I. Introduction

Two key historical developments provided the impetus for the research reviewed in this chapter. In 1964, George F. Solomon coined the term psychoneuroimmunology and published a paper that was far ahead of its time: "Emotions, immunity, and disease: A speculative theoretical integration" (Solomon & Moos, 1964). Subsequently, the landmark paper of Ader and Cohen (1975) demonstrating classical conditioning of immune function sparked a resurgence of interest in psychoneuroimmunology. In many ways, the result of this resurgence is that the immune response is being reexamined in the context of an integrated system and no longer as a body system that

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II. Major Stressful Life Changes

There is a large and relatively consistent literature on stressful life events that suggests that individuals who have experienced recent major negative life changes may be at greater risk for a variety of illnesses, including infectious disease. Although the correlations are not large, generally accounting for only about 10% of the variance (Cohen & Syme, 1985), the effects are remarkably consistent across populations and different kinds of life events. In particular, events associated with the loss of important personal relationships appear to put individuals at greater risk, and these same events have also been the focus of psychoneuroimmunological studies.

A. Bereavement

Epidemiological studies have demonstrated clear differences between married and unmarried individuals in both mental and physical health. Although there are a number of methodological problems in this literature (Minkler, 1985), bereaved spouses generally appear to have greater morbidity and mortality than nonbereaved controls, and they experience a greater incidence of cancer mortality than the general population (Bloom, Asher, & White, 1978; Verbrugge, 1979).

In an attempt to explore physiological mediators of these effects, the immunologic consequences of bereavement have been studied. For example, bereaved spouses had a poorer lymphocyte proliferative response to mitogen stimulation 2–6 weeks after the death of their spouse compared to nonbereaved comparison subjects (Bartrop, Luckhurst, Lazarus, Kiloh, & Penny, 1977). In a subsequent prospective bereavement study, men whose wives were dying of breast cancer were assessed before and after their wives’ deaths (Schleifer, Keller, Camerino, Thornton, & Stein, 1983). Lymphocytes obtained from these men showed a poorer proliferative response to mitogens following the death of their spouses compared to the blastogenesis data obtained prior to bereavement.

In a subsequent study, Irwin, Daniels, Smith, Bloom, and Weiner (1987) examined immune function in three groups: 16 women whose husbands were being treated for metastatic lung cancer, 10 women whose husbands had died of lung cancer 1–6 months prior to their research participation, and 11 women whose husbands were in good health. Widows showed the greatest depression and impairments in immune function, consistent with the prospective data from Schleifer et al. (1983). Thus, convergent data from several laboratories suggest that bereavement may be associated with downregulation of some components of the immune response.

B. Divorce

Epidemiological data also suggest that separated and divorced individuals are at 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 et al., 1978; Verbrugge, 1979).

To assess possible immunologic alterations associated with divorce, separated or divorced women and sociodemographically matched married comparison women completed questionnaires and provided blood samples for immunological evaluations (Kiecolt-Glaser, Fisher, et al., 1987). The immunological assays included three qualitative or functional assays and three quantitative or enumerative measures. The 16 women in the separated/divorced subgroup who had been separated 1 year or less had significantly poorer immune function on five of the six immunological assays than the 16 well-matched married community counterparts.

Also of interest were psychological factors within a larger cohort of 38 separated/divorced women that might be related to greater distress and poorer immune function (Kiecolt-Glaser, Fisher, et al., 1987). Evidence from the divorce literature suggests that continued preoccupation with the (ex)spouse (“attachment”) leads to distress-related symptoms (Weiss, 1975). While attachment feelings generally decline as time increases after marital separation, there is considerable variability in the amount of continued attachment in separated and divorced individuals, even for those separated for similar time periods. Consistent with hypotheses based on this literature, we found that both shorter separation periods and stronger feelings of attachment were negatively correlated with immune function.

