Psychological Influences on Immunity

Implications for AIDS

Janice K. Kiecolt-Glaser and Ronald Glaser
Ohio State University College of Medicine

ABSTRACT: There is considerable variability in the clinical course of individuals infected with the human immunodeficiency virus (HIV), the acquired immune deficiency syndrome (AIDS) virus. Because there is good evidence for psychological mediation of immune function, psychosocial or behavioral variables are among the possible cofactors that may influence HIV infection and disease progression. This article reviews relevant psychoimmunology research and addresses the implications of these data for the lives and medical treatment of HIV-infected people.

The human immunodeficiency virus (HIV) is the etiologic agent for the acquired immunodeficiency syndrome (AIDS). The extreme suppression of the immune system that is characteristic of AIDS leaves individuals vulnerable to "opportunistic" infections, diseases that are generally not a threat to healthy individuals. However, exposure to HIV does not necessarily result in seroconversion (i.e., immunologic changes reflecting HIV infection); moreover, HIV-infected individuals do not necessarily exhibit any clinical symptoms. The reasons for the progression from an asymptomatic seropositive status to the development of AIDS-related complex (ARC) are not well understood; similarly, only a certain percentage of ARC patients thus far have developed AIDS, and the time between development of AIDS and death is highly variable (Solomon & Temoshok, 1987). Physical cofactors that appear to promote seroconversion and disease progression include drug use, repeated exposure to HIV, other concurrent viral infections, and poor nutrition (Kaplan, Johnson, Bailey, & Simon, 1987).

Because studies with both humans and animals have provided good evidence that behavior can influence immune function, psychosocial or behavioral variables are additional potential cofactors for HIV infection and disease progression. In this article we summarize relevant literature addressing psychological influences on immunity and discuss possible implications of this work for the lives and medical treatment of HIV-infected individuals.

Background: Basic Immunological Concepts

In order to measure immune function, the numbers and functional abilities of subgroups of lymphocytes (white blood cells) are assessed. Different lymphocyte subpopulations perform specialized functions, and there is no single immunological assay that provides a global measure of immune system competence. Because of the interdependence of various immunological components, adverse changes in one lymphocyte subpopulation can produce cascading effects.

Behavioral influences on immunity are thought to be mediated in part through the endocrine system. The endocrine system is responsive to a variety of emotional states (Baum, Grunberg, & Singer, 1982), and there is good evidence for endocrine and neuroendocrine modulation of immunity (Ader, 1981).

Unlike many autonomic and hormonal changes that can occur within seconds or minutes, most of the immunological components we will discuss take days or weeks to change significantly. Although some biochemical mediators may be synthesized in hours, significant changes in most lymphocyte subpopulations take considerably longer amounts of time. Therefore, a bad afternoon is probably not a sufficient stimulus to produce immunological changes of importance; however, several days of heightened dysphoria can alter a number of immunological parameters.

Several immunological terms will be used in this article. The *cellular immune response,* one of the immune system's two arms, is particularly important for the defense against viruses such as HIV; cellular immunity refers to immune functions that primarily involve T-lymphocytes. *T-lymphocytes,* derived from the thymus, have a number of subgroups with important functions; for example, T-lymphocyte subclasses synthesize *lymphokines,* such as gamma interferon and the interleukins that function as communication links between immune and nonimmune cells and thus serve as potent immunological mediators. *Helper T-lymphocytes* stimulate the production of a number of other immunological activities, particularly the production of antibodies by B-lymphocytes. *Suppressor T-lymphocytes* act in a feedback loop to shut off the activities of helper T-lymphocytes when sufficient antibody has been produced to ward off a specific infection. HIV infects and ultimately destroys helper T-lymphocytes, disabling a very important immunological function. Whereas there are normally about twice as many helper T-lymphocytes as suppressor T-lymphocytes, excessively low helper–suppressor ratios are characteristic of AIDS because of the depletion of helper cells.

For *blastogenesis,* a common assay, lymphocytes are

Copyright 1988 by the American Psychological Association, Inc. 0003-066X/88/$00.75
Vol. 43, No. 11, 892-898

cultured for several days with a mitogen, a substance that stimulates cell growth and cell division. The assay is thought to provide a model for the body's lymphocyte proliferative response to foreign substances such as viruses or bacteria. Blastogenesis is clearly depressed among AIDS patients (Schechter et al., 1987).

Natural killer (NK) cells are thought to provide an important defense against virus-infected cells and cancer cells (Bloom, 1980), and the ability of NK cells to destroy infected cells is clearly impaired in AIDS (Schechter et al., 1987). *Interferon*, a lymphokine, is a potent enhancer of various immune functions, including NK cell activity. Interferon has been of considerable interest as an antiviral agent; it also inhibits tumor growth in several tumor systems (Bloom, 1980).

