Data from prospective studies suggest that stressful life events are associated with transient changes in a number of facets of the immune response. In this chapter, we review these studies, with a focus on the relationship between immune function and commonplace stressors, including examination stress, bereavement, and separation and divorce. Potential immunologic mechanisms of these effects of stress on immune function will be discussed. Finally, the impact of psychosocial interventions on immune function will be considered, as well as the relationship between psychosocial variables, immune function, and disease outcome in individuals with cancer or human immunodeficiency virus (HIV) infection.

IMMUNOLOGIC CHANGES DURING ACADEMIC EXAMINATIONS

We have used first- and second-year medical students in the Ohio State University College of Medicine to study the effects of academic stress on immune function. Our medical students have seven or eight 3-day examination blocks during their first 2 years of medical school; during these 3-day periods, students are tested on all subjects they are studying in the current curriculum. Thus the preclinical medical student classes cycle as a group through these higher-stress examination periods, as well as through lower-stress periods when there are no examinations. We have used examination stress as a model for examining the response to commonplace stressful events.

We found significant declines in natural killer (NK) cell activity in blood samples obtained from 75 medical student subjects during final examinations, in contrast to baseline blood samples collected 1 month previously (Kiecolt-Glaser et al. 1984). NK cells are believed to play an important role in providing natural protection against neoplasms and viral infections. The significant decrease in NK cell activity was replicated in two follow-up studies (Glaser et al. 1986; Kiecolt-Glaser et al. 1986). Moreover, two different, independent methods were used to quantify the percentage of NK cells (versus activity), including an NK cell–specific monoclonal antibody and the percentage of large granular lymphocytes (the NK cell phenotype). Both methods showed significant decrement in NK cell percentage (Glaser et al. 1986). These NK cell data suggest that 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.

We also found that production of gamma-interferon, a lymphokine that stimulates the cellular immune response, was decreased during examinations. Gamma-interferon is a major regulator of NK cells, stimulating their growth and differentiation, as well as enhancing their ability to destroy target tumor cells (Herberman et al. 1982). In two separate studies, we found dramatic cyclical changes in gamma-interferon production by lymphocytes stimulated with concanavalin A during examinations (Glaser et al. 1986, 1987).

It is noteworthy that we have also found large and reliable stress-related changes in antibody titers to latent herpesviruses (Glaser et al. 1985, 1987). Elevated antibody titers to latent herpesviruses are thought to occur following enhanced expression of the latent virus because of changes in, or dysfunction of, the cellular immune response (Glaser and Gotlib-Stematsky 1982). For example, patients on immunosuppressive therapies like chemotherapy or radiation or patients with immunosuppressive diseases like acquired immunodeficiency syndrome (AIDS) have characteristic elevated antibody titers to one or more of the herpesviruses, and often, but not always, shed infectious virus (Glaser and Gotlib-Stematsky 1982). The elevated antibody titers are thought to reflect the increased production of viral antigens that have subsequently stimulated the production of antibodies (Glaser and Gotlib-Stematsky 1982). Thus, although somewhat counterintuitive, higher antibody titers may reflect altered cellular immune system control of herpesvirus latency. We found more than sixfold higher antibody titers to Epstein-Barr virus (EBV) virus capsid antigen before and during examinations, compared with titers after students returned from summer vacation (Glaser et al. 1985). In addition, there were elevations in antibody titers to herpes simplex virus type 1 (HSV-1), as well as smaller but statistically significant changes in antibody to cytomegalovirus (Glaser et al. 1985).

In more recent studies in our laboratory, we have followed students across the academic year, across three lower-stress baselines and three higher-stress examination periods. Antibody titers to EBV virus capsid antigen were again significantly elevated during examinations (Glaser et al. 1987). In addition, we found that the activity of a lymphokine, leukocyte migration–inhibition factor, suppressed during recrudescence of herpes simplex virus type 2 (HSV-2) infections (Sheridan et al. 1982), was also suppressed during examinations.

In this same study, we found that the ability of EBV-specific memory (cytotoxic) T lymphocytes to inhibit the outgrowth of EBV-infected autologous B lymphocytes fluctuated with examination stress, with less cell killing observed at the time of examinations. The utility of this assay to measure specific T cell killing was previously demonstrated by Harada et al. (1982) in immune-suppressed X-linked lymphoproliferative patients. In these patients, there was a significant decrease in the cytotoxic T cell response to autologous EBV-infected B cells (Moss et al. 1972; Rickinson et al. 1979), which was interpreted as an impaired lymphocyte response to an EBV specific antigen and defective memory or helper T cell function(s). In subsequent work, we found evidence for incomplete reactivation of latent EBV, with only selective expression of the latent virus genome (Glaser et al. 1991).