In a similar study, Kiecolt-Glaser et al. (1988) compared self-report data and immune function from 32 separated or divorced men and 32 sociodemographically matched married men. Separated/divorced men were more distressed and lonelier and reported significantly more recent illnesses than married men; the former also had significantly poorer values on two functional indices of immunity, although not differing on quantitative indices. Those separated/divorced men who had separated within the last year and who had initiated the separation were less distressed and reported better health than noninitiators.

It appears that there is some consistency in studies that have investigated
the consequences of marital disruption occurring either through bereavement or through divorce. In both cases, cross-sectional studies have shown differences between individuals who have recently experienced the disruption of their marriage and comparable married adults. However, there only is one prospective study on marital disruption to date (Schleifer et al., 1989), and there are a number of other important potential behavioral mediators, which are discussed shortly.

III. Depression and Chronic Stressors

A. DEPRESSION

One of the common consequences of major stressful life events like bereavement or divorce is increased anxiety and depression, albeit usually within a normal (nonclinical) range. A number of researchers have also investigated immune changes in clinically depressed patients (i.e., patients with a major depression diagnosis). Whereas there is considerable variability in the data, depressed patients generally have poorer immune function than nondepressed controls. For example, some data suggest that depressed patients have lower percentages of helper T lymphocytes (Denney, Stephenson, Penick, & Weller, 1988; Krueger, Levy, Cathcart, Fox, & Black, 1984), fewer suppressor and total T lymphocytes (Denney et al., 1988), and a poorer T-cell response to mitogen stimulation (Kronful & House, 1984; Schleifer et al., 1984) than nondepressed matched counterparts.

Although these data are interesting, the use of other data collection methods has produced divergent results. In a carefully controlled study in which only nonmedicated patients with a major depression diagnosis were used, peripheral blood lymphocytes (PBLs) were collected simultaneously from the depressed patient and an age- and sex-matched control subject (Schleifer, Keller, Bond, Cohen, & Stein, 1989). Use of this paradigm revealed no significant differences between the two groups. However, regression equations that were based on the difference scores between these carefully matched pairs showed that there were increasing differences associated with age, in other words, depression had an increasingly negative association with immunity as age increased.

There are data that suggest that depressed individuals may be at greater risk for malignant disease. For example, in an excellent 17-year prospective study that included over 2,000 nonpsychiatric men and controlled for a number of risk factors, the investigators found a significantly higher incidence of cancer associated with higher depression scores on the Minnesota Multiphasic Personality Inventory (MMPI) (Shekelle et al., 1981).

In order to explore possible relationships between psychological stress and cancer, we performed a study using PBLs obtained from 28 newly admitted, nonpsychotic, nonmedicated psychiatric inpatients (Kiecolt-Glaser, Stephens, Lipetz, Speicher, & Glaser, 1985); the majority of these patients had a major depression diagnosis. The inpatients were divided into high and low distress subgroups using a median split on their MMPI scale 2 (depression). Subjects' lymphocytes were exposed to X-irradiation in order to damage cellular DNA and thus induce DNA repair mechanisms. The lymphocytes obtained from the more distressed inpatients had significantly poorer DNA repair than lymphocytes obtained from low distress subjects. The finding is important because faulty DNA repair is associated with an increased incidence of cancer: most carcinogens appear to induce cancer by damaging the DNA in cells, thereby producing mutant cells (Setlow, 1978).

In a follow-up study using rats which were given the chemical carcinogen dimethylnitrosamine in the drinking water, we determined that rotational stress depressed the ability of splenic lymphocytes to synthesize O6-methylguanine DNA methyltransferase, an enzyme central to the DNA repair metabolic pathway (Glaser, Thorn, Tarr, Kiecolt-Glaser, & D'Ambrosio, 1985). These data are consistent with the data from the DNA repair study, suggesting one possible explanation for the differences observed in DNA repair in the two groups of patients examined. Further studies will be needed to explore this interesting interaction between psychological stress, modulation of DNA repair, and the implications for increased risk for the development of abnormal cells.