Immunological Changes Associated with Commonplace, Transient Events

Commonplace stressful events can have significant immunological consequences. In a series of studies, it has been shown that immunological changes occur in medical students' blood samples taken during examinations compared with "baseline" samples taken one month previously when the students were not taking examinations. Examination blood samples had lower NK cell activity than samples obtained one month earlier (Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986); in addition, lonelier students had lower levels of NK cell activity than their less lonely colleagues (Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984). Gamma interferon showed precipitous, cyclical decrements (i.e., values during examination periods that were 5% or less of baseline values) in students followed across an academic year (Glaser et al., 1987). Blastogenesis was also lower during examinations (Glaser, Kiecolt-Glaser, Stout et al., 1985). Although not a consistent finding, examination stress has been associated with decrements in helper T-lymphocytes as well (Glaser, Kiecolt-Glaser, Stout et al., 1985; Kiecolt-Glaser et al., 1986).

The data from the medical student studies are important because medical students have long histories of successful test-taking behavior. In spite of their familiarity with this stressor, they still show reliable affective changes (i.e., greater distress during examinations), as well as concomitant immunological changes. These data suggest that even very commonplace or frequently experienced stressors can affect immune function.

Interpersonal Relationships and Immunity

There is good evidence that interpersonal relationships have health-related consequences. Some of the most persuasive evidence comes from prospective epidemiological studies that show greater morbidity and mortality in people with fewer close relationships (Cohen & Syme, 1985). Epidemiological and immunological data suggest that both the quality of relationships and their disruption are important (Bloom, Asher, & White, 1978; Renne, 1971).

Separation or Divorce

Marital disruption, either through divorce or death, appears to be one of the most stressful of life events (Bloom et al., 1978; Verbrugge, 1979). Both bereavement and divorce are associated with very high rates of physical and emotional disorders; marital disruption is the single most powerful sociodemographic predictor of physical and emotional illness (Somers, 1979). Although most of the epidemiological literature on marital disruption does not separate causes of morbidity or mortality, studies that have done so have shown higher rates of both infectious disease and cancer (Ernster, Sacks, Selvin, & Petrakis, 1979; Lynch, 1977; Somers, 1979).

On the basis of these epidemiological data, a cross-sectional study was designed to explore the possibility of immunological changes associated with adaptation to separation and divorce. Those women who had been separated one year or less had poorer immune function (across five of six assays) than their well-matched married community counterparts (Kiecolt-Glaser, Fisher et al., 1987). Moreover, among separated and divorced women, both shorter separation periods and greater continued attachment or preoccupation with the (ex)husband were associated with poorer immune function and greater depression and loneliness. Similar data were obtained in a study with men (Kiecolt-Glaser et al., 1988).

Bereavement

Consistent with the epidemiological data described earlier, bereavement has been associated with poorer immune function in cross-sectional and longitudinal studies. Bartrop, Luckhurst, Lazarus, Kiloh, and Penny (1977) showed that bereaved spouses had a poorer lymphocyte proliferative response to mitogen stimulation several weeks after their spouse's death than similar nonbereaved community subjects. Men whose wives were dying of breast cancer showed poorer lymphocyte proliferation after their spouse's death than prior to the death (Schleifer, Keller, Camerino, Thornton, & Stein, 1983). Similarly, recently bereaved women had lower NK cell activity than age-matched nonbereaved women (Irwin, Daniels, Smith, Bloom, & Weiner, 1987).

Marital Quality

Although the disruption of a relationship is stressful, the simple presence of a partner is not a panacea. Data from Renne (1971) and others suggest a relation between marital quality and health: Unhappily married persons report poorer health than either divorced or happily married individuals of the same sex, age, and race. Using the data from the married women described earlier, poorer marital quality was significantly associated with greater distress and loneliness in hierarchical regression equations after entering subject's education, husband's socioeconomic

Work on this article was supported in part by Grants R01 MH42096 and R01 MH40787 from the National Institute of Mental Health.

Correspondence concerning this article should be addressed to Janice K. Kiecolt-Glaser, Department of Psychiatry, Ohio State University College of Medicine, 473 W. 12th Ave., Columbus, OH 43210.

status (SES), and the number of negative life events (Kiecolt-Glaser, Fisher et al., 1987). Moreover, poorer marital quality was also associated with a poorer response on three qualitative immunological indexes.

A prospective study by Levenson and Gottman (1985) provides evidence of one physiological pathway through which chronically abrasive relationships like poor marriages might modulate immunity. They showed that greater autonomic arousal in interacting married couples was strongly predictive of subsequent declines in marital satisfaction. Furthermore, poorer health ratings at a three-year follow-up were strongly correlated with greater declines in marital satisfaction. If a partner's presence in a disturbed relationship is associated with persistent physiological arousal as the data suggest, then there could be concurrent alterations in endocrine function (Baum et al., 1982) that could contribute to the relation found between marital quality and immunity.

