Psychological and Immunological Predictors of Genital Herpes Recurrence

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The relationships among stressful life experience, mood, helper-inducer (CD4+) and suppressor-cytotoxic (CD8+) T cells and genital herpes simplex virus (HSV) recurrence were investigated prospectively in 36 patients with recurrent HSV. The following factors were measured monthly for six months: stressful life experience (including current acute and ongoing stressors, residual effects of previous stressors, and anticipation of future stressors), negative mood, health behaviors, other possible HSV triggers, HSV recurrences, and the proportion of CD4+ and CD8+ cells (in half the sample). Results averaging monthly scores over the six-month study period indicated that: 1) subjects with high levels of stressful experience had a lower proportion of both CD4+ and CD8+ cells, 2) subjects with high levels of depressive mood, anxiety, or hostility had a lower proportion of CD8+ cells, and 3) subjects with high levels of depressive mood who did not report many symptoms of other infections had a higher rate of HSV recurrence. A model is proposed linking depressive mood, CD8+ cells, and HSV recurrence.

INTRODUCTION

A growing body of evidence indicates that psychosocial factors influence disease etiology and progression (1, 2). For example, various human studies have suggested that stressful life experiences may be related to infectious disease etiology (3–5) and severity (6,7). Immunity is believed to be an important mediator in the relationship between psychosocial factors and infectious, autoimmune, and neoplastic diseases. Animal studies have found that environmental conditions (such as maternal separation) and experimental stressors (for example, foot shock) can in fact depress aspects of immune functioning (8, 9). In human studies, experimentally induced stressors (e.g., a simulated battle task), naturally occurring stressors (e.g., examinations, bereavement), and negative psychological states (e.g., depression, loneliness) have been shown to covary with alterations in a variety of immune parameters including natural killer cell activity, the proportion of helper-inducer T cells, gamma interferon production, and lymphocyte proliferation in response to mitogenic stimulation (10–13) (see reviews by Kiecolt-Glaser and Glaser (14), Palmblad (15), and Stein et al. (16)).

The role of immune functioning as a mediator in the relationship between psychological factors and specific disease processes remains inferential, however. No human studies have yet shown that stress-induced immune changes can increase the probability of subsequent disease (see Shavit et al. (9) and Ader and Cohen (7), for animal studies that suggest

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a stress- or central nervous system-immunity-disease link). Instead, these changes may fall within the normal range of immunological variability and fail to alter the host's susceptibility to disease (18). Elliott and Eisdorfer (1) argue that, to understand the relationship between stress and disease, all of the processes involved in an "X-Y-Z" model must be studied simultaneously, with X referring to potential activators or stressors, Y referring to short-term physiological responses such as immune changes, and Z referring to long-term health consequences such as infectious disease. Studies have shown X-Y links (that stress and psychological factors affect immunity) and others have shown X-Z links (that psychological factors influence some immunologically related diseases), but there are few studies which examine all three links simultaneously.

Genital herpes was used in this study as a model for assessing the relationships among stress, mood, immunological change, and disease course. The herpes simplex virus (HSV) remains latent in the sacral ganglia following a primary genital herpes infection. There is wide variability in the rate of recurrent episodes both across individuals and within individuals over time. A number of factors have been suggested which might "activate" a herpes recurrence and explain this variability, including sunlight, a cold or infection, heat fatigue, trauma to the skin, the menstrual cycle, food allergy, and emotional stress (19). However, these suggested activators have not been studied systematically, and the relationship between them and lesion formation is based largely on anecdotal evidence.

The physiological mechanisms which would allow such factors as sunlight or emotional stress to activate a recurrent episode of HSV are still not well understood. It has been suggested (20, 21) that the mechanisms are either neural (inciting viral replication in the sacral ganglia) or local (causing local immunological controls to fail to protect host cells from viral invasion). Human studies in support of an immunological pathway to HSV recurrence have demonstrated defects in a variety of aspects of immune function associated with episodes of HSV (e.g., refs. 22–24; see review by Rouse (25)), although other researchers have failed to replicate some of these findings (26).