B. CHRONIC STRESS

We were interested in determining if accommodation takes place in the immune response over time to a psychological stressor, namely, whether the body adapts so that values appear to return to normal baseline values as shown by well-matched controls. In order to explore this question, we studied caregivers of Alzheimer's disease patients. Alzheimer's disease affects 2 million older adults in this country. The progressive cognitive impairments that are characteristic of Alzheimer's disease lead to increasing needs for supportive care of afflicted individuals (Heckler, 1985). Since the modal survival time after onset is approximately from 8 to 20 years (Heston, Mastro, Anderson, & White, 1981), long-term care of these patients by family members may be conceptualized as a chronic stressor (Fiore, Becker, & Coppol, 1983).

Cross-sectional data from several laboratories suggest that the stresses of Alzheimer's disease caregiving leave family members at high risk for depression (Crook & Miller, 1985; Fiore et al., 1983). Moreover, there may be some progressive deterioration in the well-being of caregivers over time. George and Gwyther (1984) found substantial deterioration in the well-being of caregivers when measures were taken at 1-year intervals. The changes were particularly noteworthy because the baseline levels of well-being in these
caregivers were already quite low in absolute terms. Furthermore, caregiving responsibilities have been associated with self-reported health impairments (Brookehurst, Morris, Andrews, Richards, & Laycock, 1981; Sainsbury & Grad de Alarcon, 1970).

To investigate possible immunologic consequences of this long-term, chronic stressor, blood samples and psychological data were obtained from 34 Alzheimer’s disease family caregivers and 34 sociodemographically matched comparison subjects. Family caregivers for Alzheimer’s disease victims were more distressed than comparison subjects without similar responsibilities, and caregivers also had generally poorer immune function as measured by a battery of five assays. These preliminary data suggest that chronically stressed Alzheimer’s disease family caregivers do not show immunologic or psychological adaptation to the level of well-matched age peers (Kiecolt-Glaser, Glaser et al., 1987).

Other data also suggest that chronic stressors may have immunologic implications. Baum and co-workers (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989) have shown persistent behavioral and endocrinological differences between residents of the Three Mile Island area, where a damaged nuclear power plant threatened to create an enormous disaster in 1979, and a demographically comparable group who lived 80 miles from the threatened area. Over a 6-year period after the incident, the subjects living in the Three Mile Island area had consistently higher levels of urinary epinephrine and norepinephrine and also occasionally showed higher levels of cortisol than the control group. In addition, the same group showed higher levels of blood pressure and elevated heart rates (Baum, Gatchel & Schaeffer, 1983; Davidson & Baum, 1986).

The Three Mile Island residents were also evaluated for changes in immune status. It was found that Three Mile Island residents had fewer B lymphocytes, natural killer (NK) cells, and T suppressor/cytotoxic lymphocytes than comparison subjects; moreover, two other kinds of immunologic data were also consistent with immunologic downregulation in Three Mile Island residents compared to controls, namely, differences in numbers of neutrophils and antibody titers to a latent herpesvirus. The authors suggested that these differences may be related to the Three Mile Island residents’ greater psychological distress, behavioral difficulty, and physiological arousal, all of which have been persistently different in the regular follow-ups after the incident.

The data from Alzheimer’s disease family caregivers and Three Mile Island residents suggest that chronic stress in humans does not lead to immunologic adaptation to the level of well-matched community peers. These data differ from a study with rodents in which acute stress appeared immunosuppressive, whereas chronic stress was associated with adaptation or even immune enhancement (Monjan & Collector, 1977). Further studies will have to be performed in order to explore other aspects of chronic stress and its impact on the immune response.

IV. Academic Stress

We were interested in determining if relatively commonplace stressful events were associated with suppression of the immune response and if the suppression could have implications for risk for infectious disease such as colds and flu. To explore this issue, we performed several studies which involved first- and second-year medical students at Ohio State University Medical Center using academic stress as an acute cyclical stressor. The medical school curriculum is such that the students have seven or eight 3-day examination blocks over the academic year. Thus, the medical class as a whole cycles through these examination periods.