Caregiving as a Chronic Stressor

The process of providing care for a friend or family member with a severe, long-term illness such as AIDS or Alzheimer's disease (AD) has been conceptualized as a chronic stressor (Light & Lebowitz, 1988). The 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 strain of providing care, caregiving has negative effects on other facets of caregivers' lives. The time available for caregivers' own activities diminishes as the disease progresses and more care is required. Thus, although the increased strain may enhance caregivers' needs for support, caregiving time demands often limit other relationships and the support that they provide (Light & Lebowitz, 1988).

Caregiving can have significant consequences for caregivers' mental and physical health. Data from several laboratories suggest that there are relatively high rates of depression among AD caregivers (Light & Lebowitz, 1988). Moreover, comparisons between AD caregivers and well-matched noncaregivers showed that the former were more distressed and had significantly poorer immune function than the latter (Kiecolt-Glaser, Glaser et al., 1987).

These data suggest that chronic stress does not lead to immunological adaptation in humans, at least not to the level of well-matched peers. In addition, the longer term adaptation that follows important personal losses appears to be associated with continued immunologic down-regulation during adaptation (Kiecolt-Glaser et al., 1988; Kiecolt-Glaser, Fisher et al., 1987; Kiecolt-Glaser, Glaser et al., 1987).

Stress, Herpesvirus Latency, and Immunity

There are strong convergent data implicating stress as a risk factor in the development of herpesvirus infections, as well as in the control of latent herpesviruses (Kasl, Evans, & Niederman, 1979; Kiecolt-Glaser & Glaser, 1987). Unlike other common viruses such as rubella (measles) or poliovirus that are usually eliminated by the immune response, individuals will remain latently infected for life after infection with a herpesvirus; because HIV can latently infect T-lymphocytes, it is possible that there are parallels between the two.

There are five well-characterized human herpesviruses (Glaser & Gotlieb-Stematsky, 1982). Herpes simplex virus type 1 (HSV-1), ubiquitous in adults, is primarily responsible for cold sores; its latent infection site is in the trigeminal nerve. Herpes simplex virus type 2 (HSV-2) is primarily responsible for genital lesions, and the latent infection site is in the sacral nerve. Varicella-zoster virus (VZV) appears as chickenpox in the primary infection, and as shingles in recurrences; latent VZV also resides in neurons. Cytomegalovirus (CMV) produces a mononucleosis syndrome; CMV's latent infection site is not established, but it may latently infect lymphocytes and endothelial cells of certain blood vessels. Epstein-Barr virus (EBV) is the etiologic agent for infectious mononucleosis and is also implicated in certain human cancers, including B-cell lymphomas in AIDS patients. Though many adults do not recall having a clinical case of infectious mononucleosis, seroepidemiological data show that 80% to 90% of adults will be EBV seropositive by their mid-20s (Henle & Henle, 1982); the primary site for latent infection seems to be B-lymphocytes.

The competence of the cellular immune system is thought to be a critical factor in controlling the primary herpesvirus infection, as well as subsequent control of virus latency (Glaser & Gotlieb-Stematsky, 1982). With compromised cellular immunity (e.g., in patients with immunosuppressive diseases like AIDS or in patients undergoing immunosuppressive therapies such as chemotherapy), the immune system's control over latent herpesvirus replication is impaired. In these cases, reactivation of latent herpesviruses can occur and may result in disease. Furthermore, there are also characteristic elevations in herpesvirus antibody titers that can occur in the absence of any symptoms (Glaser & Gotlieb-Stematsky, 1982). These elevations in herpesvirus antibody titers are thought to reflect the antibody response to increased synthesis of the virus or virus proteins. When the cellular immune system becomes more competent (e.g., after cessation of immunosuppressive therapies), there are normally decrements in herpesvirus antibody titers. Thus, although counterintuitive, higher antibody titers to latent herpesviruses suggest that the cellular immune system is less competent in controlling herpesvirus latency (Henle & Henle, 1982).

Stressors may enhance susceptibility to primary herpesvirus infections and may also increase the severity of the initial infection (Kiecolt-Glaser & Glaser, 1987). For example, West Point cadets who were EBV seronegative on entry into the military academy were followed for four years (Kasl et al., 1979). Those men who had a triad of psychosocial risk factors (a high level of motivation for a military career, poor academic performance, and fathers who were "overachievers") were more likely to develop an EBV infection and were hospitalized longer

in the infirmary. Furthermore, the same risk factors were associated with elevated EBV antibody titers among the cadets who had been infected without showing clinical symptoms.

The recurrence of both HSV-1 and HSV-2 lesions has been associated with dysphoria. For example, general unhappiness was predictive of recurrent cold sores in nursing students on a one-year follow-up (Luborsky, Mintz, Brightman, & Katcher, 1976). Similarly, more distressed individuals had higher recurrence rates of genital HSV-2 lesions (Goldmeier & Johnson, 1982).