Many physicians and herpes patients contend that emotional stress activates recurrent HSV episodes; however, the research evidence is relatively weak. The evidence linking psychosocial factors to genital herpes recurrence is based largely on case reports (e.g., ref. 27) or studies in which subjects reported retrospectively on stressful life events, other psychological factors, and HSV recurrence (28, 29; cf. refs. 30 and 31), or retrospectively on life stresses and psychological factors during an HSV outbreak (32). Most of these studies suffer from problems of retrospective reporting (33), inadequate definition of psychological terms (in the case reports), and lack of adequate controls. However, more recent prospective studies have shown that psychological symptoms such as anxiety, depression, and obsessive symptoms (34) as well as trait unhappy mood (35–37) are associated with the likelihood of an HSV recurrence during a follow-up period. In addition, stress in medical students taking examinations has been shown to increase levels of antibody to HSV, suggesting that the virus may be triggered out of latency under such stressful conditions (38). Two stress-related hormones, norepinephrine and epinephrine, have been shown to block the capac-

ity of gamma interferon to activate murine macrophages to kill HSV-2-infected cells in vitro (39). Despite such suggestive evidence, the immune system has not been studied as a mediator between psychological factors and HSV recurrence.

Objectives

The first objective was to determine the relationship between stressful life experience and negative mood and herpes recurrence in a sample of patients with frequent outbreaks of the disease. Stressful life experience was defined to include life change events, chronic or ongoing stressors ("daily hassles"), "anticipated" stressors, and residual effects of past stressors.

The second objective was to determine whether changes in the proportion of helper-inducer (CD4+) and suppressor-cytotoxic (CD8+) T cells mediate the relationships between stressful life experience, negative mood, and HSV recurrence. These T cell subsets were selected for evaluation because they have important functions in responding to viral infection, and previous research has indicated that they may play an important role in relation to HSV recurrence (22).

The third objective was to compare the effects of psychological factors with other potential HSV triggers (including infection, fatigue, and the menstrual cycle) and health behaviors (alcohol consumption, sleep, and exercise) which might influence recurrence rate or immune parameters (e.g., refs. 40 and 41; see Weiner (2), for a discussion of this issue).

METHODS

Subjects

The 36 subjects (30 females, 6 males) were recruited from clinics and physicians treating herpes patients, from local herpes support groups, and from ads in local newspapers Individuals who contacted the investigator and who met the following criteria were asked to participate in the study: English-speaking; not actively homosexual; over the age of 18; carriers of HSV for six months or longer with two or more recurrences in the previous six months; free from infectious, autoimmune, neoplastic, or venereal diseases; and not undergoing medical treatment that has immunological effects (e.g., taking corticosteroids). None of the subjects were taking oral acyclovir. Subjects were predominantly white and single with a mean age of 33.4 (SD=9.5, range 18–69 years). They had, on the average, four years of college, and 4.8 recurrences over the past six months. Nineteen subjects (18 females, 1 male) who could schedule the monthly interviews on the days of the week when immune assessments could be conducted by the laboratory formed the immunological subgroup. The immune subgroup did not differ significantly from the overall sample in age, years of education, sex, race, marital status, or number of HSV recurrences over the prior six months.

Procedure

Each consenting subject was interviewed and filled out questionnaires once a month for six months. In addition, the 19 immunologic subjects had a blood sample drawn by a phlebotomist at each monthly interview. Subjects were asked to go to participating physicians for clinical documentation of suspected HSV outbreaks during the six-month study period.

Psychological Measures

Stress measures. We chose to assess stress broadly in order to go beyond the narrow focus of the life events approach (measuring only actue life changes) to include other types of stressors (e.g., ongoing stressors, anticipated stressors) hypothesized to have a significant effect on physiological processes and health (42, 43). The stress scales were selected to measure distress over the past month that resulted from events from three different time periods: *current* (i.e., over the past month), *past* (i.e., events from the past six months that still produced distress), and *future* (i.e., anticipated to occur in the following six months). Current stressors included major life changes, ongoing problems of daily living (daily has-

sles), and concerns associated with having herpes. To assess the impact of past stressors, subjects rated the amount of "residual stress" resulting from major life changes that had taken place over the prior six months. Future stressors included any negative events that were anticipated to occur in the upcoming six months. Subjects rated how much distress they currently felt in relation to each of these possible upcoming events.

Current *major life change* was measured using a modified version of Sarason's Life Experiences Survey[1] (LES) (44, 45). On the LES the subject indicated which of 57 life change events occurred over the past month, whether the event was good or bad, and the effect of the event on the subject's life. The LES score consisted of a summation of these effect ratings. The presence of *ongoing problems of daily living* was measured using the Daily Hassles Scale (DHS) (46). The DHS consists of 117 items ranging from minor annoyances (e.g., traffic noise) to major problems or concerns (e.g., problems with children). The subject indicated whether or not the hassle occurred and how much of a problem each hassle was over the past month. The DHS score was a sum of the problem ratings. The Herpes Stress Scale was developed during pilot work to measure specific *situations of concern associated with having herpes*. The subject rated his or her upset and worry over the past month in relation to each of six situations (e.g., pressure from partner about herpes, worry about infecting others); these ratings were summed.

Residual stress, that is, current distress over situations that had occurred in the past six months, was measured by asking subjects at the beginning of the study to fill out the LES for the previous six months and then to review the events they had listed (updated each month) and report their current level of upset and worry over each past event. *Anticipated life stress*, that is, current effects of anticipated events, was measured by asking subjects to report any life events they were worried might occur in the subsequent six-month period and the level of upset and worry they currently felt in anticipation of each event (47).

Factor analysis of the five stress scales indicated that all five scales loaded highly on a single factor. As a result, monthly scores on each of the five stress scales were z-transformed and combined into an overall stress score for each month. An overall stress score for the entire six-month period was derived by summing the monthly overall stress scores for each subject.

Mood measures. Three subscales of the Profile of Mood States (POMS) (48)—tension-anxiety, depression-dejection, and anger-hostility—were used to measure negative mood. Subjects indicated how much they felt each of 65 affects over the past month. Subscale scores were calculated for each month and for the entire study period.[2]

Measures of Nonpsychological Predictors of Recurrence

The presence of infection (e.g., a cold, flu) was measured using an infection score derived from the Symptom Status Scale of the Duke-University of North Carolina Health Profile (49), a list of 28 symptoms suggestive of illness. The infection score consisted of those seven symptoms that indicate the presence of an infection (e.g., fever) multiplied by the subject's rating of how much trouble he or she had with each symptom (ratings were none = 0, some = 1, or a lot = 2). Although this score could be considered to be biased toward illness behavior, it does provide a rough measure of the severity of infections experienced by each subject.

Each menstruating female subject (n = 28) was asked during the monthly interview for the date her menstrual period began.

Health behaviors were also assessed during the monthly interview. Subjects indicated the average number of hours slept per night, amount and type

[1] All stress measures used a seven-point Likert scale. This involved a modification of the LES and the DHS.

[2] The mean, standard deviation, and range for monthly psychological scale scores, averaged over the six months, were as follows. Overall Stress Score: mean = 0.04, SD = 0.63, range = −1.21 to 1.94, POMS Depression: mean = 13.59, SD = 8.91, range = 0.33 to 39.33; POMS Anxiety: mean = 9.56, SD = 5.51, range = −2.17 to 21.25; POMS Hostility: mean = 12.77, SD = 8.50, range = 1. 33 to 42.40. The correlations between the averaged Overall Stress Score and the POMS scales were as follows. POMS Depression: $r = 0.37$, $p < 0.05$; POMS Anxiety: $r = 0.62$, $p < 0.005$; POMS Hostility: $r = 0.75$, $p < 0.005$.

of exercise engaged in, and amount and type of alcohol consumed. Fatigue was measured using the POMS fatigue-inertia subscale.

Immunological Measures

The proportions of CD4+ and CD8+ cells were assessed monthly in the immunological subgroup. In most cases, each monthly blood sample for a subject was drawn at approximately the same time of day, i.e., subjects who were able to have blood drawn at 6 p.m. were drawn each month at 6 p.m. In the majority of subjects blood was drawn in the late afternoon to early evening. Blood specimens were drawn by peripheral venipuncture into heparinized tubes. Samples were maintained at room temperature a maximum of 18 hr after blood drawing. T cell subset enumeration was conducted in the Clinical Immunology Laboratory at the University of California, San Francisco, under the direction of Conrad Casavant, Ph.D. Heparinized blood was separated on Ficoll-Hypaque. Peripheral blood mononuclear cells (PBMCs) were washed and resuspended to the desired concentration. Indirect immunofluorescence was used to measure T cell subsets. PBMCs were added to the monoclonal antibodies OKT4 or OKT8 (Ortho Diagnostic, Raritan, NJ) and incubated on ice for 30 min. The cells were washed, and then fluorescein-labeled goat anti-mouse IgG (Meloy Laboratories, Springfield, VA) was added and incubated on ice for an additional 30 min. Normal mouse IgG was used as a control for background fluorescence due to nonspecific staining of lymphocytes. The cells were washed twice, and the percentage of positive-staining lymphocytes, determined by size and morphological characteristics, was counted with a Zeiss phase contrast microscope with epifluorescence. For each sample, five fields were counted with 40 to 50 cells counted per field. A healthy laboratory control was evaluated each time the assay was conducted, and control values were compared against normal ranges for the laboratory. If the values were found to be outside the normal range, the assay was repeated for both the subject and the control to ensure reliable values.

HSV Recurrence

Subjects reported their recurrences monthly. HSV recurrence rate for each monthly period and for the entire study period was the sum of all the reported recurrences. Subjects were also asked to have all recurrences verified by the medical staff or the study physicians.[3] At the visit the dermatologist or nurse practitioner examined the lesions and determined if they were clinically typical of HSV or not. Our intention was to verify all herpes recurrences. However, this proved impractical. Some recurrences occurred on weekends or vacations; in other cases the subject's and physician's available times did not coincide. Approximately 40% of all recurrences were examined. In almost all cases the physician's examination verified the recurrence as herpes.

RESULTS

The results will be described using the X-Y-Z model proposed by Elliott and Eisdorfer (1) for reference. First, cross-sectional (between subjects) analyses will be described for X-Y relationships (e.g., stress and immunity), X-Z relationships (e.g., stress and HSV recurrence), and Y-Z relationships (immunity and HSV recurrence). Then, based on cross-sectional analyses, a particular X-Y-Z pathway will be tested using within-subject analyses. Unless otherwise indicated, all analyses on immune variables were conducted on the 19 subjects in the immune subgroup; all analyses on HSV recurrence were conducted on the entire sample of 36. Since there was no association between age or gender and immune or HSV recurrence variables, age and gender are not entered into analyses as covariates.

[3] Study physicians were Dr. Marcus Conant, Department of Dermatology, University of California, San Francisco; Dr. Edward Becker (Dermatologist), El Cerrito, CA, and the PRN Clinic for herpes-related problems, Oakland, CA.

Stress, Mood, and T Cell Subsets (X-Y Relationships)

Stress. The average overall stress score over the six-month study period was found to be highly negatively correlated with the average proportion of CD4+ cells ($r = -0.47$, $p = 0.02$) and with the average proportion of CD8+ cells ($r = 0.41$, $p = 0.04$). In both cases, the more stress reported over the study period, the lower the proportion of each T cell subset in the peripheral blood.

In order to explore the relationship between specific types of stress and subset levels, the correlations between each of the five stress scores and CD4 and CD8 levels were computed (Table 1). The anticipated and residual stress scores were significantly negatively correlated with CD4 levels; only the DHS score was significantly correlated with CD8 levels.

Mood. The correlations between the three mood scales and CD4 and CD8 levels are shown in Table 1. All three moods had large and significant negative correlations with CD8 levels and small insignificant correlations with CD4 levels. Figure 1 displays the size of the difference in CD8 levels depending on degree of anxiety, depressive mood, and hostility.

TABLE 1. Correlations Between Average Stress and Mood Scale Scores and T Cell Subset Values[a]

Scale Scores	Percentage Positive Cells	
	CD4	CD8
Overall Stress Scale	−0.47*	−0.41*
Major Life Change	−0.36	−0.30
Daily Hassles	−0.15	−0.47*
Residual Stress	−0.51**	−0.25
Anticipated Life Stress	−0.50**	−0.22
Herpes Stress	−0.35	−0.18
POMS Depression	−0.07	−0.49*
POMS Anxiety	−0.16	−0.47*
POMS Hostility	−0.07	−0.57**

[a] Correlations are based on means over the six-month period of the monthly stress and mood scale scores and T cell subset values.
* $p < 0.05$.
** $p < 0.01$.

Stress, Mood, and HSV Recurrence (X-Z Relationships)

Subjects had an average of 2.56 recurrences during the six-month study period (range from 0 to 6). The average overall stress score over the six months was found

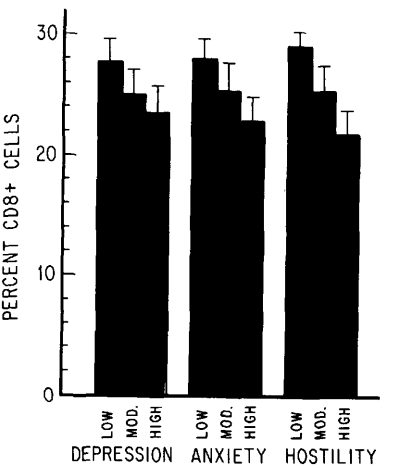

Fig. 1. Average percentage of CD8+ cells in subjects reporting high, moderate and low mood scores. Depression, hostility, and anxiety scores averaged over the six-month study period were divided into high (subjects reporting the top third scores on each mood scale), moderate (the middle third), and low (the bottom third). The average percentages of CD8+ cells in the three depression, anxiety, and hostility groups are displayed.

to be uncorrelated with HSV recurrence rate over the study period. The three mood scales were also uncorrelated with HSV recurrence rate.

Infection, Fatigue, the Menstrual Cycle and HSV Recurrence

Correlations were computed between the infection and fatigue scores and the rate of recurrence over the six-month study period. No significant relationships were found. Only the infection score had a close to significant ($r = 0.27$, $p = 0.07$) relationship with recurrence rate. There were no significant differences in the number of recurrences reported during any of the defined phases of the menstrual cycle (i.e., the five days prior to the menstrual period, the five days of the menstrual period, and the five days following the end of the menstrual period).

Stress, Mood, and HSV Recurrence in Subjects Without Infections

Infection may trigger recurrences in some individuals, while others may have recurrences that are psychologically triggered. To test this possibility, analyses were conducted on subjects who did not report a large number of infection symptoms during the study period (i.e., the subjects who reported the highest level of infection symptoms over the six months of the study—the top one-third—were removed from the analyses). Again, the overall stress score was uncorrelated with recurrence rate. However, the depressive mood score was significantly correlated with recurrence rate ($r = 0.34$, $p < 0.05$). Figure 2 indicates that the most depressed individuals (the top one-third of the sample in depression scores) had twice as many recurrences over the study period as did the least depressed subjects.

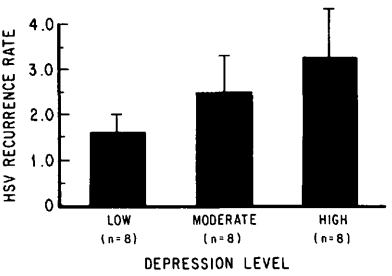

Fig. 2. HSV recurrence rate in subjects reporting high, moderate, and low depression scores. Depression scores in the subjects with low to moderate infection scores ($n = 24$) were divided into high (subjects reporting the top third depression scores), moderate (the middle third), and low (the bottom third). HSV recurrence rates in the three groups are displayed.

Health Behaviors and HSV Recurrence

An analysis was conducted in order to determine whether the relationship between depressive mood and recurrence rate was attributable to depression-related changes in health behaviors. Scores for the six-month study period were calculated for the following health behaviors: the average number of hours slept per night, average consumption of alcoholic beverages (including wine, beer, and mixed drinks), and the average hours of exercise. However, there was a significant positive correlation only between the amount of alcohol consumed and recurrence rate ($r = 0.34$, $p < 0.05$).[4]

[4] The alcohol consumption score was found to be uncorrelated with both CD4 and CD8 values.

A simultaneous multiple regression analysis was conducted to determine if alcohol consumption and depressive mood had unique or overlapping relationships with HSV recurrence rate. While the entry of alcohol consumption into the equation rendered the p value for depressive mood below significance, the magnitude of the semi-partial correlation was not diminished ($r = 0.34$, $sr = 0.33$, $t = 1.8$, $p = 0.09$). Thus, the lack of significance is attributable to the shift in degrees of freedom with another variable in the equation. The fact that the matnitude of the correlation remains the same suggests that both alcohol consumption and depressive mood contribute uniquely to the variance in HSV recurrence rate.

T Cell Subsets and HSV Recurrence (Y-Z Relationships)

The average proportion of CD4+ cells was uncorrelated with recurrence rate over the six-month study period. The average proportion of CD8+ cells was negatively correlated with recurrence rate ($r = 0.45$, $p = 0.03$). That is, the lower the CD8 levels over the course of the study, the more recurrences the subjects experienced.

Within-Subjects Test of Depression-CD8-Recurrence (X-Y-Z) Pathway

Considering the between-subjects data presented above, it appears that some subjects may have recurrences triggered by the presence of infections. In other subjects, depressive mood may increase the subject's vulnerability to recurrence. This may be the result of lower levels of CD8+ cells or an associated immune change found in the more depressed subjects. Our data on the relationship between CD8 levels and HSV recurrence support this pathway since lower CD8 levels over the course of the study were associated with more recurrences.

In order to test this possible predictive pathway more fully, a within-subjects perspective must be used. Months in which subjects report high levels of depressive mood should correspond with low CD8 levels, and high levels of depressive mood and low levels of CD8+ cells should *precede* outbreaks of HSV.

Depressive mood as a predictor of CD8 levels (X-Y) and recurrence (X-Z). Two statistical approaches were used to determine whether monthly changes in depressive mood predicted CD8 levels and HSV recurrence over time. First, a correlated *t* test procedure was performed. For each subject, the month in which the subject reported the maximum depressive mood was compared with the month in which the subject reported the minimum depressive mood. Differences in concurrent CD8 levels and HSV recurrence rate over the following month were examined. It would be expected that CD8 levels would be lower in the maximum depression month and that recurrences would be more likely to follow the maximum depression month when compared to the minimum depression month.

Second, a repeated measures analysis of variance was performed. Monthly depressive mood scores were entered as covariates paired with the dependent variable (e.g., CD8 levels) at each monthly assessment point. The strength of the relationship between the covariate and the dependent variable is represented by the regression coefficient beta, which is the weighted average of the regression coefficients of each dependent variable on

each covariate at each monthly measurement point.

Results from both of these analyses indicated no significant within-subjects relationships between depressive mood and CD8 values or HSV recurrence rate. These analyses were conducted with the entire sample (the sample of 19 in the immunological subgroup was used when immune parameters were the dependent variable) as well as with the subsample of subjects with low infection scores (as described above). Thus, acute changes in depressive mood were not associated in time with acute changes in CD8 levels or with increased susceptibility to HSV recurrence in the upcoming month period.

CD8 levels as a predictor of recurrence (Y-Z). In order to test the relationship between CD8 values and the timing of HSV recurrences, a different approach was required. Five phases of HSV recurrence were defined and *t* tests were used to compare each phase of the quiescent phase for differences in CD8 levels. Three of the phases (recurrence, convalescnce, and quiescence) were defined based on the work of Sheridan et al. (22), who studied T cell subsets and HSV outbreaks. Two pre-recurrence phases were defined for the purposes of this study—one week and two weeks before the beginning of the recurrence phase. Table 2 indicates the definitions for each phase. CD8 data that were available from blood draws that coincided with each of these phases were then averaged (thus, the *n* differs for each group). CD8 levels were found to be significantly lower during the one to two weeks prior to the recurrence phase when compared to the quiescent phase ($t(39) = 3.02$, $p = 0.01$). In addition, CD8 levels were lower during convalescence ($t(45) = 2.72$, $p = 0.01$). (CD4 levels did not significantly vary across the time periods.)[5]

TABLE 2. Mean T Cell Subset Values During Each HSV Recurrence Phase

HSV Recurrence Phase (no of samples)[a]	Percentage Positive Cells[b]	
	CD4	CD8
Two weeks Pre-recurrence Phase (8) (8–14 days pre-recurrence)	46.9	20.6*[c]
One week Pre-recurrence Phase (9) (1–7 days pre-recurrence)	43.8	24.4
Recurrence Phase (11) (last 2 days of prodrome and first 3 days of recurrence)	49.6	24.0
Convalescence (15) (4–14 days past first day of recurrence)	43.8	20.9*
Quiescence (33)	47 4	27.1

[a] Since all subjects did not have blood draws coinciding with each recurrence phase, a different number of samples was used to calculate the means for each phase.
[b] T cell subset values from blood draws that coincided with each phase of HSV recurrence were averaged.
[c] Significance tests are based on *t* tests comparing the T cell subset value for each phase to the value during the quiescent phase.
* $p < 0.05$.

DISCUSSION

The results of this study suggest that both stressful life experience and negative mood are associated with levels of T cell subsets in the peripheral blood of patients with recurrent genital herpes. Using a cross-sectional approach averaging monthly scale scores over a six-month period, it appeared that stressful life ex-

[5] This analysis must be considered an exploratory test of the relationship between HSV recurrence and T cell subset values since each subject did not contribute a value for each recurrence phase.

periences (including acute life changes, ongoing problems of daily living, concerns related to having herpes, residual distress from past events, and distress in anticipation of future negative events) were associated with helper-inducer (CD4+) and suppressor-cytotoxic (CD8+) T cell levels; negative moods (depression, anxiety, hostility) appeared to be associated with suppressor-cytotoxic T cell levels only.

Among the factors considered to be possible predictors of herpes recurrence rate (including stressful life experience; moods of depression, anxiety, and hostility; fatigue, infections; and the menstrual cycle), only depressive mood level over the six-month period was associated with the number of recurrences experienced. The depressive mood-recurrence association was found only in subjects who did not report high levels of symptoms of other infections. The relationship between depressive mood and HSV recurrences was not attributable to changes in the consumption of alcohol, level of exercise, or amount of sleep.

Suppressor-cytotoxic (CD8+) T cell levels, depressive mood, and HSV recurrence rate over the six-month study period were all intercorrelated, suggesting the possibility that CD8 levels or an associated immunological parameter may mediate the relationship between depressed affect and herpes recurrence. Thus, the reduced proportion of CD8+ cells or an associated immune alteration during depressed mood may render depressed individuals more vulnerable to a herpes recurrence. The decreased percentage of CD8+ cells one to two weeks prior to a recurrence supports this notion. This decrease could represent a deficit in the availability of cytotoxic CD8+ cells necessary to kill virally infected cells. This model is consistent with the research linking depression to changes in immunity (16, 50) and the findings showing that trait unhappy mood (35,36) and negative psychological symptoms (34) were prospectively associated with herpes recurrence rate.