In our first study, we found a decline in NK activity in blood samples obtained from 75 medical students during final examinations, in contrast to baseline blood samples collected 1 month previously; psychological distress increased during examinations (Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984). Natural killer cell activity is thought to be important in the defense against cancer and certain viruses (Bloom, 1980). In a subsequent study we found similar decreases during examinations in the number of NK cells using two independent measures, the number of large granular lymphocytes (the NK cell phenotype) and the number of cells expressing an NK antigen detected with a monoclonal antibody (Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986; Kiecolt-Glaser, Garner, et al., 1984). These data suggest that the decrements in NK cell function in our studies (and in studies from other laboratories) may reflect, at least in part, a decrease in NK cell numbers in the blood samples.

Because the immune response can be affected by poor nutrition, two nutritional markers were included in these and most other studies from our laboratory. The two markers assessed were plasma albumin and transferrin, which provide good indicators of protein intake (Chandra & Newberne, 1977). Both albumin and transferrin levels in plasma were within normal ranges; therefore, the changes observed in cellular immunity associated with academic stress (as well as other stressors) were probably not a function of nutritional deficiencies.

Other changes in the cellular immune response have been associated with examination stress. These include changes in total T-lymphocyte numbers and T4/T8 ratios, mitogen responsiveness, interferon-γ (IFN-γ) production by PBLs stimulated with concanavalin A (Con A), and the ability of the cellular immune response to maintain control over latent herpesviruses (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985; Glaser et al., 1986; Kiecolt-Glaser et al., 1986).

Significant changes in antibody titers to latent herpesviruses may reflect stress-related changes in the competence of the cellular immune system (Henle & Henle, 1982). Elevated antibody titers to latent herpesviruses are thought to occur following enhanced expression of latent virus owing to
In this same study we found that academic stress can downregulate specific T-cell killing as measured by T-cell-mediated immunity to EBV (Glaser et al., 1987). The ability of T-cell-mediated immunity to inhibit the outgrowth of EBV-infected autologous B lymphocytes fluctuated with examination stress. The specificity of these results is supported by the fact that, as expected, lymphocytes from EBV-seronegative students showed no cell-killing activity; their T cells had not been previously exposed to EBV. These data are consistent with previous reports (Moss, Richardson, & Pope, 1978; Richardson, Moss, & Pope, 1979). The usefulness of such an assay to measure specific T-cell killing has been previously demonstrated in immunosuppressed X-linked lymphoproliferative (XLP) patients by Harada, Bechtold, Seeley, and Purtill (1982). They found a significant decrease in the cytotoxic T-cell response to autologous EBV-infected cells from such patients, suggesting an impaired lymphocyte response to EBV-specific antigens and defective memory or helper T-cell function(s).

Evidence consistent with these laboratory data comes from a clinical study by Kasl, Evans, and Niederman, (1979), who obtained psychological and immunologic data from West Point cadets who were seronegative for EBV (not latently infected) on entry into the military academy. Data collected over the 4 years the cohort was followed showed that a triad of psychosocial risk factors (higher levels of motivation for military career, poorer academic performance, and having a father who was an "overachiever") was associated with three illness indices: an increased risk for seroconversion to EBV, longer hospitalizations in the inpatient following seroconversion, and higher antibody titers to EBV among those who seroconverted in the absence of clinical symptoms. Other clinically related evidence also showed a convergence among psychological stress, HSV-2 lesions, and immune function (Kemeny, Cohen, & Zegans, in press).