Antibody titers to latent herpesviruses show reliable changes in response to psychosocial stressors in asymptomatic individuals. Medical students had higher titers to EBV, HSV-1, and CMV during final examinations, with lower titers after summer vacation (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985); moreover, medical students who were followed across the academic year showed cyclical changes, with higher antibody titers during examination periods when other herpesvirus-related immune functions were also adversely affected (Glaser et al., 1987).

Higher herpesvirus antibody titers have been linked to psychosocial stressors in other populations. Recently separated women had higher EBV antibody titers than well-matched married comparison women (Kiecolt-Glaser, Fisher et al., 1987); separated and divorced men had higher antibody titers to both EBV and HSV-1 than comparable married men (Kiecolt-Glaser et al., 1988). Family caregivers for AD victims had higher antibody titers to EBV than their matched community counterparts (Kiecolt-Glaser, Glaser et al., 1987). Psychiatric inpatients had higher HSV-1 antibody titers than comparison subjects who were not being treated for psychiatric disorders (Halonen, Rimon, Arohonka, & Jantti, 1974). Finally, as described later, a relaxation intervention has been associated with decrements in HSV-1 antibody titers in an older adult sample (Kiecolt-Glaser et al., 1985).

These data provide consistent evidence that stressors can modulate control of herpesvirus latency. Although it is not known if there is similar modulation of HIV, there are parallel methods for reactivation of latent HIV and EBV in vitro (Glaser & Kiecolt-Glaser, 1987). Moreover, the addition of stress-related hormones to laboratory cell cultures enhances HIV replication (Markham, Salahuddin, Veren, Orndorff, & Gallo, 1986).

It is also possible that stress-related changes in herpesvirus latency could have consequences for HIV infection because HIV activation has been demonstrated to follow the direct interaction of HSV-1 gene expression (Ostrove et al., 1987). In addition, T-lymphocytes are activated in response to infections, including herpesvirus infections. Because the activation of T-lymphocytes that contain previously latent HIV also activates HIV in the cells, greater HIV replication could be one consequence.

Intervention Studies

Data from diverse populations suggest that stressors can down-regulate immunity. Thus, several studies have explored the possibility that distress-reducing interventions might have positive consequences. Older adults were the subjects for one study because positive immunological changes might have greater potential benefits for them: Immune function declines with age, and poorer cellular immune function is associated with greater mortality in individuals over 80 years old (Roberts-Thomson, Whittingham, Youngchaiyud, & MacKay, 1974). Moreover, previous research with institutionalized older adults has suggested that brief interventions (e.g., college student visits) have been associated with improvements in mood, activity levels, memory, urinary cortisol levels, and self-reported and physician-rated health status (Rodin, 1980; Schulz, 1980).

Subjects were recruited from local retirement homes and randomly assigned to one of three protocols: relaxation training, social contact, or no intervention (Kiecolt-Glaser et al., 1985). Subjects in the relaxation training and social contact conditions were visited three times a week for a month. Relaxation subjects had significantly higher levels of NK cell activity after the intervention than at baseline, and significantly lower antibody titers to HSV-1, suggesting some enhancement of cellular immunity associated with relaxation.

Another study explored a possible protective role for relaxation practice preceding a stressor. Medical students' blood samples were obtained one month before examinations and on the last day of a three-day examination block (Kiecolt-Glaser et al., 1986). There were significant declines in both NK activity and helper T-lymphocytes during examinations. However, half of the sample had been randomly assigned to a hypnotic/relaxation group that met in the interval between blood draws. Although there were no differences between the subgroups, intervention subjects showed wide variability in the frequency of relaxation practice, with a range of 5 to 50 sessions. Regression analyses showed that more frequent practice was related to more helper T-lymphocytes after controlling for baseline levels, without similar relations for NK cell activity.

A subsequent study investigated the possibility that self-disclosure might have positive physiological consequences (Pennebaker, Kiecolt-Glaser, & Glaser, 1988). Fifty healthy undergraduates were randomly assigned to write about either traumatic experiences or superficial topics for 20 minutes on four consecutive days. The individuals who wrote about traumatic or upsetting events demonstrated a higher mitogen response following baseline, compared to control subjects. Replicating prior health data (Pennebaker & Beall, 1986), trauma subjects' average number of monthly health center visits dropped following the study, compared to an increase in control subjects' visits. Moreover, individuals who wrote about experiences they had not previously discussed with others had a better lymphocyte proliferative response than those subjects who had discussed the experiences previously.

In contrast to these data, a stress reduction intervention did not result in changes in a battery of immunological measures in HIV-seropositive men compared to wait-list controls (Coates, McKusick, Kono, & Sites,

in press). 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 HIV infection, or the group's focus on psychological issues related to AIDS may have simultaneously provoked some anxiety.