In contrast to cross-sectional analyses demonstrating that subjects with higher depressive mood scores over the course of the study period had more recurrences than less depressed subjects, intraperson analyses indicated that month-to-month fluctuations in depressive mood did not predict *when* a recurrence would take place. There are a number of possible explanations for this combination of results. First, high depressive mood scores over the six-month period may be indicative of a depressive disorder such as dysthymia or a stable tendency toward negative affectivity (as described by Watson and Clark (51)). A review of the monthly depressive mood scores indicates a high degree of consistency over time for many of the subjects. A stable disposition to experience depressive affect may create an immunological milieu inadequate to protect host cells from viral invasion. However, short-term changes in depressive mood state may not create this immunological vulnerability because depressive mood states differ from depressive disorders or dispositions both quantitatively and qualitatively. The timing of recurrences may then depend on other triggering factors.

Alternatively, the association found between depressive mood and herpes recurrence may be attributable to the feelings of depression that result from having a high rate of recurrences. Research has shown that many individuals with genital herpes report high levels of negative affect including depressive mood, possibly as a result of the social stigma attached to the disease and its impact on their social rela-

tionships and self-image (52, 53). However, the Herpes Stress Scale used in the current study to measure the individual's distress concerning herpes-realted situations accounted for only 10% of the variance in depressive mood level ($r = 0.34$, $p = 0.05$). In addition, responses to the stress and coping interview conducted each month (54) indicated that the majority of events reported to trigger feelings of depression were unrelated to having herpes (e.g., death in the family, loss of job). However, having herpes may decrease the threshold for depressive feelings in response to situations unrelated to herpes. It is also possible that both causal directions are true. Having multiple outbreaks may cause some individuals to feel depressed; and increased levels of depressive mood over time may create a biological environment conducive to more recurrences—a "vicious cycle." Further research is required to clarify the nature of the relationship between depressive affect and HSV recurrence.

The data from this study raise two important issues about the effects of "stress." First, aspects of stressful life experience other than current life change events and ongoing problems of daily living were associated with quantitative aspects of immunity. The residual stress scale and the anticipated life stress scale scores were both highly correlated with the proportion of CD4+ cells. It is important to recognize that individuals may be responding psychologically and biologically to current upset and worry over events that took place in the past as well as to the prospects for upcoming difficulties.

Second, "stress" is reported anecdotally to be a potent activator of herpes recurrences. However, stressful life experience, measured broadly, did not predict who would have more recurrences or when they would take place. These results suggest that exposure to stressful life experiences alone may be insufficient to trigger a recurrence of genital herpes. A variety of factors such as the nature of interpersonal relationships, methods of coping, past experience, and personality may determine whether individuals respond to stressful circumstances with the negative affective changes that may produce immunological vulnerability to HSV recurrence. It is important to recognize, however, that stressful experiences may not be required at all for the activation of herpes lesions. Instead, a tendency to experience depressive affect, or unhappy mood, independent of life events, may create the appropriate vulnerability to lesion formation.

SUMMARY

Stressful life experience, negative mood, helper-inducer (CD4+) and suppressor-cytotoxic (CD8+) T cells and genital HSV recurrence rate were investigated every month for six months in 36 individuals with recurrent HSV. Subjects with high levels of stressful life experience over the study period (including current acute and ongoing stressors, residual effects of previous stressors, and anticipation of future stressors) tended to have a low percentage of CD4+ and CD8+ cells. Subjects with high levels of negative moods (anxiety, depression, or hostility) tended to have low levels of CD8+ cells only. Only depressive mood averaged over the study period, in the subjects without many symptoms of other types of infections, was associated with herpes recurrence rate. The depressive mood-HSV recurrence relationship was not dependent on changes in health behaviors such

as alcohol consumption, sleep, or exercise. Month-to-month changes in depressive mood level, however, did not predict when subjects were most susceptible to HSV recurrences. It is suggested that chronic levels of depressive affect may result in decreased levels of CD8+ cells or an associated immunological parameter which may create a biological environment conductive to HSV viral replication and lesion formation.

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