A recent finding in our laboratory is related to examination stress-induced alterations in apoptosis, or programmed cell suicide. Apoptosis is a process of molecular self-destruction or cell suicide following cellular insults such as low-level irradiation exposure or exposure to a toxic chemical (Williams, Little, & Shipley, 1974). Apoptosis protects organisms from the accumulation of cells with induced heritable changes in cellular DNA, for example, induced by irradiation, by clearance of these cells by effector immune cells (Duvall, Wyllie, & Morris, 1985). In this study we demonstrated reversible changes in apoptosis in the response of PBLS to low-level γ-radiation and to exposure to a tumor-promoting phorbol ester; these reversible changes were related to the stress of examinations (Tomei, Kiecolt-Glaser, Kennedy, & Glaser, in press). These data provide additional evidence of one mechanism through which psychological distress could contribute to increased defects in cellular immunity and cancer risk through modulation of programmed cell suicide. Considering the stress-related changes in NK cell activity and changes in DNA repair associated with psychological stress already discussed in the context of these preliminary findings, it is possible
that any one of the "defects" alone or in combination could increase cancer risk. Taken together, these data suggest that academic stress may modulate a variety of different immunological activities.

V. Intervention Studies

Is it possible that CNS-mediated immune regulation can be influenced using a stress-reduction intervention? In order to explore this question, we conducted a study using a standard relaxation paradigm. The relaxation intervention was associated with an enhancement of certain immunologic markers in a sample of 45 geriatric residents from four retirement homes in Columbus, Ohio. The older adults had been randomly assigned to one of three protocols: relaxation training, social contact, or no intervention. Blood samples and self-report data were collected at baseline, at the end of the intervention (1 month), and at a 1-month follow-up. Subjects in the relaxation training group showed a statistically significant enhancement in two different assays of cellular immune function at the end of the intervention (NK cell activity and control of latent HSV-1 as measured by a decrease in antibody titers to this virus). There was a concomitant significant decrease in distress-related symptomatology, in comparison to nonsignificant changes in the other two groups (Kiecolt-Glaser, Glaser, et al., 1985).

A different kind of intervention study was conducted with 34 first-year medical students (Kiecolt-Glaser et al., 1986). Half of the medical students were randomly assigned to a hypnotic/relaxation group that met in the interval between baseline and examination blood draws. The first blood sample was obtained 1 month before the second block of examinations, and the second blood sample was obtained on the last day of the 3-day examination period. The percentages of helper T lymphocytes declined across both groups of students; NK cell activity decreased as well, consistent with our previous studies (Kiecolt-Glaser, Stephens, et al., 1984). There were no significant differences between the hypnotic/relaxation group and the no intervention group; however, the number of times subjects had practiced the relaxation exercise ranged from 5 to 50. Subsequent regression analyses showed that frequency of relaxation practice was a significant predictor of the percentage of helper T cells in the examination sample, after controlling for baseline levels, but did not reliably predict either the percentage of suppressor cells or NK cell activity.

A subsequent study tested the hypothesis that actively confronting upsetting experiences might have positive physiological consequences (Pennebaker, Kiecolt-Glaser, & Glaser, 1988). Fifty healthy college students were randomly assigned to write about either traumatic experiences or superficial topics for 20 min per day on 4 consecutive days. The PBLs obtained from those subjects who wrote about traumatic events demonstrated an overall higher mitogen response following baseline in comparison to control subjects. Comparisons of the average monthly number of health center visits in the 15 weeks prior to the study with those during the 6 weeks of the study showed a significant drop in the number of visits for trauma subjects relative to those of controls. In addition, those participants who wrote about experiences that they had previously "actively held back" in discussions with others had a better T-cell proliferative response that those subjects who had not similarly held back. Consistent with the results of our intervention study with older adults (Kiecolt-Glaser, Glaser, et al., 1985), these data suggest that psychotherapy or other distress-reducing therapies may have positive consequences for immune function and health. There is some evidence that even brief psychotherapy or psychological consultation is associated with fewer outpatient medical visits, fewer days of hospitalization, and lower medical costs (Jones & Vischi, 1980; Mumford, Schlesinger, & Glass, 1981). Neither the mechanisms underlying these effects nor their generalizability is known.

In contrast to these generally positive results from intervention studies, a stress-reduction intervention did not result in a change in a battery of immunologic measures in human immunodeficiency virus (HIV)-seropositive men compared to wait-list controls (Coates, McKusick, Kuno, & Stites, 1989). The researchers speculated that the absence of significant effects could reflect the possibility that immune function may not be influenced by stress-reduction techniques in the presence of the immune suppression resulting from HIV infection and/or that the group's focus on psychological issues related to acquired immune deficiency syndrome (AIDS) may have simultaneously provoked some anxiety that had an adverse impact on immunity.

