
**Psychosocial Influences on Herpesvirus Latency**

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1. **INTRODUCTION**

There are convergent animal and human data implicating stress as a risk factor in the development and duration of primary herpesvirus infections (Rasmussen et al., 1957; Gross, 1972; Kasl et al., 1979). There is also evidence that more distressed individuals have more frequent recurrences of herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) lesions after the primary lesion (Luborsky et al., 1976; Goldmeir and Johnson, 1982). Competency of the cellular immune response is thought to be a critical factor in limiting primary herpesvirus infections as well as in the subsequent control of latent virus (Glaser and Gotlieb-Stematsky, 1982). This chapter reviews literature on the psychosocial modulation of herpesvirus infections in conjunction with related data on the psychological mediation of cellular immune function.

The five human herpesviruses are listed and described in Table 1. Unlike other common viruses such as rubella, the infected individual will remain latently infected for life after primary infection with a herpes virus (Glaser and Gotlieb-Stematsky, 1982).

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical manifestations</th>
<th>Site of latent infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex type 1 (HSV-1)</td>
<td>Cold sores; neonatal herpes</td>
<td>Trigeminal nerve</td>
</tr>
<tr>
<td>Herpes simplex type 2 (HSV-2)</td>
<td>Genital infections; neonatal herpes</td>
<td>Sacral nerve</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Mononucleosis syndrome; mental retardation and deafness in neonates</td>
<td>Not established; possibly lymphocytes</td>
</tr>
<tr>
<td>Varicella-zoster (VZV)</td>
<td>Chickenpox (primary infection); shingles (recurrence)</td>
<td>Neurons, multiple tissues</td>
</tr>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>Infectious mononucleosis; B-cell lymphoma; Burkitt’s lymphoma; nasopharyngeal carcinoma</td>
<td>B lymphocytes; epithelial cells</td>
</tr>
</tbody>
</table>

2. **IMMUNOSUPPRESSION AND CHANGES IN THE CONTROL OF LATENT HERPES VIRUSES**

When cellular immunity is compromised (e.g., in patients with immunosuppressive diseases such as AIDS or in patients undergoing immunosuppressive therapies), immunologic control over replication of latent herpesviruses is impaired. Reactivation of latent virus can occur and result in disease. In addition, there are also elevations in herpesvirus antibody titers, often in the absence of disease. These elevated antibody titers are thought to reflect a response to the increased viral antigens synthesized after reactivation. Improvements in cellular immune system function (such as after the cessation of immunosuppressive therapy) are normally followed by decrements in herpesvirus antibody titers. Although both the humoral and cellular arms of the immune system are thought to be important in controlling herpesvirus infections, cellular immunity appears to be more important; e.g., recovery from herpes zoster (VZV) is normal in hypogammaglobulinemic patients who have little or no detectable VZV antibody titers (Ruckdeschel et al., 1977).

3. **STRESS AND CELLULAR IMMUNE FUNCTION**

If cellular immunity is important for control of herpesvirus infection and latency, then stress-related decrements in cellular immunity may impact on the control of primary or latent herpesvirus infections. Consistent with this rationale is the growing evidence that even commonplace stressful events can have significant adverse effects on cellular immunocompetence.

Natural killer (NK)-cell activity, thought to be an important antiviral and antitumor defense, has been shown to be responsive to stress. For example, NK activity decreased significantly in blood samples taken from 75 medical students during final examinations in contrast to baseline blood samples drawn 1 month previously. In addition, lonelier students (those scoring above the median on a loneliness scale) had significantly lower levels of NK activity (Kiecolt-Glaser et al., 1984a). There was a similar association between higher levels of loneliness and poorer cellular immune function in newly admitted, nonmedicated, nonpsychotic psychiatric inpatients (Kiecolt-Glaser et al., 1984b). The lonelier psychiatric patients had significantly lower levels of NK activity as well as a poorer T-lymphocyte response to mitogen stimulation.

Another study with 40 second-year medical student subjects provided further evidence of stress-related changes in NK cell function. Three different NK-cell assays showed significant decrements during examinations in comparison to baseline samples taken 6 weeks earlier: (1) lysis of MOLT-4 cells (we had previously found similar decrements using K-562 cells as targets), (2) percentage of NK cells as assessed by a monoclonal

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antibody, and (3) percentage of large granular lymphocytes, the NK cell phenotype. There was also a major effect on the ability of peripheral blood lymphocytes to produce interferons after stimulation with concanavalin A (Con A), dropping sharply from a base-line mean of 2003.03 U/ml to 80.00 U/ml on the day of examinations (Glaser et al., 1986). The large decrements in interferon production may be related in part to the changes observed in NK numbers and activity, since interferon is an important regulator of NK cells. Interferon affects the growth and differentiation of NK cells from their progenitor cells. Interferon also activates the lytic properties of target-binding cells, enhances cytolysis of target cells, and increases the number of target cells that can be killed by an effector cell (Herberman et al., 1982). Further studies are being performed to determine the mechanisms for these observations.

