Glaser et al., 1987a). The immunological assays included three qualitative assays (blastogenesis with PHA and Con A, and antibody titers to EBV) and three quantitative measures (percentages of NK cells and helper and suppressor T-lymphocytes).

As hypothesized, marital quality was a significant predictor of depression and loneliness in hierarchical multiple regression equations, after entering subject's education, the husband's socioeconomic status, and the number of negative life events on previous steps. In addition, poorer marital quality was significantly associated with a poorer response on the three qualitative measures of immune function.

The predictions concerning psychological and immunological relationships in the separated/divorced cohort were based on attachment theory, the central conceptual framework used in the divorce literature to account for differences in post-separation symptomatology (Bowlby, 1975; Weiss, 1975). Within this framework, continued preoccupation with the inaccessible spouse (including either positive or negative affect) leads to "separation distress" and the associated distress-related symptoms. Not surprisingly, attachment feelings generally decline as separation time increases; however, there is considerable variability in the amount of continued attachment in separated and divorced individuals, even for those separated for about the same length of time. Based on these factors, we expected that both shorter separation periods and stronger feelings of attachment would be significantly and inversely related to immune function, while both would be directly related to distress. These predictions were confirmed.

Two sets of comparisons were of interest between the separated/divorced cohort and the married group. The separated/divorced cohort had separation times ranging from three months to six years, with a mean of 1.72 years. We found that the 16 women who had been separated a year or less had significantly poorer immune function on five of the six assays than 16 sociodemographically-matched married women; contrary to predictions, differences in distress did not reach statistically significantly levels.

We did not predict overall group differences, since the average time since separation in our marital disruption group was almost two years. However, in comparisons of the data from all of the 38 separated/divorced women and the 38 married women, the former group had significantly poorer immune function across three of the six immunological assays than the latter, and they were also significantly more distressed.

It has been suggested that marital disruption might have adverse effects on health because of differences in risk-related health behaviors; for example, separated and divorced individuals might drink, smoke or use drugs more than married individuals, and/or they might have poorer diets and get less sleep (Verbrugge, 1979). We used good health and the absence of prescription or nonprescription drug use as screening criteria for all our subjects, and we excluded subjects who drank more than 10 alcoholic drinks per week. We did not find evidence of differences in sleep or nutritional status that were of sufficient magnitude to account for the observed differences in immune function (Chandra & Newberne, 1977). Thus, while some of the differences in the epidemiological literature may be a function of life-style variables, it is also possible that there are persistent distress-related physiological changes that could make an additional contribution to the observed differences in health as a function of marital status.

There are obvious difficulties in inferences about causality using cross-sectional data such as these. However, there are some remarkable data from Levenson and Gottman (1985) that provide evidence of a pathway through which chronically abrasive relationships could mediate immune function. Their data showed that greater autonomic arousal in interacting married couples was strongly predictive of greater declines in marital satisfaction three years
later, and greater decrements in marital satisfaction were also strongly correlated with subsequent ratings of poorer health. If the presence of a spouse is associated with relatively consistent physiological arousal in a disturbed relationship, then there could be concurrent alterations in endocrine function that could have an impact on the immune response (O’Dorisio et al., 1985).

Another form of separation distress has been associated with significant immunological and endocrinological alterations. Completely weaned squirrel monkeys separated from their mothers showed decrements in humoral immune function at 7 and 14 days post-separation, compared to pre-separation samples. Greater immunosuppression was found in individually caged monkeys compared to those caged with others (Coe & Levine, in press). In related research with unweaned squirrel monkeys, the characteristic behavioral response to repeated one-hour maternal separations adapted over time; in contrast, plasma cortisol elevations in response to the separation continued to reliably occur, even after 20 such separations.

So, What Does It All Mean?

Despite the astonishing growth in social support research in recent years, remarkably little is known about possible physiological mechanisms mediating the impact of supportive or nonsupportive relationships on health. The studies reviewed in this paper provide evidence that the quality of interpersonal relationships may be related to immune function. Lonelier medical students and psychiatric patients have poorer immune function than their counterparts who describe themselves as less lonely (Glaser et al., 1985a; Kiecolt-Glaser et al., 1984a,b). Chronically unsatisfying marital relationships are associated with greater depression and a poorer response on three qualitative measures of immune function. Separated and divorced women who continue to be more attached to their (ex)spouse are more depressed and have poorer immune function; those separated/divorced women who reported having a new and satisfying relationship with a man reported lower attachment (Kiecolt-Glaser et al., 1987a). Another form of separation distress has also been associated with immunological and endocrinological alterations in monkeys (Coe & Levine, in press). Men whose wives had died had a poorer blastogenic response than age-matched nonbereaved counterparts (Schleifer et al., 1983). These data are consistent with epidemiological evidence on morbidity and mortality, and provide evidence of one possible physiological pathway though which such effects may occur.

One potentially important psychological issue that is only peripherally addressed in these psychoimmunological studies is the possible negative impact of nonsupportive relationships. Within the social support literature there is growing evidence suggesting that "negative" support may have stronger effects than positive support (Antonucci & Jackson, in press; Suls, 1982); the simple presence of others is not equivalent to a satisfying relationship. Consistent with this, women who were less satisfied with the quality of their marriages had poorer immune function (Kiecolt-Glaser et al., 1987a). Relationships that are reliably associated with increased distress may also have a longer-term impact on immunity.

Moreover, it is reasonable to assume that particular kinds of support may interact with different individuals’ needs under varying circumstances (Cohen & Syme, 1985). Different kinds of support may have different consequences, interacting with individuals’ characteristics and life circumstances. This specificity has not been addressed in any depth in the social support literature to date (Cohen & Syme, 1985).

Finally, it should be noted that the critical connection between stress-related immunological alterations and actual health changes is not well-established. While it is reasonable to assume that both shorter- and longer-term alterations in immunity may have deleterious consequences for health, the longitudinal studies that will help understand the magnitude of the relationship and its association with the incidence, duration, and intensity of infectious disease are largely absent. Recent data from our laboratory suggest a confluence of increased distress, poorer immune function, and increased infectious illness (primarily colds and flu) in medical student subjects using a longitudinal design (Glaser et al., 1987). Additional prospective studies with at-risk groups like the elderly will provide a clearer picture of the impact on health.

References