Preliminary data from another laboratory suggest that HIV-positive individuals may benefit less from aerobic training than HIV-negative persons (Fletcher et al., 1988). Seropositive and seronegative healthy gay men were randomly assigned to aerobic training or a control group. The PBLs from HIV-negative subjects showed significant increases in blastogenesis, mature B cells, and a subset of helper T lymphocytes after a 10-week training period. In contrast, neither subjects in the control group nor subjects who were HIV-seropositive showed similar significant changes.

There are other intervention studies that have included immunologic measures. Consistent with demonstrations by Ader and Cohen (1975) on the classical conditioning of certain aspects of immune function, some data suggest possible conditioning of the delayed hypersensitivity response in humans. In one such study subjects were less reactive to a tuberculin skin test when they expected their reactions to be negative, following previous injections of saline in the test arm (Smith & McDaniels, 1983). In contrast, hypnotic suggestion did not alter the immune response to antigens as measured by delayed-type hypersensitivity following a well-controlled study using hypnotic suggestion (Locke et al., 1987).

The data from these intervention studies are very preliminary. Although
the possibility of enhanced immune function is enticing, the data offer mixed evidence for the efficacy of psychosocial interventions, particularly for immune-compromised individuals, such as HIV-seropositive patients and cancer patients.

**VI. Social Relationships and Immune Function**

There is solid scientific evidence linking interpersonal relationships and health (House, Landis, & Umberson, 1988). The data are robust and suggest that social relationships do not simply have a correlational relationship to health, but actually have a causal impact: prospective studies that have controlled for baseline health status have reliably shown greater mortality among individuals with fewer relationships (House et al., 1988). Although this association is now well established, the biopsychosocial mechanisms that underlie these effects are not well understood. In this section we discuss immunity and social relationships.

Levy, Herberman, Lippman, and d'Angelo (1987) found a connection between immune function and social support in patients with breast cancer. They measured NK cell activity and psychological status at baseline and 3 months into treatment; they could account for 30% of the variance in NK cell activity at the 3-month follow-up on the basis of baseline NK cell activity, fatigue/depression, and lack of social support. These were particularly important data, because neither radiation nor chemotherapy appeared to affect NK cell activity.

Two studies suggested an association between loneliness and immune function. Loneliers medical students (those scoring above the median on the UCLA Loneliness Scale) had significantly lower levels of NK cell activity than students who described themselves as less lonely (Kiecolt-Glaser, Gerner, et al., 1984). Loneliers students also had higher antibody titers to EBV VCA (Glaser, Kiecolt-Glaser, Speicher, et al., 1985). In addition, loneliers psychiatric patients had significantly lower levels of NK cell activity than less lonely patients, a poorer T-cell proliferative response to the mitogen phytohemagglutinin (PHA), and higher levels of stress-related urinary cortisol (Kiecolt-Glaser, Ricker, et al., 1984).

Whereas loneliness can be a consequence of social isolation, the presence of others does not necessarily reflect support. Certain kinds of relationships may have deleterious consequences. For example, unhappy marital relationships may actually place individuals at greater risk than the absence of a partner; unsatisfactory relationships may themselves be a source of stress, while simultaneously placing limits on one's ability to seek support in other relationships (Goyne & DeLongis, 1986). Thus, it is not surprising that poorer marriages are reliably associated with increased distress: unmarried people are happier on average than those in troubled marriages, and unhappily married individuals also report poorer health than either happily married or divorced people of the same race, sex, and age (Renne, 1971).