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 control groups. After the 10-week training period the HIV-negative subjects showed significant increases in blastogenesis, mature B-cells, and a subset of helper cells. In contrast, neither subjects in the control group nor subjects who were HIV-positive showed similar significant changes. The researchers are continuing to collect further data.

The data from these intervention studies are preliminary and offer mixed evidence for the efficacy of psychosocial interventions for HIV-seropositive individuals. Conditioning studies, described later, provide good evidence that other behavioral interventions can modulate immunity and health.

Classical Conditioning of Immune Function

Immune function can be elevated or suppressed by classical conditioning (Ader & Cohen, 1981). The taste aversion paradigm (Ader, 1985) involves pairing the injection of an immunosuppressive drug (e.g., cyclophosphamide) with a distinctively flavored drinking solution such as saccharin water. When rodents are later exposed to saccharin water alone, they show conditioned immunosuppression; control animals for whom injections and drinking solutions were not paired and animals with no previous saccharin exposure do not show conditioned immunosuppression.

Ader and Cohen (1982) have demonstrated that immunological conditioning can have clear survival value. Autoimmune diseases involve an overactive immune system that attacks the body's own tissue because it cannot successfully discriminate self from nonself; immunosuppressive drugs are a frequent treatment because they dampen immunological activity. Groups of New Zealand hybrid mice (used as an animal model for studying lupus, an autoimmune disease) received weekly solutions of saccharin, the conditioned stimulus. The conditioned mice received injections of cyclophosphamide on half of the weekly occasions after saccharin administration. Unconditioned animals received the same dosage of cyclophosphamide as the conditioned mice, but their weekly saccharin was never paired with the drug. Other control groups included mice that received weekly saccharin without cyclophosphamide (untreated animals) and animals that received weekly saccharin administration paired with weekly cyclophosphamide injections.

The differences between the conditioned and unconditioned groups of mice are particularly important. The conditioned animals survived significantly longer than the unconditioned animals that received exactly the same dosage of cyclophosphamide, and their survival time did not differ from the fully treated animals that had received twice the dosage of cyclophosphamide. Although unconditioned animals also differed significantly from conditioned animals in the rate that autoimmune disease developed, nonconditioned groups were not reliably different from nontreated controls. Thus, although the drug was used in quantities that would normally have had little impact on the disease's course, conditioned animals showed significant delays in disease onset and mortality.

Other data suggest that it may be possible to condition the delayed hypersensitivity (allergic) response in humans. Subjects were less reactive to a tuberculin skin test when they expected their reactions to be negative, following repeated previous injections of saline in the test arm (Smith & McDaniel, 1983).

Although most of the studies have addressed conditioned immunosuppression, at least two studies have shown that the immune response may be augmented or enhanced in response to conditioned stimuli alone. One study demonstrated conditioned rejection of skin grafts in mice, a process mediated through the cellular immune response (Gorczynski, Macrae, & Kennedy, 1982). Another laboratory showed conditioned elevations in NK cell activity in mice using a camphor smell as the conditioned stimulus (Ghanta, Hiramoto, Solvason, & Spector, 1985). As discussed later, these data have important implications for HIV drug trials.

Implications of Psychoneuroimmunological Research for AIDS

In humans, distressing psychological responses appear to be a common denominator through which psychosocial events or other psychologically related variables affect the immune system. Psychological resources that reduce distress (e.g., supportive interpersonal relationships) may concurrently attenuate adverse immunological changes. Theoretically, individuals who have poorer immunological defenses at a stressor's onset are at greater risk, because smaller stress-associated immune changes could have more important health consequences.

The psychoimmunological data summarized in this article have disturbing implications in view of psychosocial aspects of the AIDS epidemic. The perception that one is in a high-risk group for AIDS is distressing (Joseph et al., 1987). Although HIV-seropositive individuals would ideally be the recipients of additional social support during these trying times, the simple presumption that an individual is in a high-risk group can produce considerable animosity (Kaplan et al., 1987). Moreover, similar to AD caregivers (Light & Lebowitz, 1988), caregivers of people with AIDS are likely to experience considerable distress. Finally, losses can become frequent events among formerly close-knit groups. Thus, high-risk individuals probably experience more stressors than the general population, and many stressors are chronic or long term.

Temoshok, Zich, Solomon, and Stites (1987) have been conducting an intensive psychoimmunologic study of men with AIDS. Because their small sample had 12

men with various opportunistic infections, third-order partial correlations were computed between psychosocial and immune measures, averaged across seven weeks of measurements, controlling for having either *Pneumocystis carinii* pneumonia or Kaposi's sarcoma, as well as number of months since diagnosis. Although the authors emphasized the limitations of their small subject sample, there were striking patterns of correlations between psychological variables and immunological measures.