A naturalistic study using West Point cadets has provided evidence supporting the potential clinical importance of these changes in EBV virus capsid antigen antibody titers. Kasl et al. (1979) followed West Point cadets who were seronegative for EBV (not later infected) on entry into the New York State military academy. The data they collected on the cadets over 4 years showed that a triad of psychosocial risk factors (poor academic performance, high levels of motivation for a military career, and having a father who was an “overachiever”) was associated with three illness indices: a greater risk for EBV seroconversion, longer hospitalizations in the infirmary following seroconversion, and elevated EBV antibody titers among those who
seroconverted but had no clinical symptoms. Other researchers have shown a similar convergence for psychological stress and immune function with HSV-2 lesions (Kemeny et al. 1989).

Two investigators have compared herpesvirus antibody titers in psychiatric patients and control subjects to identify a possible viral etiology for various psychiatric illnesses. Depressed psychiatric patient subgroups have had significantly higher herpesvirus antibody titers than nonpsychiatric controls. In contrast, no differences between the patient and control groups have been found when antibody titers to other viruses were assayed (e.g., measles or rubella [Halonen et al. 1974; Lycke et al. 1974]). These elevated herpesvirus antibody titers in psychiatric patients have led some researchers to speculate on the possible etiologic significance of herpesvirus infections for certain psychiatric disorders. However, given the stress-related changes in antibody to herpesvirus, cytomegalovirus, and EBV in medical students (Glaser et al. 1985, 1987) and the associated impairments in a variety of cellular immune mechanisms responsible for control of latent herpesvirus (Glaser et al. 1986, 1987; Herberman et al. 1982), a more parsimonious explanation for the higher herpesvirus antibody titers in psychiatric patients may well be related to the greater distress of psychiatric patients than that of controls.

In an attempt to explore the cell-cell interactions affected by psychological stress, we explored the expression of a receptor for an important lymphokine, the interleukin-2 (IL-2) receptor (IL-2R) (Glaser et al. 1990). We also measured the synthesis of IL-2R messenger RNA (mRNA) by peripheral blood leukocytes (PBLs) obtained from medical students in three independent studies. The PBLs obtained at low-stress baseline periods had significantly higher percentages of IL-2R-positive cells when compared with cells obtained from the same individuals during examinations. Moreover, in one study (Glaser et al. 1990), IL-2R mRNA in the PBLs decreased significantly during examinations in a subset of 13 of these students. We also found an increase in the level of IL-2 in cultures of cells from stressed students, possibly related to the down-regulation of IL-2R expression. These data suggest that the inhibition of the expression of the IL-2R on the surface of these PBLs was due to a decrease in IL-2R mRNA, possibly as a result of decreased gene expression or changes in the stability or degradation of the IL-2R mRNA. Moreover, whether stress induces further posttranslational inhibition or modification of IL-2R precursor proteins is not known.

IL-2 is involved with the regulation of IL-2R expression, because studies have shown that the addition of IL-2 to mitogen-stimulated PBLs augments IL-2R expression (Dupper et al. 1985; Reedl et al. 1985). The fact that there was reduced IL-2R expression in the presence of increased IL-2 suggests that IL-2-induced up-regulation of IL-2R expression was not sufficient to overcome the stress-induced inhibition of IL-2R expression. In addition to the obvious physiologic importance of these data, these are the first data suggesting that stress-associated decrements in immunity may be observed at the level of gene expression. The data provide evidence of one immunologic mechanism whereby the central nervous system can modulate the immune response during psychological stress.

Data from our laboratory also suggest that examination stress can alter phorbol ester inhibition of radiation-induced apoptosis in human PBLs (Tomei et al. 1990). Apoptosis is the process of genetically programmed alterations of cell structure that leads to the failure of proliferation and differentiation, and eventually to cell death. Apoptosis may be induced by a variety of toxic insults, including growth factor deprivation and ionizing radiation, and the process is thought to function to protect the appearance of heritable phenotypic changes in cells. Normally, phorbol esters inhibit apoptosis, although the process is poorly understood.