Two cross-sectional studies have explored the possibility that marital quality might be related to immune status. In the first study, poorer marital quality in 38 women was a strong and significant correlate of dysphoria and loneliness in hierarchical multiple regression analyses, even after controlling for the subject's educational level, her husband's socioeconomic status, and the number of negative life changes in the previous year (Kiecolt-Glaser, Fisher, et al., 1987). Poorer marital quality was strongly and positively related to EBV VCA IgG antibody titers. Similarly, poorer marital quality was also related to poorer blastogenic responsiveness to PHA and Con A. There were no significant relationships between marital quality and three quantitative or enumerative immunologic assays.

Similar results were obtained in a sample of married men (Kiecolt-Glaser et al., 1988). Men who described their marriages as poorer had higher antibody titers to EBV VCA IgG and lower T helper/suppressor ratios. Taken together, the data from both women and men are consistent with the previous reports linking the quality of the marital relationship with mental and physical health.

There are a number of obvious problems in making inferences about the direction of causality in cross-sectional studies such as these. For example, married women or men who are more depressed might view their relationship as less supportive, and/or depressive symptoms might have had maladaptive consequences for the marital relationships. Although these possibilities cannot be excluded, other evidence also supports alternative explanations (e.g., Menaghan 1985).

Moreover, data from Levenson and Gottman (1985) provide evidence of a physiological pathway through which chronically abrasive marital relationships might affect immunity and health. They found that greater autonomic arousal in interacting married couples was strongly predictive of declines in marital satisfaction 3 years later: the magnitude of the relationship was particularly impressive, with correlations from .70 to over .90. In addition, greater declines in marital satisfaction were strongly correlated with poorer health ratings at follow-up. If there is consistent physiological arousal in the presence of a partner in a disturbed relationship, then there might be concomitant persistent endocrine alterations that could have a significant impact on immunity.

Corroborative evidence suggests that endocrinological adaptation may not easily occur with a repeated psychosocial stressor. Unweaned squirrel monkeys showed a characteristic behavioral response to repeated 1-hour separations from their mothers that 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 (Coe, Lubach, & Ershler, 1989). Furthermore, separation distress has also been associated with significant immunologic alterations. Completely weaned squirrel monkeys that were separated from their mothers showed decrements on several indices of humoral immunity at 7 and 14 days after the separation, compared to preseparation samples (Coe, Lubach, & Ershler, 1989); those monkeys who were caged with others showed less immunosuppression than those who were caged alone.

Finally, Thomas, Goodwin, and Goodwin (1985) found low but statistically significant correlations between "satisfying confidant relationships" and two immunological indices, total lymphocyte counts and mitogen responsiveness, 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 data may significantly underestimate the magnitude of the relationship.

Summarizing the data on immunity and interpersonal relationships described thus far, we have presented evidence linking greater loneliness and poorer immune function in medical students and psychiatric inpatients (Glaser, Kiecolt-Glaser, Speicher, et al., 1985b; Kiecolt-Glaser, Garner, et al., 1984; Kiecolt-Glaser, Ricker, et al., 1984). The marital quality data suggest that the mere presence of a partner is not equivalent to a supportive relationship (Kiecolt-Glaser, Fisher, et al., 1987; Kiecolt-Glaser et al., 1988). The data are consistent with endocrinological evidence from primate studies (Coe, Lubach, & Ershler, 1989). Marital disruption is associated with lower immune function, as described earlier, albeit primarily in cross-sectional studies (Bartrop et al., 1977; Irwin et al., 1987; Kiecolt-Glaser, Fisher, et al., 1987; Kiecolt-Glaser et al., 1988; Schleifer et al., 1983). These data are relevant for the growing literature on social relationships and health.