Several other laboratories are actively exploring the question of psychological influences on HIV progression. Although there is considerable interest in the issue, there are a number of complex methodological problems (Kiecolt-Glaser & Glaser, 1988). For example, some asymptomatic individuals show progressive immunological decrements after HIV infection (Schechter et al., 1987); the time lapse since infection is an important variable but is rarely known. If an HIV-seropositive individual is depressed, it might be a response to the kinds of chronic strains that are described previously. However, it could be the cumulative product of a number of other factors. The HIV virus can infect the brain, and organically based depression can be one consequence. Opportunistic infections are frequently viral, and there is a biologically based depression that is associated with some viral infections (Glaser & Gotlieb-Stematsky, 1982). Moreover, the unpleasant side effects of drugs like AZT have deleterious consequences for psychological well-being (Wood & Geddes, 1987).

The actual impact of psychosocial stressors on immunity in HIV-seropositive individuals is likely to vary depending on the stage of disease because immune function can differ widely at each step. The implications of psychosocial down-regulation of the immune response for disease outcomes in HIV have yet to be determined.

Psychologists can play very important roles as AIDS researchers in many ways. For example, classical conditioning has obvious and direct applications for HIV drug trials. There is evidence that conditioning using significantly reduced drug doses may approximate the unconditioned effects and, at the same time, might partially reduce deleterious side effects (Ader, 1985). Conditioning procedures could be a very valuable adjunct in the use of drugs like AZT that have many unpleasant side effects. Moreover, the association of drug tolerance and drug sensitization with conditioning is well established, and HIV drug trials would do well to maximize desired drug effects by using these procedures (Siegel, 1985). Although the bulk of the literature on conditioning and immunity has used rodents, the learning phenomena that underlie classical conditioning are equally applicable to humans (Ader, 1985).

The full impact of the AIDS epidemic has yet to be realized. It has been difficult to develop effective and nontoxic antiviral drugs for any viral infection, and therefore development of an effective antiviral drug for HIV is likely to take considerable time. Furthermore, because it has been established that HIV can latently infect lymphocytes and other cells, a major concern is whether any HIV vaccine will be able to block the latent infection of cells, even in the presence of circulating, neutralizing antibodies, similar to the situation that exists for the herpesviruses. Psychologists can make very important contributions to the AIDS epidemic by applying their knowledge of behavior and behavior change strategies, and it is imperative for them to do so as soon as possible.

REFERENCES

Ader, R. (Ed.). (1981). *Psychoneuroimmunology.* New York: Academic Press.

Ader, R. (1985). Conditioned immunopharmacological effects in animals: Implications for a conditioning model of pharmacotherapy. In L. White, B. Tursky, & G. E. Schwartz (Eds.), *Placebo: Theory, research, and mechanism* (pp. 316–320). New York: Guilford.

Ader, R., & Cohen, N. (1981). Conditioned immunopharmacologic responses. In R. Ader (Ed.), *Psychoneuroimmunology* (pp. 281–320). New York: Academic Press.

Ader, R., & Cohen, N. (1982). Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science, 215,* 1534–1536.

Bartrop, R. W., Luckhurst, E., Lazarus, L., Kiloh, L. G., & Penny, R. (1977). Depressed lymphocyte function after bereavement. *Lancet, 1,* 834–836.

Baum, A., Grunberg, N. E., & Singer, J. E. (1982). The use of psychological and neuroendocrinological measurements in the study of stress. *Health Psychology, 1,* 217–236.

Bloom, B. R. (1980). Interferons and the immune system. *Nature, 284,* 593–595.

Bloom, B. R., Asher, S. J., & White, S. W. (1978). Marital disruption as a stressor: A review and analysis. *Psychological Bulletin, 85,* 867–894.

Coates, T. J., McKusick, L., Kuno, R., & Stites, D. P. (in press). Stress reduction training changed number of sexual partners but not immune function in men with HIV. *American Journal of Public Health.*

Cohen, S., & Syme, S. L. (Eds.). (1985). *Social support and health.* New York: Academic Press.

Ernster, V. L., Sacks, S. T., Selvin, S., & Petrakis, N. L. (1979). Cancer incidence by marital status: U.S. Third National Cancer Survey. *Journal of the National Cancer Institute, 63,* 585–587.

Fletcher, M. A., Caralis, P., Laperriere, A. R., Ironson, G., Klimas, N. G., Perry, A., Ashmar, M., & Schneiderman, N. (1988, June). *Immune function and aerobic training as a function of anti-HIV status in healthy gay male.* Paper presented at the 4th International Conference on AIDS, Stockholm, Sweden.

Ghanta, V. K., Hiramoto, R. N., Solvason, H. B., & Spector, N. H. (1985). Neural and environmental influences on neoplasia and conditioning of NK activity. *Journal of Immunology, 135,* 848s–852s.

