

Psychoneuroimmunology

An Interdisciplinary Introduction

Edited by

Manfred Schedlowski

*Institute of Medical Psychology
University of Essen
Essen, Germany*

and

Uwe Tewes

*Department of Medical Psychology
Hannover Medical School
Hannover, Germany*

27 The Effects of Stress on the Immune System

Implications for Reactivation of Latent Herpesviruses

Katherine L. Applegate, John Hay,
John T. Cacioppo, Janice K. Kiecolt-Glaser,
and Ronald Glaser

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27.1. Introduction

There are presently seven known and characterized human herpesviruses: herpes simplex virus type 1 (HSV-1), HSV-2, cytomegalovirus (CMV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), human herpesvirus-6 (HHV-6), and HHV-7. Recently, another human herpesvirus has been linked to Kaposi's sarcoma and designated HHV-8; studies are still under way to characterize this virus.

Five of these human herpesviruses have been well studied and characterized; e.g., HSV-1 has been associated with cold sores, keratitis, and encephalitis, HSV-2 with herpes

Katherine L. Applegate and Janice K. Kiecolt-Glaser • Department of Psychiatry, Ohio State University College of Medicine, Columbus, Ohio 43210. John Hay • Department of Microbiology, State University of New York at Buffalo, Buffalo, New York 14260. John T. Cacioppo • Department of Psychology, Ohio State University, Columbus, Ohio 43210-1222. Ronald Glaser • Department of Medical Microbiology and Immunology, Ohio State University College of Medicine, Columbus, Ohio 43210.

genitalis. VZV is the etiologic agent for chicken pox and shingles. EBV is a human tumor virus that has been associated with African Burkitt's lymphoma, nasopharyngeal carcinoma, and the most common form of infectious mononucleosis (IM), and CMV can cause a type of IM and pneumonia. Little is known of the pathophysiology and clinical manifestations of HHV-7. Somewhat more is known of HHV-6, which has been linked to an IM-like illness as well as exanthem subitum (roseola infantum), which is commonly observed in young children or infants.

After primary infection (which may or may not manifest clinical symptoms), each of these viruses latently infects one or more specific cells in the body where, for the remainder of the person's life, it is thought to persist in a latent state. Depending on the herpesvirus, a very high percentage (in some cases 100%) of individuals become infected by the time they reach middle age in industrialized countries. However, in poorly developed countries, individuals become infected with these viruses at a much earlier age. These differences have clinical implications. e.g., individuals in poorly developed countries who get infected with EBV generally do not develop IM, while individuals in North America get infected with middle teens or early twenties and will often manifest clinical IM.

Stress has been implicated as a risk factor in the development, duration, and recurrence of herpesvirus infections. This chapter will briefly review research that addresses relationships between stress and herpesvirus infections.

Among the herpesviruses, HSV-1 and HSV-2 have been studied most intensively in association with psychosocial stressors; in addition, a number of studies have demonstrated psychosocial modulation of the steady-state expression of latent EBV. The impact of psychosocial stressors on VZV has not been as well studied as either HSV or EBV; however, stress-related alterations in the competency of the cellular immune response have implications for VZV as well.

The cellular immune response plays a central role in control of primary herpesvirus infections as well as in the subsequent control of viral latency (Glaser & Jones, 1994). Thus, this chapter will briefly review the broader evidence linking stress to immunological changes. Psychological and behavioral characteristics associated with increased risk for primary and recurrent herpesvirus infections will also be discussed, as well as data from psychosocial interventions.

27.2. Stress and the Herpesviruses: Clinical Manifestations

Psychosocial stressors have been linked to more frequent recurrences among individuals latently infected with HSV-1 and HSV-2. Both major, negative events and a high level of daily hassles may constitute psychosocial stress; moreover, these stressors may also be interpersonal, such as relationship difficulties, or individual problems relating to life satisfaction, one's ability to cope with challenges, or a sense of being supported by others. Concomitant increases in psychological distress or negative affective states may contribute to increased rates of infectious illness (Cohen & Williamson, 1991). For example, greater unhappiness was associated with more frequent cold sores in nurses during their first year of training (Luborsky, Mintz, Brightman, & Katcher, 1976). Consistent with the data from student nurses, 18 individuals with recurrent HSV-1 lesions reported increases in stressful life events, anxiety, and daily hassles in the week prior to the appearance of a cold sore (Schmidt, Zyzanski, Ellner, Kumar, & Arno, 1985).

between a cluster of dysphoric symptoms (including anxiety, depression, and hypochondriasis) and recurrence rates in 58 patients who were followed for up to 30 weeks after their first clinically confirmed HSV-2 lesion. More distressed patients experienced significantly more recurrences. Similarly, Stout and Bloom (1986) studied 37 individuals who reported recurrent genital herpes lesions. Participants who were above the median on recurrence rates had significantly higher scores on nine of the ten clinical scales of the Minnesota Multiphasic Personality Inventory, compared with subjects with fewer recurrences, suggesting greater depression, anger, anxiety, worry, and interpersonal troubles in the former.

Personality traits and characteristic response styles to stressful events may predispose individuals to psychological symptoms that place them at higher risk for recurrence of herpesvirus infections. Life event stress was associated with duration of reactivation episodes in a sample of male and female genital herpes patients (Silver, Auerbach, Vishniavsky, & Kaplowitz, 1986). Patients with an external locus of control, a proneness toward emotion-focused wishful thinking, and avoidance of cognitive strategies to cope with the stress of HSV-2 infection showed higher recurrence rates and symptom discomfort. In other work, psychosocial variables were better predictors of pain and itching symptoms in patients with recurrent HSV-2 than were somatic symptoms (Levenson, Hamer, Myers, Hart, & Kaplowitz, 1987). Somatization was the single best predictor of pain; interpersonal sensitivity and somatization were the most reliable predictors of itching.

Recurrence rates in patients with HSV-2 infection were examined prospectively to investigate psychological and immunological correlates (Kemeny, Cohen, Zegans, & Conant, 1989). This study explored the mechanisms linking potential stressors, physiological responses, and health outcomes by examining the interactions among stress, mood, immune function, and disease course simultaneously. Although previous research has examined ties between stress and immune function or between stress and some diseases, few studies have incorporated all three components at once. Kemeny *et al.* (1989) interviewed participants monthly for 6 months to assess current and past stressors, negative mood, health behaviors, and number of HSV-2 recurrences. Stressful life events were associated with lower proportions of CD4⁺ and CD8⁺ cells, and depressed mood was associated with a lower proportion of CD8⁺ cells. Depressive mood was also linked to a higher HSV-2 recurrence rate.

Taken together, these studies suggest that individuals who report more unhappiness, anxiety, depression, and frustration are more likely to experience recurrent HSV than those who report less distress. Dysphoria and negative life events appear to have a detrimental effect on the course of HSV-1 and HSV-2 infections. The next section describes evidence linking stress with the downregulation of cellular immune function, the likely pathway for the observed clinical link between stress and more frequent recurrences.

27.3. Stress-Related Alterations in Cellular Immune Function

Stressful events can alter a wide range of immunological activities. For example, even commonplace aversive events like academic exams are associated with transient immunological changes (see Chapter 16). Comparisons of immunological data collected from medical students during a 3-day exam block in contrast to a "baseline" or lower-stress blood sample collected a month previously showed significant declines in natural killer (NK) cell activity; NK cells are thought to have important antiviral and antitumor functions

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Genital herpes recurrences also appear to be more prevalent among individuals who report feeling more distressed. Goldmeier and Johnson (1983) investigated the relationship

between a cluster of dysphoric symptoms (including anxiety, depression, and hypochondriasis) and recurrence rates in 58 patients who were followed for up to 30 weeks after their first clinically confirmed HSV-2 lesion. More distressed patients experienced significantly more recurrences. Similarly, Stout and Bloom (1986) studied 37 individuals who reported recurrent genital herpes lesions. Participants who were above the median on recurrence rates had significantly higher scores on nine of the ten clinical scales of the Minnesota Multiphasic Personality Inventory, compared with subjects with fewer recurrences, suggesting greater depression, anger, anxiety, worry, and interpersonal troubles in the former.

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Speicher, Pinsky, Kotur, Post, Beck, & Kiecolt-Glaser, 1987; Kiecolt-Glaser, Speicher, Holliday, & Glaser, 1984b). IFN γ , a lymphokine, serves as a major regulator of NK cells by stimulating their growth and differentiation; it also enhances their ability to destroy target cells (Herberman, Ortaldo, Riccardi, Timonen, Schmidt, Maluish, & Djeu, 1982). Two separate studies also showed dramatic decreases in IFN γ production by lymphocytes *in vitro* during exams (Glaser *et al.*, 1986, 1987).

The proliferative response of lymphocytes cultured with a mitogen, a substance that stimulates cell replication, is thought to provide a laboratory model of the immune system's ability to respond to infectious agents such as bacteria or viruses. Medical students showed a poorer proliferative response to mitogens during exams compared with baseline (Glaser, Kiecolt-Glaser, Stout, Tarr, Speicher, & Holliday, 1985b). IL-2 is a lymphokine important for T-lymphocyte proliferation, and the IL-2 receptor, to which IL-2 binds, is an important component of this response. The percentage of peripheral blood T lymphocytes expressing the IL-2 receptor was lower during exams compared with lower-stress baseline periods in three independent medical student studies (Glaser, Pearson, Jones, Hillhouse, Kennedy, Mao, & Kiecolt-Glaser, 1991). Moreover, the level of mRNA to the IL-2 receptor in peripheral blood leukocytes (PBLs) decreased during exams in a subset of these students (Glaser *et al.*, 1991).

Thus, these studies demonstrate that even something as transient, predictable, and relatively benign as exam stress modulates a wide range of immunological activities. Other studies have addressed the question of whether longer-term adaptation occurs when a stressor is more chronic, such as living near a damaged nuclear reactor (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989), or caregiving for a family member with a progressive dementia (Kiecolt-Glaser, Glaser, Dyer, Shuttlesworth, Ogrocki, & Speicher, 1987b). The weight of the evidence to date suggests that chronic stressors are associated with continued downregulation of immune function, rather than adaptation.

27.4. Stress and Herpesvirus Reactivation: Immunological Evidence

Although both the humoral and cellular arms of the immune system appear to be important in controlling herpesvirus infections, cell-mediated immunity may play a more critical role in controlling the reactivation of latent herpesviruses (Bonneau, 1994). For example, recovery from herpes zoster is normal in hypogammaglobulinemic patients who have little or no detectable VZV antibody (Ruckdeschel, Schimpff, & Smyth, 1977).

Herpesvirus-specific cytotoxic T lymphocytes (CTL) combat the spread of the herpesvirus infections by destroying virus-infected cells before progeny viruses are released. Memory CTL and helper T lymphocytes promote a more rapid response during subsequent reactivation of herpesvirus after the initial infection. When derivatives of these memory cells are later exposed to a herpesvirus, they lyse the infected cells, stimulate antibody, and secrete lymphokines to enhance the efficacy of the immune response. The ability of the immune system to fulfill these functions is mediated in part by signals from the nervous and endocrine systems. For further discussion of cellular and molecular mechanisms underlying reactivation of latent herpesviruses, see Bonneau (1994), Glaser and Jones (1994), and Jenkins and Baum (1995).

The large and reliable increases in antibody titers to latent herpesviruses during academic exams, particularly EBV and HSV-1, appear to reflect alterations in the competence of the cellular immune response. The characteristic elevations in EBV antibody titers

are thought to occur in response to the increased synthesis of the virus or virus proteins (Glaser *et al.*, 1991); although counterintuitive, elevated antibody titers to a latent herpesvirus reflect poorer cellular immune system control over virus latency (Henle & Henle, 1981). Consistent with the elevations in herpesvirus antibody titers, specific T-cell killing of EBV-infected target cells decreased during exams, and a herpesvirus-relevant lymphokine was also altered (Glaser *et al.*, 1987). Moreover, medical students showed a lower memory T-cell proliferation response to five of six EBV polypeptides after a 3-day exam block compared with 3 weeks prior to exams (Glaser, Lafuse, Bonneau, Atkinson, & Kiecolt-Glaser, 1993a).

One study suggested that stress may also be associated with risk for EBV infection, as well as the severity of the primary infection. Kasl, Evans, and Neiderman (1979) followed cadets at West Point over 4 years who were seronegative for EBV on entry into the Naval Academy. They found that higher motivation for a future military career, poorer academic performance, and having a father who was an "overachiever" were associated with a greater chance for seroconversion, longer hospitalization with IM in the infirmary after seroconversion (i.e., more severe illness episodes), and higher antibody titers among those students who seroconverted but did not develop clinical symptoms. Stressful life situations can downregulate the cellular immune response, adversely affecting EBV and other herpesviruses.

Other studies have assessed alterations in herpesvirus latency associated with chronic or long-term stressors. Caregiving for a spouse with a progressive dementia such as Alzheimer's disease is clearly a chronic stressor: the progressive and degenerative disease course as well as the unpredictable and uncontrollable nature of symptom presentation represent significant challenges to caregivers over a period of years. Caregivers had higher antibody titers to EBV virus capsid antigen (VCA) compared with matched controls, as well as a poorer blastogenic response of PBLs to mitogenic stimulation (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991). In another study, caregivers had higher antibody titers to an HSV-1 total viral antigen and a lower HSV-1 specific T-cell response than controls (Glaser & Kiecolt-Glaser, 1997). Other researchers have also shown that a longer-term environmental stressor is associated with elevated HSV-1 antibody titers (McKinnon *et al.*, 1989).

27.5. Psychological Interventions

The research reviewed above provides good evidence that psychological distress and stressful life events can downregulate the immune response and increase the risk for recurrences among individuals latently infected with a herpesvirus. Based on these data, researchers have assessed the potential immunological benefits of psychological interventions directed toward stress reduction. For example, older adults were trained in progressive muscle relaxation and guided imagery over the course of 1 month (Kiecolt-Glaser, Glaser, Williger, Stout, Messick, Sheppard, Ricker, Romisher, Briner, Bonnell, & Donnerberg, 1985). Blood samples were taken at baseline, at the end of intervention, and at a 1-month follow-up. Following the intervention, participants in the intervention condition showed significant increases in NK cell activity and decreases in antibody titers to HSV-1 and self-reported distress; in contrast, subjects who did not receive the stress-reduction intervention did not show these significant immunological changes.

Several studies have assessed the tie between self-disclosure and immune function. A widespread notion within the psychotherapy literature suggests that individuals may best deal with trauma by trying to understand the event and assimilating this information (Pennebaker, Kiecolt-Glaser, & Glaser, 1988b). To accomplish this, individuals can describe

the trauma in detail, either orally or in writing, which would allow for a reexamination of the event, incorporation of the information in new ways, and a general release of any thoughts and feelings they may have been holding back. In the first study 50 undergraduates were randomly assigned to one of two groups; half the subjects wrote about traumatic or troubling experiences for 20 min on 4 consecutive days, while the remainder wrote about trivial events and experiences (Pennebaker *et al.*, 1988b). The individuals who wrote about traumatic or upsetting events demonstrated a higher mitogen response following baseline compared with control subjects. "Trauma" subjects' average number of monthly health center visits dropped following the study, while control subjects' visits increased, replicating health data from similar studies. Most importantly, individuals who wrote about experiences they had not shared previously with other people had a better lymphocyte proliferative response than those subjects who had discussed the experiences previously.

Lutendorf, Antoni, Kumar, and Schneiderman (1994) used a very similar paradigm to assess the effect of self-disclosure on control of latent EBV; they also measured antibody titers to EBV VCA. Although the students in their disclosure condition did not show significant decreases in antibody titers relative to controls, the degree to which students involved themselves in the disclosure process and abandoned avoidance of the stressful topic for the 3-week intervention period predicted decreases in antibody titers to EBV VCA. Esterling, Antoni, Fletcher, Margulies, and Schneiderman (1994) demonstrated that students who either wrote or spoke about upsetting events showed decrements in EBV VCA antibody titers compared with students who were randomly assigned to write about trivial events. Together, these studies suggest that interventions like psychotherapy that enhance personal relationships, decrease distress, and/or enhance perceived self-efficacy could also have positive effects on at least certain components of the immune response. The two studies described below have assessed the effects of psychological interventions on an important health outcome, frequency and duration of HSV-2 recurrent lesions.

Behavioral intervention studies with HSV-2 patients with recurrent lesions have produced promising results. An intervention consisting of disease information, relaxation training, stress management techniques, and an imagery sequence produced significant improvements in recurrent genital herpes patients at follow-up (Longo, Clum, & Yaeger, 1988). The frequency of lesions, episode duration, and self-reported severity ratings for HSV-2 infections decreased in the intervention group compared with controls. Psychosocial measures showed lower levels of emotional distress and loneliness and elevated levels of internality for patients in the intervention group.

To test whether one particular element of the multicomponent intervention approach was effective, eight recurrent genital herpes patients were trained in progressive muscle relaxation (Burnette, Koehn, Kenyon-Jump, Hutton, & Carman, 1991). Five of these patients reported significant decreases in recurrence frequency, while a sixth showed a 30% decrease in episode frequency. Six of the eight patients also reported decreases in the duration of the episodes. Thus, collectively, these studies offer support for improving control of latent herpesvirus or decreasing the episode frequency via psychological interventions that reduce psychological distress.

27.6. Aging and Immunological Control of Latent Herpesviruses: Implications for Varicella Zoster

Immune function declines with age, particularly functional aspects of the cellular immune response (Wayne, Rhyne, Garry, & Goodwin, 1990). As one consequence, primary

herpesvirus infections may become increasingly severe with age (Glaser & Jones, 1994). Not surprisingly, immunological data demonstrate age-related decrements in the control of latent herpesviruses. For example, Glaser *et al.* (1985c) found significantly higher antibody titers to latent EBV in the elderly than in a younger group of subjects.

Age-related immunological declines also appear to be linked to the greatly increased risk for VZV reactivation in older adults (Grose, 1994). Moreover, zoster is a much more common event in the immunosuppressed patient (Grose, 1994). Importantly, older adults show greater immunological impairments related to depression or stress than younger adults (Schleifer, Keller, Bond, Cohen, & Stein, 1989). Thus, it is not surprising that stress has been anecdotally reported as a risk factor for zoster, particularly among older adults (Schmader, Studenski, MacMillan, Grufferman, & Cohen, 1990).

To investigate the role of stressful life events in the reactivation of VZV, Schmader *et al.* (1990) compared individuals with acute herpes zoster with controls matched on age, sex, and race. Participants were asked about major life events that had occurred during the year prior to onset: the subjective meaning of these events was evaluated by asking "Did this have a negative, neutral, or positive effect on you?" The authors defined an event stressful only if the participant perceived it as negative. The number of life events defined as negative by the subject was significantly higher in zoster patients at 2, 3, and 6 months before onset compared with controls. Based on these findings, the authors suggest that negative life events may constitute a risk factor for VZV reactivation.

A prospective study by Dworkin, Hartstein, Rosner, Walther, Sweeney, and Brand (1992) examined the relationship between psychological variables and chronic pain before pain onset. Herpes zoster patients, assessed shortly after diagnosis of acute herpes zoster, were followed for 12 months to determine if psychological antecedents could predict development of chronic pain symptoms. Among the 19 patients in their sample, those who developed chronic pain over the following 12 months had higher pain intensity ratings at the initial assessment. Chronic pain sufferers also had higher levels of anxiety, greater depression, and lower life satisfaction at initial assessment than zoster patients who did not develop chronic pain. These findings suggest that greater distress or dysphoria during the early stages of an acute recurrence may be associated with more chronic herpes zoster pain.

In a recent study we measured antibody titers to VZV in 48 women who were providing care for a husband with a progressive dementia and 48 women from the community who were matched on age and education who had no caregiving responsibilities; the average age of both groups was 68, and caregivers reported significantly more stress and depression than controls. Antibody titers to a total viral antigen preparation were measured by enzyme-linked immunosorbent assay (ELISA); the average titers across four tests showed a trend for caregivers to have higher titers than controls. In a previous study (Glaser *et al.*, 1991) we found evidence for partial reactivation of latent EBV in medical students using the academic stress model: this conclusion was based on data obtained from experiments with four purified viral polypeptides that were used singularly to measure specific antibody levels to the respective polypeptide by ELISA. Antibody to only one of the four polypeptides (P52/50) showed changes in multiple serum samples tested across the academic year. The particular antibody that showed stress-related change is associated with viral DNA polymerase activity and is classified as an early nonstructural protein. As a follow-up to these observations, two purified VZV polypeptides (ORF 62 and ORF 63) were used with the caregivers and controls. Once again, using each viral polypeptide to probe for a specific antibody, ELISA tests were performed. The two groups did not differ on their antibody levels against the major structural viral polypeptide but caregivers had significantly higher titers to the VZV ORF 63 protein. ORF 63 appears to represent a major latency-associated transcript protein.

27.7. Conclusions

Collectively, the data obtained with EBV and VZV suggest that partial expression of the latent viral genome can occur for these two viruses (and perhaps other latent herpesviruses), and this can be measured by using purified viral polypeptides to probe for specific antibody titers by ELISA. Importantly, these data demonstrate that stress can modulate the steady-state expression of latent VZV as well as EBV.

In summary, there is ample evidence that stress can modulate reactivation of EBV, HSV-1, and HSV-2; VZV has not been studied as intensively. However, if psychological stress is associated clinically with both reactivation of VZV (Schmader *et al.*, 1990) as well as more chronic herpes zoster pain (Dworkin *et al.*, 1992), both psychological and pharmacological interventions that reduce distress may prove to be helpful.

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