VII. Psychosocial Stressors, Immunity, and Health Consequences

This chapter has highlighted data from such diverse groups as bereaved spouses, separated and divorced men and women, psychiatric patients with a major depression diagnosis, and family caregivers of Alzheimer's disease victims (Kiecolt-Glaser, Fisher, et al., 1987; Kiecolt-Glaser, Glaser, et al., 1987; Kiecolt-Glaser et al., 1988; Schleifer et al., 1983; Stein, Keller, & Schleifer, 1985). These studies have shown that subjects from such groups are more distressed and show relatively poorer immune function than well-matched community counterparts. Similarly, prospective longitudinal studies have suggested that there is some suppression of immune function in medical students during examinations, compared to similar measures collected 1 month previously when subjects were less distressed (Glaser, Kiecolt-Glaser, Speicher, et al., 1985; Glaser, Kiecolt-Glaser, Stout, et al., 1985; Kiecolt-Glaser, Garner, et al., 1984). Finally, distress-reducing interventions have been associated with improvements in some aspects of immune function in healthy adults (Kiecolt-Glaser, Stephens, et al., 1985; Kiecolt-Glaser et al., 1986; Pennebaker et al., 1988). Distressing psychological responses may be a common denominator through which psychosocial events or other psychologically related variables have an impact on the immune system.

It is commonly assumed that these immunological alterations are at least in part a consequence of distress-related changes in endocrine function (Hall & Goldstein, 1981). However, the literature suggests a range of psychological responses in each of the groups noted above, as well as differences among populations. For example, bereaved individuals may have depressed mood, major depressive disorder, and/or anxiety states or disorders. Just as the psychological "distress" response(s) may vary, the neurobiological concomitants may vary in turn, and thus have differential effects on the immune system.

Although it is clear that gross alterations in immunity can be associated with greater morbidity and mortality (e.g., AIDS), the actual health consequences of these less extreme immune alterations are unknown. Only a few studies have prospectively shown a confluence among psychosocial stressors and actual health changes in the presence of immunologic alterations (Glaser et al., 1987; Kasl et al., 1979; Kiecolt-Glaser et al., 1988; McKinnon et al., 1989; Pennebaker et al., 1988).

It is not known how far above or below a mean level of competence the immune response must fluctuate in order to increase risk for pathology, for example, autoimmune disease, risk for infectious disease, and perhaps malignant disease. Indeed, very little is known about the pathophysiology of disease and the association of immunological changes with risk for disease except in extreme cases where the immune response, particularly the cellular immune response, is very depressed. In such cases, for example, in AIDS, we know that risk for secondary infections is great. What is not known, however, is the kinetics of the immunologic changes vis-à-vis disease risk or how depressed the immune response must be before one is at some risk. The long-term, longitudinal studies examining psychological stress, the immune system, and health which are now in progress in several laboratories should yield information that will help understand some of these relationships.

Although the data obtained in the studies outlined in this chapter are consistent with epidemiological data which suggest that more distressed populations have significantly higher rates of morbidity and mortality, it should be emphasized that there are a number of behavioral differences which probably contribute to the observed epidemiological differences in risk. For example, in the case of marital disruption, Verbruggen (1979) has
suggested that nonmarried individuals may have riskier lifestyles than married persons, for example, they may drink, smoke, or use drugs more; nutrition and sleep may also differ by marital status. In addition, there are a number of other behaviors that have adverse immunologic consequences (Kiecolt-Glaser & Glaser, 1988a). In the studies reported from our laboratory, we have routinely excluded subjects who reported drug or alcohol abuse. Weight, sleep, and nutrition are also variables that are carefully considered in evaluating immunologic differences. Although it is likely that distress-related behaviors contribute to the morbidity and mortality observed in epidemiologic studies, our data suggest there may be potentially important immunologic differences in individuals who do not differ in obvious health behavior-related variables.

We speculate that distress-related immunosuppression may have its most important health consequences in those individuals whose immune function is already impaired before the onset of a stressor, because further downward changes might lower immune function to a range where health effects might be more profound. In particular, older adults are one obvious at-risk group because there are reliable age-related decrements in immunity; in fact, poorer cellular immune function is associated with greater mortality in individuals over 80 years of age (Roberts-Thomson, Whittingham, Younchayiud, & MacKay, 1974). Another obvious at-risk group is patients with an immunosuppressive disease, for example, AIDS (Kiecolt-Glaser & Glaser, 1986b). In these and other at-risk groups, emotional distress may affect morbidity and mortality.

References


Human Studies: Stress and Immunity