Glaser, R., & Gotlieb-Stematsky, T. (1982). *Human herpesvirus infections: Clinical aspects.* New York: Marcel Dekker.

Glaser, R., & Kiecolt-Glaser, J. K. (1987). Stress-associated depression in cellular immunity: Implications for acquired immune deficiency syndrome (AIDS). *Brain, Behavior, and Immunity, 1,* 107–112.

Glaser, R., Kiecolt-Glaser, J. K., Speicher, C. E., & Holliday, J. E. (1985). Stress, loneliness, and changes in herpesvirus latency. *Journal of Behavioral Medicine, 8,* 249–260.

Glaser, R., Kiecolt-Glaser, J. K., Stout, J. C., Tarr, K. L., Speicher, C. E., & Holliday, J. E. (1985). Stress-related impairments in cellular immunity. *Psychiatry Research, 16,* 233–239.

Glaser, R., Rice, J., Sheridan, J., Fertel, R., Stout, J., Speicher, C. E., Pinsky, D., Kotur, M., Post, A., Beck, M., & Kiecolt-Glaser, J. K. (1987). Stress-related immune suppression: Health implications. *Brain, Behavior, and Immunity, 1,* 7–20.

Glaser, R., Rice, J., Speicher, C. E., Stout, J. C., & Kiecolt-Glaser, J. K. (1986). Stress depresses interferon production by leukocytes concomitant with a decrease in natural killer cell activity. *Behavioral Neuroscience, 100,* 675–678.

Goldmeier, D., & Johnson, A. (1982). Does psychiatric illness affect the recurrence rate of genital herpes? *British Journal of Venereal Diseases, 58,* 40–43.

Gorczynski, R. M., Macrae, S., & Kennedy, M. (1982). Conditioned immune response associated with allogeneic skin grafts in mice. *Journal of Immunology, 129,* 704–709.

Halonen, P. E., Rimon, R., Arohonka, K., & Jantti, V. (1974). Antibody levels to herpes simplex type 2, measles, and rubella viruses in psychiatric patients. *British Journal of Psychiatry, 125,* 461–465.

Henle, W., & Henle, G. (1982). Epstein-Barr virus and infectious mononucleosis. In R. Glaser & T. Gotleib-Stematsky (Eds.), *Human herpesvirus infections: Clinical aspects* (pp. 151–165). New York: Marcel Dekker.

Irwin, M., Daniels, M., Smith, T. L., Bloom, E., & Weiner, H. (1987). Impaired natural killer cell activity during bereavement. *Brain, Behavior, and Immunity, 1,* 98–104.

Joseph, J. G., Montgomery, C. E., Kirscht, J. P., Kessler, R. C., Ostrow, D. G., Wortman, C. B., O'Brien, K., Eller, M., & Eshleman, S. (1987). Perceived risk of AIDS: Assessing the behavioral and psychosocial consequences in a cohort of gay men. *Journal of Applied Social Psychology, 17,* 231–250.

Kaplan, H. B., Johnson, R. J., Bailey, C. A., & Simon, W. (1987). The sociological study of AIDS: A critical review of the literature and suggested research agenda. *Journal of Health and Social Behavior, 28,* 140–157.

Kasl, S. V., Evans, A. S., & Niederman, J. C. (1979). Psychosocial risk factors in the development of infectious mononucleosis. *Psychosomatic Medicine, 41,* 445–466.

Kiecolt-Glaser, J. K., Fisher, L., Ogrocki, P., Stout, J. C., Speicher, C. E., & Glaser, R. (1987). Marital quality, marital disruption, and immune function. *Psychosomatic Medicine, 49,* 13–34.

Kiecolt-Glaser, J. K., Garner, W., Speicher, C. E., Penn, G., & Glaser, R. (1984). Psychosocial modifiers of immunocompetence in medical students. *Psychosomatic Medicine, 46,* 7–14.

Kiecolt-Glaser, J. K., & Glaser, R. (1987). Psychosocial influences on herpesvirus latency. In E. Kurstak, Z. J., Lipowski, & P. V. Morozov (Eds.), *Viruses, immunity, and mental disorders* (pp. 403–412). New York: Plenum.

Kiecolt-Glaser, J. K., & Glaser, R. (1988). Methodological issues in behavioral immunology research with humans. *Brain, Behavior, and Immunity, 2,* 67–78.

Kiecolt-Glaser, J. K., Glaser, R., Dyer, C., Shuttleworth, E., Ogrocki, P., & Speicher, C. E. (1987). Chronic stress and immunity in family caregivers of Alzheimer's disease victims. *Psychosomatic Medicine, 49,* 523–535.

Kiecolt-Glaser, J. K., Glaser, R., Strain, E., Stout, J., Tarr, K., Holliday, J., & Speicher, C. (1986). Modulation of cellular immunity in medical students. *Journal of Behavioral Medicine, 9,* 5–21.

Kiecolt-Glaser, J. K., Glaser, R., Williger, D., Stout, J., Messick, G., Sheppard, S., Ricker, D., Romisher, S. C., Briner, W., Bonnell, G., & Donnerberg, R. (1985). Psychosocial enhancement of immunocompetence in a geriatric population. *Health Psychology, 4,* 25–41.

Kiecolt-Glaser, J. K., Kennedy, S., Malkoff, S., Fisher, L., Speicher, C. E., & Glaser, R. (1988). Marital discord and immunity in males. *Psychosomatic Medicine, 50,* 213–229.

Levenson, R. W., & Gottman, J. M. (1985). Physiological and affective predictors of change in relationship satisfaction. *Journal of Personality and Social Psychology, 49,* 85–94.

Light, E., & Lebowitz, B. (Eds.). (1988). *Alzheimer's disease treatment and family stress: Directions for research.* Washington, DC: National Institute of Mental Health (U.S. Government Printing Office).

Luborsky, L., Mintz, J., Brightman, U. J., & Katcher, A. H. (1976). Herpes simplex and moods: A longitudinal study. *Journal of Psychosomatic Research, 20,* 543–548.

Lynch, J. (1977). *The broken heart.* New York: Basic Books.

Markham, P. L., Salahuddin, S. Z., Veren, K., Orndorff, S., & Gallo, R. C. (1986). Hydrocortisone and some other hormones enhance the expression of HTLV-III. *International Journal of Cancer, 37,* 67–72.

Ostrove, J. M., Leonard, J., Week, K. E., Rason, A. B., & Volsky, D. J. (1987). Activation of the human immunodeficiency virus by herpes simplex type 1. *Journal of Virology, 61,* 3726–3732.

Pennebaker, J. W., & Beall, S. (1986). Confronting a traumatic event: Toward an understanding of inhibition and disease. *Journal of Abnormal Psychology, 95,* 274–281.

Pennebaker, J. W., Kiecolt-Glaser, J. K., & Glaser, R. (1988). Disclosure of traumas and immune function: Health implications for psychotherapy. *Journal of Consulting and Clinical Psychology, 56,* 239–245.

Renne, K. S. (1971). Health and marital experience in an urban population. *Journal of Marriage and the Family, 23,* 338–350.

Roberts-Thomson, I. C., Whittingham, S., Youngchaiyud, U., & MacKay, I. R. (1974). Aging, immune response, and mortality. *Lancet, 2,* 368–370.

Rodin, J. (1980). Managing the stress of aging: The role of control and coping. In S. Levine & H. Ursin (Eds.), *Coping and health* (pp. 171–202). New York: Plenum.

Schecter, M. T., Boyko, W. J., Craib, K. J., McLeod, A., Willoughby, B., Douglas, B., Constance, P., & O'Shaughnessey, M. (1987). Effects of long-term seropositivity to human immunodeficiency virus in a cohort of homosexual men. *AIDS, 1,* 77–82.

Schleifer, S. J., Keller, S. E., Camerino, M., Thornton, J. C., & Stein, M. (1983). Suppression of lymphocyte stimulation following bereavement. *Journal of the American Medical Association, 250,* 374–377.

Schulz, R. (1980). Aging and control. In J. Garber & M. E. P. Seligman (Eds.), *Human helplessness: Theory and applications* (pp. 261–277). New York: Academic Press.

Siegel, S. (1985). Drug-anticipatory responses in animals. In L. White, B. Tursky, & G. E. Schwartz (Eds.), *Placebo: Theory, research, and mechanisms* (pp. 288–305). New York: Guilford.

Smith, G. R., & McDaniel, S. M. (1983). Psychologically mediated effect on the delayed hypersensitivity reaction to tuberculin in humans. *Psychosomatic Medicine, 45,* 65–70.

Solomon, G. F., & Temoshok, L. (1987). A psychoneuroimmunologic perspective on AIDS research: Questions, preliminary findings, and suggestions. *Journal of Applied Social Psychology, 17,* 286–308.

Somers, A. R. (1979). Marital status, health, and use of health services. *Journal of the American Medical Association, 241,* 1818–1822.

Temoshok, L., Zich, J., Solomon, M. D., & Stites D. P. (1987, November). *An intensive psychoimmunologic study of men with AIDS.* Paper presented at the First Research Workshop on the Psychoneuroimmunology of AIDS, Tuburon, CA.

Verbrugge, L. M. (1979). Marital status and health. *Journal of Marriage and the Family, 41,* 267–285.

Wood, M. J., & Geddes, A. M. (1987). Antiviral therapy. *Lancet, 2,* 1189–1193.