Moreover, there were also decrements in the percentages of total T lymphocytes and in the proliferative response of T lymphocytes to two different mitogens, phytohemagglutinin (PHA) and Con A, during examinations (Glaser et al., 1985c; Kiecolt-Glaser et al., 1986a). The percentages of helper and suppressor T-lymphocyte subpopulations were lower during the examination period as well. Taken together, these data suggest that even relatively commonplace stressful events are associated with significant decrements in a number of facets of cellular immune function.

In order to explore the possibility that the changes in immune function observed across studies might simply reflect underlying changes in nutritional status, we have measured three plasma nutritional markers: transferrin, total iron-binding protein, and albumin. There are well-documented impairments in various aspects of immune function in undernourished individuals, and moderate to severe protein-calorie malnutrition is associated with increased frequency and severity of infection (Chandra and Newberne, 1977). The three plasma protein markers have been well within normal limits during both high- and low-stress periods in our studies.

4. STRESS AND HERPESVIRUS-ASSOCIATED MORBIDITY AND MORTALITY

There are several animal studies that suggest that various stressors may increase the severity of herpesvirus infections, including mortality. For example, Rasmussen, Marsh, and Brill (1957) found that mice subjected to shock-avoidance stress or restraint 2 to 4 weeks prior to injections of HSV-1 (intraperitoneal) had enhanced susceptibility to the virus as demonstrated by shorter survival times and higher mortality rates than in control mice. Alterations in the incidence of Marek's disease, an oncogenic herpesvirus that induces malignant and neurological disease in poultry, have also been associated with stress. Chickens introduced into new pecking orders had a higher incidence of Marek's disease (Gross, 1972).

There are some parallel data from human studies suggesting that susceptibility to Epstein-Barr virus (EBV) is enhanced by certain psychosocial stressors. West Point cadets who were seronegative for EBV on entry into the military academy were followed for 4 years (Kasl et al., 1979). Those individuals with particular psychosocial risk factors (high levels of motivation and poorer academic performance) were more likely to develop EBV infection and were likely to be hospitalized longer. In addition, these risk factors were also significantly associated with elevated EBV antibody titers among individuals who seroconverted without apparent clinical symptoms.

There are data suggesting an association between the recurrence rate of HSV-1 and HSV-2 lesions and psychological stress. For example, higher scores on a test assessing nonpsychotic distress-related psychiatric symptoms were associated with a greater recurrence rate of genital herpes lesions in 58 patients followed for 30 weeks after their primary lesion; the relationship between distress and recurrence was not significantly related to sex, age, or social class (Goldmeier and Johnson, 1982).

Similarly, greater general unhappiness was associated with more frequent cold sores in a sample of student nurses (Luborsky et al., 1976), even though mood ratings made 4 days before each episode were not good predictors of lesion frequency. More intense and/or sustained distress may be necessary to change immune function significantly to the point at which clinical symptoms as well as changes in antibody titers are observed.

5. STRESS-RELATED CHANGES IN HERPESVIRUS ANTIBODY TITERS

Elevations in herpesvirus antibody titers have been reported in latently infected distressed populations without any obvious organic dysfunction. In one such study, a prospective design was used to assess changes in antibody titers to three latent herpesviruses [EBV, cytomegalovirus (CMV), and HSV, using a type 1 antigen] associated with academic stress (Glaser et al., 1985b). Three blood samples were obtained from 49 first-year medical students: the first sample was drawn 1 month before final examinations, the second on the first day of final examinations, and the third during the first week after their return from summer vacation. Across the sample points, the antibody titers to all three herpesviruses changed significantly, with the lowest levels found in the third sample, where students were the least distressed as measured by the Brief Symptom Inventory (Derogatis and Spencer, 1982). In addition, lonelier students had significantly higher antibody titers to two different EBV antigens in contrast to their classmates who described themselves as less lonely on the UCLA Loneliness Scale (Russell et al., 1980).

The magnitudes of the changes in antibody titers to EBV and HSV were noteworthy. For example, the geometric mean antibody titers (GMT) to EBV virus capsid antigen (VCA) were greater than 1:640 in blood samples obtained on the two occasions in the late spring of their first year of medical school. The GMT declined to 1:93 after summer vacation, as shown in Fig. 1. Seroepidemiologic studies have shown that the VCA GMT in the adult population in North America is approximately 1:80, a level consistent with students’ titers after summer vacation (Henle and Henle, 1982).