We found reversible changes in apoptosis in the response of PBLs to low levels of irradiation and to the tumor-promoting phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA), and this interaction was related to the stress of examinations (Tomei et al. 1990). Considering the stress-related changes in NK cell activity previously discussed and the association of NK cells with tumor cell surveillance, in addition to stress-induced changes in cellular DNA repair (Kiecolt-Glaser et al. 1985a) and modulation of apoptosis, there is good evidence that academic stress can influence a wide range of immunologic activities. It remains to be determined if these influences may have implications for the development of immune-related disorders, including cancer.

MARITAL DISRUPTION AND IMMUNE FUNCTION

Bereavement

Another significant and commonplace stressor is the loss of a loved one, or bereavement. Several studies have explored the association between bereavement and immune function because epidemiologic studies have demonstrated that bereavement is associated with increased morbidity and mortality (Bloom et al. 1978; Verbrugg 1979). Although the effects may be somewhat stronger for men, many of the studies in this genre have methodological limitations (Minkler 1985). Even though epidemiologic data on bereavement have been an important link for many of the investigators who study immune function, no studies have shown that bereavement-related changes in immune function are associated with greater mortality.

Comparisons between bereaved spouses 2–6 weeks after the death of their spouse and nonbereaved control subjects showed decreased lymphocyte proliferation in the former (Bartrop et al. 1977). A subsequent prospective bereavement study showed that men whose spouses were dying of cancer had decreased mitogen responses following the death of their spouse compared with their proliferative responses prior to bereavement (Schleifer et al. 1983).

Irwin et al. (1987) examined immune function in three different groups: 16 women whose husbands were undergoing treatment for metastatic lung cancer, 10 women whose husbands had died of lung cancer 1–6 months prior to their participation in the research project, and 11 women whose husbands were in good health. The widowed group showed the greatest depression and the greatest impairments in immune function, consistent with the prospective data from Stein and his colleagues (Schleifer et al. 1983). Taken together, these convergent data from several laboratories suggest that bereavement may be associated with decreases in some facets of the immune response.

Separation and Divorce

Marital disruption in the form of separation and divorce is also associated with increased morbidity and mortality. For example, divorced individuals have six times the number of deaths from pneumonia as married people (Lynch 1977), and separated women have 30% more acute illnesses and physician visits than married women (Somers 1979). To examine immunologic and psychological correlates of
separation and divorce, we obtained blood samples for immunologic analyses and psychological data from 38 separated or divorced women and 38 sociodemographically matched married women (Kiecolt-Glaser et al. 1987).

We found significant differences between the two groups in all the immunologic measures, with these differences mainly associated with women who had separated more recently: the 16 women who had been separated a year or less had more significant decreases in immune function than their married counterparts. Among the 38 separated and divorced women, those women who had been separated for shorter periods and who continued to be more attached (more preoccupied) with their ex-husband had lower immune responses and greater distress.

A similar study with separated or divorced and married men showed that the former were more distressed and lonely and had higher antibody titers to two latent herpesviruses, EBV and HSV-1 (Kiecolt-Glaser et al. 1988). Those men who had separated within the last year and who had initiated the separation were less distressed and reported better health than those who had not initiated the separation.

Data from a study by Levenson and Gottman (1985) suggest one possible physiologic pathway through which chronically abrasive relationships might influence immune function. They found that greater autonomic arousal in interacting married couples strongly predicted subsequent declines in marital satisfaction 3 years later. Moreover, greater declines in marital satisfaction were strongly correlated with worse health ratings at follow-up. If there is consistent physiologic arousal associated with the presence of a spouse in a disturbed relationship, then it is possible that there are concurrent and persistent alterations in endocrine function that might mediate the observed immunologic changes.

Although the immunologic data associated with marital disruption (bereavement and separation or divorce) are consistent with epidemiologic studies of increased morbidity and mortality, this does not imply that the observed immunologic differences are necessarily associated with the health outcomes. Verbrugge (1979) suggested that nonmarried individuals may have riskier life-styles than married adults. For example, they may drink, smoke, or use drugs to a greater extent, thus exposing themselves to more chronic risks; nutrition and sleep might also differ by marital status.

PERSONAL RELATIONSHIPS

Data from large, well-controlled prospective epidemiologic studies suggest that impaired social relationships, particularly social isolation, are a major risk factor for morbidity and mortality, rivaling such well-established health risk factors as smoking, high blood pressure, elevated blood lipids, obesity, and low level of physical activity (House et al. 1988). Research with diverse populations has demonstrated an association between cellular immunity and the quality of personal relationships, providing one possible physiologic pathway linking social relationships and health.

Research with primates, although beyond the scope of this chapter, should be briefly mentioned. A maternal separation paradigm has been associated with significant immunologic and endocrinologic alterations in squirrel monkeys (Coe et al. 1989). Completely weaned squirrel monkeys separated from their mothers showed decrements in humoral immune function at 7 and 14 days postseparation, compared with preseparation samples. Furthermore, greater immunosuppression was found in individually caged monkeys compared with those caged with others. In related research with weaned squirrel monkeys, the characteristic behavioral response to repeated 1-hour maternal separations adapted over time; in contrast, plasma cortisol elevations in response to the separation continued to occur reliably, even after 20 such separations (Coe et al. 1989).

Medical students who were above the median on a loneliness scale had significantly lower levels of NK cell activity than those who fell below the median (Kiecolt-Glaser et al. 1984). In addition, as described earlier, marital disruption, either through bereavement (Barrio et al. 1977; Irwin et al. 1987; Schleifer et al. 1983) or divorce (Kiecolt-Glaser et al. 1987, 1988), has been associated with decrements in immunity. Greater marital strife was also correlated with lower immune function in intact marriages (Kiecolt-Glaser et al. 1987, 1988). Finally, Baron et al. (1990) found that women whose husbands were being treated for urologic cancer who had higher levels of social support had higher immune function than women who reported less support. Thus there is growing evidence for a link between personal relationships and immune function.

CHRONIC STRESS

Baum and his colleagues (McKinon et al. 1989) have compared psychological stress, endocrine function, and immune function in a group of individuals living near the damaged Three Mile Island nuclear power plant near Harrisburg, Pennsylvania, with a demographically comparable control group. Although the cohorts were small, the differences were impressive. Area residents from Three Mile Island differed from the control group in several ways. They exhibited greater numbers of neutrophils, which were positively correlated with epinephrine levels; fewer B lymphocytes, T cytotoxic suppressor lymphocytes, and NK cells; and higher antibody titers to herpesvirus.

Other chronic stresses have also been studied. The process of providing care for a friend or family member with a severe, long-term debilitating illness such as Alzheimer’s disease has been considered a chronic stressor (Light and Lebowitz 1989). Alzheimer’s disease progresses at an unpredictable and uncontrollable rate; the only certainty is that progressive impairments will lead to increasing needs for supportive care. In addition to the strains associated with providing care, caregiving negatively affects other facets of caregivers’ lives. The caregivers find that the time available for their own activities diminishes. Thus, although the increased strain may enhance caregivers’ needs for support, the time caregiving demands often places limits on other relationships and the support that can be provided in these relationships (Light and Lebowitz 1989).

We assessed changes in depression, immunity, and health in 69 spousal caregivers who had already been providing care for an average of 5 years and 69 sociodemographically matched control subjects (Kiecolt-Glaser et al. 1991). During the 13-month interval between the initial sample and the follow-up sample, caregivers showed decrements on three measures of cellular immunity relative to controls. The caregivers also reported significantly more days of infectious illness, primarily upper respiratory tract infections. Caregivers had a substantially greater incidence of depressive disorders than the control subjects, with 25% of caregivers meeting syndromal criteria at baseline compared to no cases among controls. At follow-up 13 months later, 32% of caregivers met criteria for a depressive disorder, compared to 6% of controls. Caregivers reported fewer important personal relationships than controls; they saw members of their social network less frequently, and
both closeness and helplessness ratings of their relationships were lower (Kiecolt-Glaser et al. 1991). Those caregivers who reported the lowest levels of social support at baseline and who were most distressed by dementia-related behaviors showed the greatest and most uniform negative changes in immune function at follow-up. Neither the presence of a syndromal depressive disorder nor the severity of depressive symptoms as measured by scores on the Hamilton Rating Scale for Depression (Hamilton 1960) was related to either cross-sectional measures of immune function or changes in immunity (Kiecolt-Glaser et al. 1991).

Studies with rodents have suggested that chronic stress could have prolonged adverse consequences for older adults. Compared with young rats, aged male rats show impairments in their ability to terminate glucocorticoid secretion at the end of a stressor, consistent with data from primates (Sapolsky et al. 1986). Since glucocorticoids are known to be immune suppressive, the glucocorticoid cascade hypothesis suggests that chronic stressors could have persistent severe consequences for immune function in older adults, including acceleration of age-associated decreases in the immune response (Murasko et al. 1988; Wayne et al. 1990). In caregivers, especially those who are older, chronic stress could have longer-term potentially irreversible consequences. Immuneologic changes may also reflect alterations in other physiologic systems. For example, evaluation of the blastogenic response of lymphocytes from 403 elderly adults showed that lymphocytes from 18% of the subjects did not proliferate in response to three mitogens (Murasko et al. 1988). Although 15% of the subjects died over a 2-year period, negative responders had twice the mortality of positive responders. The major cause of death in both groups was sudden death or a diagnosable cardiovascular-related disease. Murasko et al. suggested that decrements in cellular immunity may reflect changes in other systems, providing one marker of physiologic aging. Similar data from a 20-year longitudinal study of 273 healthy adults over age 60 showed that low cell-mediated immune function was associated with subsequent morbidity and mortality (Wayne et al. 1990).

**INTERVENTION STUDIES**

Because the data from diverse populations have suggested that various stressors may have effects on immunity, several studies have explored the possibility that distress-reducing interventions might have positive immunologic consequences. Older adults were selected for our first intervention study because of the age-related declines in immunity (Murasko et al. 1988; Wayne et al. 1990). Any positive immunologic changes might have greater potential benefits in this population. In addition, previous research with older adults in nursing homes suggested that brief interventions such as college student visits are associated with improvements in mood, activity levels, memory, and self-reported and physician-rated health status (Rodin 1980; Schulz 1980). Forty-five older adults were recruited from four local retirement homes and randomly assigned to one of three protocols: relaxation training, social contact, or a no-intervention control condition (Kiecolt-Glaser et al. 1985b). Subjects in the relaxation training and social contact groups were visited individually three times a week for a month. Following the intervention, the subjects in the relaxation training group had significantly higher NK cell activity levels than at baseline and significantly lower antibody titers to HSV-1, suggesting some enhancement of cellular immune function associated with relaxation. Neither of the other two conditions showed significant alterations on these measures.

Another study explored the possibility that relaxation practice might have a possible protective role if applied prior to a stressor (Kiecolt-Glaser et al. 1986). Half of a group of 34 medical students were randomly assigned to a hypnotic-relaxation group that met in the intervals between a baseline blood draw and an examination blood draw. There were no differences between the groups. Both groups exhibited a significant decline in NK cell activity and percentages of helper T lymphocytes during examinations. However, intervention subjects showed wide variability in their frequency of relaxation practice, ranging from 5 to 50 sessions. Regression analyses showed that more frequent practice of relaxation was related to higher helper T lymphocyte percentages after controlling for baseline levels. No relationship was found between frequency of practice and NK cell activity.

A subsequent study explored the possible ties between self-disclosure and immune function (Pennebaker et al. 1988). Fifty healthy undergraduates were randomly assigned to one of two groups: those who wrote about traumatic or troubling experiences for 20 minutes on four consecutive days or those who wrote about trivial events and experiences. The individuals who wrote about traumatic or upsetting events demonstrated higher mitogen responses following baseline compared with control subjects, replicating prior health data (Pennebaker and Beall 1986), and trauma subjects' average number of monthly health center visits dropped following the study, whereas control subjects' visits increased. Most importantly, individuals who wrote about experiences they had not previously shared with other people had higher lymphocyte proliferative responses than those subjects who had discussed the experiences previously.

Preliminary data from another laboratory studying HIV-positive individuals showed significant changes on some immunologic assays following both aerobic exercise training and a cognitive-behavioral stress reduction intervention (Fletcher et al. 1988). These investigators studied both seropositive and seronegative healthy homosexual men who were randomly assigned to one of the two training groups or to a control group. After the 10-week training period, both groups showed some improvements in certain aspects of immune function in contrast to subjects who received no intervention. However, HIV-seronegative men showed the greatest positive changes.

In contrast to positive data from these intervention studies, an intensive stress-reduction intervention did not show changes in a battery of immunologic measures in HIV-seropositive men compared with waiting-list controls (Coates et al. 1989). These researchers speculated that the group's focus on psychological issues related to AIDS may have simultaneously provoked some anxiety.

Other data suggest that it may be possible to condition a delayed hypersensitivity (allergic) response. Subjects who expected their reactions to a tuberculin skin test to be negative were less reactive after repeated saline injections in the test arm prior to the injection of tuberculin (Smith and McDaniel 1983). Similarly, data from women receiving cyclic chemotherapy for ovarian cancer showed anticipatory immune suppression consistent with the hypothesis that chemotherapy patients may develop conditioned immune suppression as well as conditioned nausea after repeated pairings of hospital stimuli with the emetic and immunosuppressive effects of chemotherapy (Bovbjerg et al. 1990).
PSYCHOIMMUNOLOGIC STUDIES OF CANCER AND PERSONS INFECTED WITH HIV

In view of the findings that psychosocial factors may influence immune measures, attention has been directed to psychoimmunologic studies of patients with cancer and persons infected with HIV. The clinical course of HIV infection and associated immunologic changes show considerable variability. It has been suggested that psychological stress may act as a cofactor, contributing to HIV progression (Kiecolt-Glaser and Glaser 1988b). Unfortunately, there are a number of difficulties in studying HIV-infected individuals. Chief among these is the general absence of information on the time since seroconversion, one of the strongest predictors of immunologic status. In addition, HIV-infected individuals use a number of medications, both prescribed and nonprescribed (e.g., megavitamins), and these factors can make interpretation of data quite difficult. A thorough discussion of psychoneuroimmunology and HIV infection is presented by Kertzner and Gorman (Chapter 12, this volume).

A structured psychiatric group intervention for patients with malignant melanoma has been reported and involved the assessment of psychological distress and NK cell function (Fawzy et al. 1990). The intervention consisted of health education, enhancement of problem-solving skills regarding diagnosis, stress management (e.g., relaxation techniques), and psychological support. The groups of 7–10 patients met for an hour and a half weekly for 6 weeks. Patients in the control group did not receive the psychological or educational intervention; questionnaires were mailed to them, and blood was drawn in their homes.

The intervention and control groups did not differ at baseline (Fawzy et al. 1990). At the 6-month assessment point, the 35 patients in the intervention condition showed significant increases in the percentage of large granular lymphocytes and NK cells, concomitant with increases in NK cell function and NK cell activity. They also showed a decrease in the percentage of helper-inducer T cells, and in comparison with controls. At the earlier 6-week follow-up point, the majority of these changes had not yet been observable. Decreases in the Profile of Mood States (McNair et al. 1971) depression-dejection and tension-anxiety subscales and decreases in anger were correlated with the immunologic changes: subjects who showed the greatest immunologic changes were those who reported lower depression and anxious mood states, but more anger. The group leaders suggested that the increased anger reflected increased assertiveness, rather than irritability or rage.

Levy et al. (1990) examined the predictors of NK cell activity in 61 stage I and II breast cancer patients between the ages of 25 and 70. The researchers found that they could explain one-third of the variance in NK cell activity with five variables: perceptions of high-quality emotional support from a spouse or intimate other, perceived social support for the patient, estrogen receptor–negative tumor status, having an excisional biopsy as the surgical treatment, and actively seeking social support as a major coping strategy. The quality of emotional support from significant others was the most important predictor of NK cell activity and accounted for more variance than an important biological characteristic of the tumor, the status of estrogen receptors.

EVIDENCE FOR HEALTH CONSEQUENCES

One of the key issues in psychoimmunologic research has been the establishment of the connections between stress-related immunologic alterations and health changes. Although it is reasonable to assume that both short- and long-term alterations in immune function could have deleterious consequences for health, there are only a few studies that provide evidence of such a relationship and its association with the incidence, duration, and intensity of infectious disease (Kasl et al. 1979; Kiecolt-Glaser et al. 1988; Pennebaker et al. 1988).

There are several problems in establishing these kinds of relationships. As mentioned earlier, stressed or distressed individuals are likely to have a variety of life-style factors that could put them at greater risk for disease, including a variety of poor health habits, such as greater alcohol and drug abuse, poor sleep, poor nutrition, and less exercise (Kiecolt-Glaser and Glaser 1988b). Moreover, individuals who are socially isolated are also less likely to have contact with others and thus may be less likely to be infected.

We have argued that the largest effects of psychosocial factors on health outcome are likely to be seen in at-risk groups who already have altered immune function at the onset of a stressor, such as older adults or individuals with an immunosuppressive disease like AIDS (Kiecolt-Glaser and Glaser 1988a; Kiecolt-Glaser et al. 1988). Individuals who already have impaired immune function who encounter additional stress-related immune changes could be pushed further into a potential zone of greater risk for infection or disease severity. Further work is clearly needed to establish the magnitude of these potential interactive effects.

REFERENCES