Additional data provided support for the specificity of these changes for herpesvirus latency rather than more global antibody changes. Antibody to polyivirus type II (as a recall antigen) was also measured, because the widespread school vaccination programs provided some assurance that most students would have antibody. We did not find significant changes in poliovirus antibody titers. These data, taken together with the fact that there is no evidence for seasonal fluctuations of herpesvirus antibody titers, suggest that the changes in herpesvirus antibody titers observed in latently infected individuals reflect specific stress-related modulation of virus latency.

Finally, EBV VCA IgM antibody was also assayed in the same individual in order
to evaluate the possibility that the dramatic EBV VCA IgG antibody changes reflected an epidemic of EBV infections such as infectious mononucleosis (IM) in students who were otherwise asymptomatic. Although IgM antibody is characteristically elevated during the acute phase of IM, it is normally not at measurable levels after convalescence and recovery. The fact that no student had a measurable IgM antibody titer suggests that the changes in EBV antibody titers were not related to an epidemic of EBV infections in the medical class.

The changes in immune function observed in medical students led to further research with a different population. We reasoned that if stress can depress cellular immunity, it might be possible that interventions that can reduce distress and/or loneliness might lead to an enhancement of immune function. In order to test this hypothesis, subjects were recruited from local geriatric independent-living facilities. These subjects were chosen because previous research with institutionalized older adults indicated that increased attention reliably produced small but consistent positive effects (Schulz, 1980); brief interventions (e.g., college student visits) have been associated with significant improvements in residents’ moods, activity levels, memory, and self- and physician-rated health (Rodin, 1980; Schulz, 1980).

The 45 geriatric subjects enrolled in the study were randomly assigned to one of three protocols: progressive relaxation training, social contact, or no intervention. Subjects assigned to the relaxation training and social contact conditions were visited individually by the same student each time, three times a week for 1 month. Blood samples and self-report data were collected at baseline before the intervention began, at the end of the 1-month intervention period, and at a 1-month follow-up. The follow-up sample provided information on the maintenance of treatment effects (if they occurred) after cessation of the interventions (Kiecolt-Glaser et al., 1985a).

The relaxation group had significantly higher levels of NK-cell activity at the end of the intervention than at base line and significantly lower levels of antibody to HSV and self-rated distress. Antibody to HSV was still significantly lower at the 1-month follow-up than at base line, as shown in Fig. 2. The NK-cell activity and self-rated distress were not significantly different from base-line levels in the relaxation group at this follow-up. Neither the social-contact nor the no-intervention group showed significant changes in antibody to HSV, NK activity, or self-rated distress. However, at the end of the intervention there was a general increase across groups in the T-lymphocyte blastogenic response to PHA.

These data suggest that stress-reduction interventions may enhance at least certain components of cellular immune function and may contribute to the control of herpesvirus latency. These data have particular relevance for the elderly because significant decrements in immune function are associated with aging (Braverman, 1987). Poorer cellular immune function has been linked to greater mortality in individuals over 80 years of age (Robertson-Thomson et al., 1974).

6. CELLULAR IMMUNE FUNCTION AND HERPESVIRUS LATENCY IN PSYCHIATRIC PATIENTS

Researchers in several laboratories have compared immunologic data from depressed psychiatric patients and nonpsychiatric controls. The depressed patients used in these studies generally have poorer cellular immune function across a variety of assays. For example, depressed patients have significantly lower percentages of helper T-lymphocytes (Krugel et al., 1984) than their nondepressed matched counterparts. The number of peripheral blood T lymphocytes has been shown to be significantly lower among depressed patients than in matched controls (Schliefer et al., 1985). These psychiatric patient data are consistent with the distress-related immunologic changes found in medical student subjects using the same or similar assays. The degree of impairment within a psychiatric population appears to be related to the severity of depression or distress (Kiecolt-Glaser et al., 1985b; Schliefer et al., 1985).

There have also been studies in which investigators have compared psychiatric patients whatever their diagnostic group with nonpsychiatric controls across a variety of tests of immune function. Investigators have generally found poorer immune function in psychiatric patients. The results are summarized in Table 6.1.
There is evidence that epinephrine, a common stress hormone, may influence the immune system. Researchers have proposed that epinephrine could play a role in modulating immune responses, potentially affecting the course of diseases. This hypothesis is supported by several studies indicating that chronic stress can suppress the immune system, leading to increased susceptibility to infections and other health issues.

References:


