Herpes Simplex and Mood: A Prospective Study

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The effect of mood, the common cold, amount of sleep, and sunshine on recurring herpes simplex virus (HSV) infection was investigated using daily self-reports over a 3-month period from 23 female and 15 male patients with genital herpes and 26 female and two male patients with oral herpes. Results showed recurring genital HSV infection to be preceded by reduced and decreasing overall emotional well being over a period of 10 days, with a temporary improvement in the middle of the period. This pattern was significantly represented by rated nervousness and rated alertness. Females showed more marked trends for reported mood than did the males, which could not be attributed to the menstrual cycle. Conversely, males showed a more marked, strongly significant fourth-order trend for reported amount of sleep, with nadirs on the 8th and the 3rd day before the recurrence. Neither exposure to sunshine nor the common cold showed any relation to recurrence of genital HSV infection. The common cold appeared as the major precipitating factor in oral herpes. Except for a significant fourth-order trend for rated alertness, no relationship between mood and subsequent onset was found. This negative finding was interpreted as a masking effect of the common cold. Two alternative physiological theories, the ganglion trigger theory and the skin trigger theory, were discussed in relation to present findings. It was suggested that various possible mediators between mood states and recurring herpes should be investigated using the present approach, with structured diaries as complement to the rating scales.

Key words: Ganglion trigger theory, genital herpes, mood, oral herpes, skin trigger theory, sleep, well being.

Herpes simplex viruses (HSV) cause a wide spectrum of diseases, the most common of which are oral herpes, commonly known as fever blisters or cold sores, and genital herpes. There are two types of HSV, known as HSV-1 and HSV-2. In most cases, HSV-1 is responsible for herpes above the waist and HSV-2 for herpes below the waist. Approximately 75% of the population develop oral herpes at some time during their lives. Although not equally common, genital herpes is one of the most rapidly increasing sexually transmitted diseases, afflicting millions of people. For most people, both oral and genital herpes are relatively benign diseases, but genital herpes, and sometimes even oral herpes, may have a profound emotional impact on the victim.

After the first infection, in more than 50% of the cases, the virus (or more likely its genome, the genetic component) retreats to the sensory ganglia (the trigeminal ganglia in oral herpes and the sacral ganglia in genital herpes), where the genome is harbored in a repressed or largely repressed state compatible with the survival and normal activities of the cell. The individual never gets rid of the virus.

After the initial episode, the individual may or may not experience a recurrence of the infection. About one-third of those infected experience the infection intermittently, in some cases as often as twice a month. Among the factors that are widely believed to trigger recurrence of herpes infections are onset of colds or fever, exposure to ultraviolet radiation, emotional stress, and fatigue.

Wherever the location, the symptoms of recurrent HSV-1 and HSV-2 infections are much the same. In a prodromal phase, itching, tingling, and pain are experienced in the infected area. Within a day or two, small clusters of blisters appear that subsequently turn into a sore. Within about 1 week, tissue begins to cover the lesion, producing a scab that sloughs off in about a week.

There are two major theories about the mechanism of recurring herpes infections. According to the predominant one, known as the ganglion trigger theory, the viral genome is maintained in an entirely latent state, which intermittently becomes broken by some triggering factor. It has been suggested that immunoglobulins control the latent infection (1–2). Support for the ganglion trigger theory is provided by the findings that surgical section of distal nerve roots (3) and instillation of pneumococcal pneumonia (4) result in reactivation of the latent virus.

According to the second theory, the so-called skin

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trigger theory, the virus is always circulating in small quantities between ganglia and peripheral sites, but local host immune mechanisms continually suppress viral replication until something happens that either stimulates replication or temporarily weakens the immune response. Support for this theory comes from frequent reports of isolation of the virus from the saliva or vaginal secretion of herpes sufferers during latent periods of the infection.

Emotional stress is most often cited by individuals with herpes and physicians as the most significant factor in activation of recurrences. Scientific support for this view is not very impressive, however. A great many of the studies cited in support of a causal link between emotional factors and recurrence of HSV infections are anecdotal in nature. For example, based on case studies, hypnosis (5–7) and psychotherapeutic intervention (8) have been claimed to be able to reduce or alleviate symptoms. Even among the more rigorous studies on the activation of HSV infection recurrence by emotional factors, the results are mostly inconclusive because of the use of retrospective methods (9, 10).

Most of the published prospective studies, however, are also inconclusive because of their focus on personality traits, such as long term emotional dispositions (11, 12), rather than on acute emotional states. Exceptions are perhaps provided by two studies conducted by Goldmeir and his associates (13, 14), in which patients with higher levels of "nonpsychotic psychiatric illness," as measured by the General Health Questionnaire, showed higher recurrence rates. This questionnaire is purported to measure a state- rather than a trait-variable. However, the possibility that a trait- rather than a state-variable was in fact measured cannot be excluded.

Ideally, an intra-individual, prospective design, including measures of acute emotional states, should be used to reveal a possible link between emotional factors and recurring herpes. Such a design was used in a study performed by Luborsky and his associates (15), but the results were negative. In their study, 16 nursing students who suffered from oral herpes completed the Clyde Mood Scale daily for a 3-month period. Using a two-way analysis of variance (ANOVA) with days and subjects as factors, the authors failed to identify any trend for the time period covering the 4 days before and the 4 days after the recurrences. These negative results are inconsistent with the finding by Katcher et al. (11) of a significant positive correlation between scores on the "unhappy" factor of the Clyde Mood Scale (here used as a trait- rather than a state-variable) and recurrence of oral HSV infection during the year after the mood measurement. Again nursing students ($N = 38$) were used as subjects.

The major purpose of the present study was to replicate the Luborsky et al. study (15), with some extensions and modifications. Four differences between the present study and that of Luborsky et al. are particularly important. First, self-ratings were done not only with respect to mood but also with respect to other putative triggering factors, namely sun exposure, the common cold, and sleep. These factors were introduced mainly for comparison and control purposes. Second, a larger sample of subjects were used, representing both oral and genital herpes. Third, a larger prerecurrence period was explored. Finally, diary notes were collected as a complement to the mood data.

METHODS

Procedure

Recruitment. Patients with culture-proven genital and/or oral herpes who were seen at the South Hospital, Stockholm, from January 1982 until March 1988 and suffered from at least four recurrences per year were considered for participation in the study. Those patients who did not live in or near Stockholm were excluded. The selection procedure was halted when 300, out of approximately 350, eligible patients had been found.

The patients considered for the study were contacted by mail and informed about the study. One hundred and nineteen patients agreed to participate.

No demographic or other data were collected for the 181 patients who chose not to participate. Consequently, no systematic comparisons could be made between those patients and the participating subjects. The participants, however, did differ from a typical herpes patient at the clinic in at least one important respect: they were more severely ill with herpes, with a mean annual recurrence frequency of 8.0 as compared with one of 4 to 6. The study was approved by the ethics committee.

Meeting with the subject. Most of the subjects (110 of 119) were seen individually by either of two of the authors (EB or TBRW). Communication with the remaining subjects occurred by telephone and mail.

The subject was presented with a questionnaire asking for personal background information. The subject was told not to use preventive anti-viral medicine (acyclovir) during the study period but was given permission to use any medication that might hasten recovery from an acute HSV infection. The subject was then given a booklet to be used for collecting the daily data and was asked to read the instructions enclosed. To get a background description of the patients in terms of personality traits, a shortened version of the Eysenck Personality Inventory (EPI) (16) was administered.

The subject was asked to return the booklet in a prepaid envelope. All the subjects who had not returned the booklet within 2 weeks or so after the end of the study period received a reminder letter and were asked to return the booklet even if they had not completed the task.

The questionnaire. The questionnaire was constructed by the

authors to assess a) demographic information, b) general medical data, c) information concerning the herpes disease history (year of diagnosis and estimated yearly frequency of herpes episodes during the last 10 years), and d) data concerning the current severity of the herpes infection (frequency, duration, number of sores, and experienced discomfort during the last year).

Daily data. Daily self-ratings were made by the subjects on one unipolar and four bipolar graphic (visual analog) mood dimension scales. The unipolar dimension was defined by the adjective angry. The bipolar dimensions were defined by the following adjective pairs: calm-nervous, sluggish-alert, sad-happy, and unconcentrated-concentrated, the right-hand adjectives corresponding to the positive poles. With some minor modifications, the mood scales were chosen from a mood model derived by Sjöberg and Svensson (17) on the basis of factor analytic research on mood adjective checklists.

Self-ratings of nonvisible herpes symptoms were done on two scales, one measuring irritation and the other ache. Possible visible skin symptoms were marked in boxes indicating redness, swelling, blisters, sore, and crust, respectively. Exposure to sunshine was rated in hours per day. Perceived degree of common cold was rated on a graphic scale. The final rating concerned the number of hours of sleep during the preceding night.

The extreme points of a bipolar graphic scale, 100 mm in length, were defined by the expression "a very high degree," and the midpoint was defined by the expression "neither/nor." The upper and the lower end of a unipolar graphic scale, 50 mm in length, was defined by the expressions "a very high degree" and "not at all," respectively.

The subjects were also instructed to keep diary notes, noting any deviations from the daily routine, such as journeys, illnesses, possible medication, and unusual events during the day.

The ratings and diary notes were to be made every evening for a 3-month period. The mood ratings were to refer to the day as a whole. The study was carried out during the spring and the summer of 1988.

Analysis of Data

Rating data. To make the rating scales comparable within and between individuals, they were standardized for each subject and scaled separately by transforming the raw-values into z values. The first day in each recurrence episode, defined as the first day with a visible symptom, and the 10 preceding days were picked out for analysis. If a subject had suffered from more than one recurrence episode, the scales were averaged over the periods, so that each subject contributed equally to the analysis. Group means were then calculated for the 10 variables as described below.

Diary data. An attempt was made to construct individual positive and negative event scales from the diary data. However, because of the unstructured character of the data, a given diary note was often difficult to interpret as indicating a positive or a negative event. Moreover, most of the subjects provided a large number of blanks, and some subjects did not provide any diary notes at all.

For these reasons, the diary notes could only be analyzed tentatively, and the results will only be considered in passing in the discussion.

Statistical analysis. The data corresponding to plots of mean scales as a function of days before recurrence were analyzed statistically using orthogonal polynomial trend analysis. In this method, a dependent variable is partitioned into orthogonal, that is, statistically independent, linear, quadratic (parabolic), cubic (S-formed), or higher-order trend components. The values of the independent variable are ordered and equally spaced, as, for example, in a typical time scale. With n levels of the independent variable, n-1 trend components can be discerned. A trend component of a high order, say above four, is typically difficult to interpret. Therefore, we chose not to consider trend components of a higher degree than four, a fourth-order trend component being characterized by the occurrence of two crests and one valley, or vice versa. The significance of any component can be tested by means of ANOVA. (For a more detailed description of the method in question see, for example, Ref. 18). In the present study, the analyses were performed using the program 2V in the program library BMDP Statistical Software (19).

It is noteworthy that one or several trend components in a given data set may be significant even though a corresponding ordinary ANOVA, that is, ANOVA for differences between means, does not reach significance. This is related to the fact that a specified trend component is tested in the trend analysis, whereas a more unspecified effect is tested in an ordinary ANOVA. Orthogonal trend analysis may thus be a more powerful method than ordinary ANOVA.

Mainly to test for the existence of differences between different data sets, two-way repeated measures ANOVA was used. Overall deviations from base line were tested by means of repeated measures ANOVA for sums of means, as described in Reference 19.

Separate groups. The data were analyzed separately for the oral and the genital herpes groups. In addition, males and females were compared with respect to the rating scales in the case of genital herpes, where the number of males was large enough for a separate analysis to be meaningful.

Menstruation cycles. The menstrual cycles for the women in both groups were identified. This could not always be done exactly, however, because the cycles at the beginning and the end of the study period were not complete. Each identified menstrual cycle was divided into five phases of equal length, with the first menstruation day as the first day in phase 1. The method used represents a simplified version of a method proposed by the Society for Menstrual Cycle Research (20) as an acceptable alternative to determinations made through endocrinological assessments. When possible, the phase in which a given herpes attack occurred was identified.

RESULTS

Subject Groups

One criterion for the daily data to be included in the analysis was that the subject had suffered from at least one recurrence episode that had been preceded by at least 10 days without any visible symptom. Sixteen subjects did not satisfy this criterion.

Of the 119 distributed booklets, 20 were never returned. In addition, 11 subjects were omitted because their booklets could not be identified or the data were incomplete, eight were omitted because of lack of visible herpes symptoms, seven were omitted because they had only experienced an attack during the first week of the study period, and one subject

was omitted because of persistent herpes during the period. This resulted in a total of 72 booklets that could be used for the analysis of the daily data.

Additionally, six subjects who suffered from both oral and genital herpes were excluded from the study, because this group was too small for a separate analysis. We were, thus, left with a final group of 66 subjects (49 females and 17 males).

Characteristics of the final group are summarized in Table 1. Thirty-eight of the subjects, 23 females and 15 males, suffered from HSV-2 virus-cultured genital herpes, located below the waist. (In addition to "pure" genital herpes, nine subjects in the final group had herpes on the buttocks and/or thigh.) Twenty-eight subjects, 26 females and 2 males, suffered from HSV-1 virus-cultured oral herpes, located above the waist. (In addition to "pure" oral herpes, seven subjects in the final group had herpes at some other site.) The two groups did not differ much with respect to demographic or medical characteristics. The oral herpes patients had typically been ill with herpes for a longer time than the genital herpes subjects, whereas the genital herpes patients exhibited a somewhat larger recurrence frequency during the last year.

The subjects did not deviate significantly from a Swedish norm group (16) on either of the two personality dimensions of the present version of the Eysenck Personality Inventory, extraversion and neuroticism.

Menstruation

For both types of herpes, chi-square tests failed to reject the null hypothesis of equal recurrence frequencies across the five phases.

Distribution of Herpes Episodes

Table 2 shows the distribution of number of episodes satisfying the acceptance criterion of a 10-day symptom-free period preceding the visible symptoms for the oral and the genital herpes group. As can be seen, the most frequent number of accepted episodes was 2 for both groups.

Rating Data

Two-way repeated measures ANOVA with time and type of herpes as independent variables showed a significant time effect for the two invisible herpes symptoms, ache [$F(10/590) = 23.18$, $p < .004$] and irritation [$F(10/640) = 73.29$, $p = .000$]. A significant interaction effect was also obtained for ache [$F(10/590) = 2.66$, $p < .004$], and an interaction effect approaching significance was obtained for irritation [$F(10/640) = 1.65$, $p < .09$], reflecting the fact that the two invisible symptoms appeared 1 day before the visible ones in genital herpes whereas only on the same day in oral herpes (Figs. 1 and 2). A significant type of herpes effect was obtained for

TABLE 1. Characteristics of Patients in the Final Group

Characteristics	Type of Herpes		
	Genital	Oral	Total
Gender (*N*)			
Male	15	2	17
Female	23	26	49
Age*	37.5 ± 12.2	36.0 ± 10.2	36.6 ± 11.7
Duration (years) of recurrent herpes (*N*)			
1–5	11	2	13
5–10	15	9	24
>10	12	17	29
Severity of recurrent herpes*			
N episodes during the past year	8.8 ± 4.8	6.8 ± 3.7	8.0 ± 4.4
N days/episode	6.2 ± 2.3	7.1 ± 4.1	7.6 ± 4.0
N soars/episode	2.9 ± 2.2	2.8 ± 2.5	2.8 ± 2.4
Rated discomfort (0–4)	2.1 ± 0.9	2.1 ± 1.1	2.1 ± 1.0
N episodes/year during the past 10 years**	9.5 ± 4.6	6.2 ± 3.3	8.2 ± 4.3
Medication (*N*)			
Acyclovir, oral	7	8	15
Acyclovir, tablet	8	6	14
Acyclovir, oral and tablet	1	1	2

* Mean and standard deviation.

** For subjects with a shorter disease history, the average recurrence rate was calculated over the number of years with attacks.

TABLE 2 Distribution of Episodes in the Study Period preceded by at least 10 Days without any Symptom

Type of Herpes	N Episodes				Total
	1	2	3	4	
Genital	9	24	3	1	70
Oral	7	18	3	0	52
Total	16	42	6	1	122

calm-nervous [$F(1/64) = 4.76$, $p < .04$], indicating a higher overall level of rated nervousness for the genital herpes group than for the oral herpes group (Figs. 1 and 2). An almost significant interaction effect was obtained for the common cold [$F(10/530) = 1.84$, $p = .052$], indicating an effect of the common cold in the case of oral herpes but not in the case of genital herpes. None of the remaining six rating scales showed any significant time, type of herpes, or time-by-type of herpes effect.

Genital herpes. The standardized ratings for the genital herpes group are shown in Figure 1.

The calm-nervous scale exhibits an overall increasing trend. This trend is reflected by a significant [$F(1,37) = 4.17$, $p < .05$] linear trend component.

The sluggish-alert scale displayed a significant fourth-order trend component [$F(1,37) = 9.40$, $p < .005$], reflecting a wave-formed trend with a crest in the middle of the prerecurrence period.

Visual inspection of the graphs for the five mood dimensions in Figure 1 suggests that the subjects experienced a relatively low and decreasing level of subjective well being during the prerecurrence period, with a temporary improvement during the middle of the period. To test this hypothesis, a mean well being scale was constructed. This was done on the basis of individual well being scales obtained by averaging the five mood scales after reversing the signs of the calm-nervous and angry scores. The scale obtained is shown in Figure 3. Consistent with the hypothesis, the curve is characterized by a significant first-order trend component [$F(1,34) = 4.84$, $p < .034$] as well as a significant fourth-order component [$F(1,34) = 4.84$, $p < .036$]. Moreover, again in agreement with the hypothesis, a repeated measures

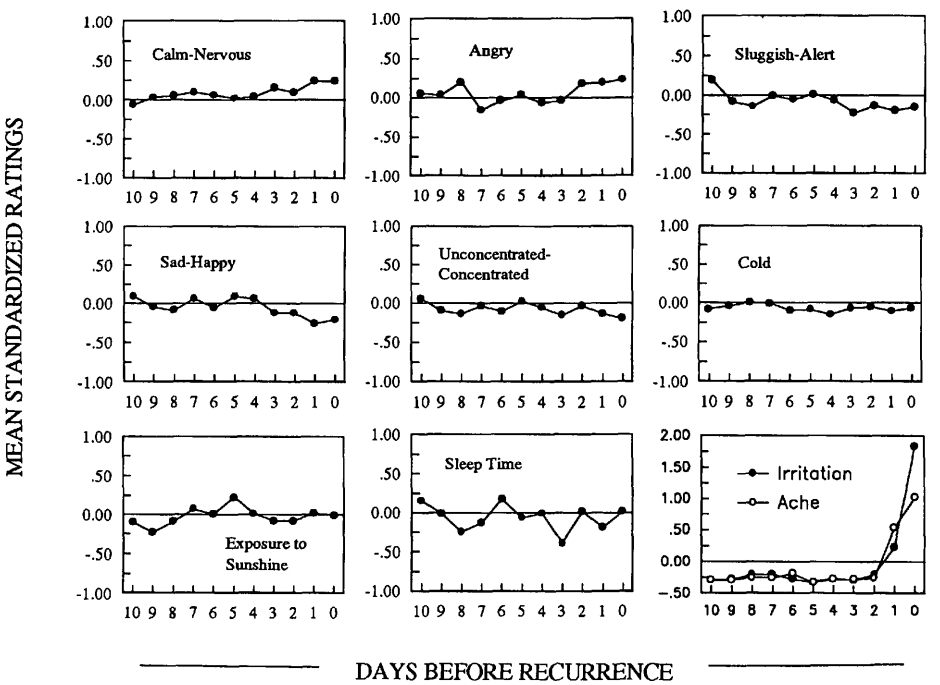

Fig. 1. Mean standardized ratings for the genital herpes group as related to number of days before recurrence.

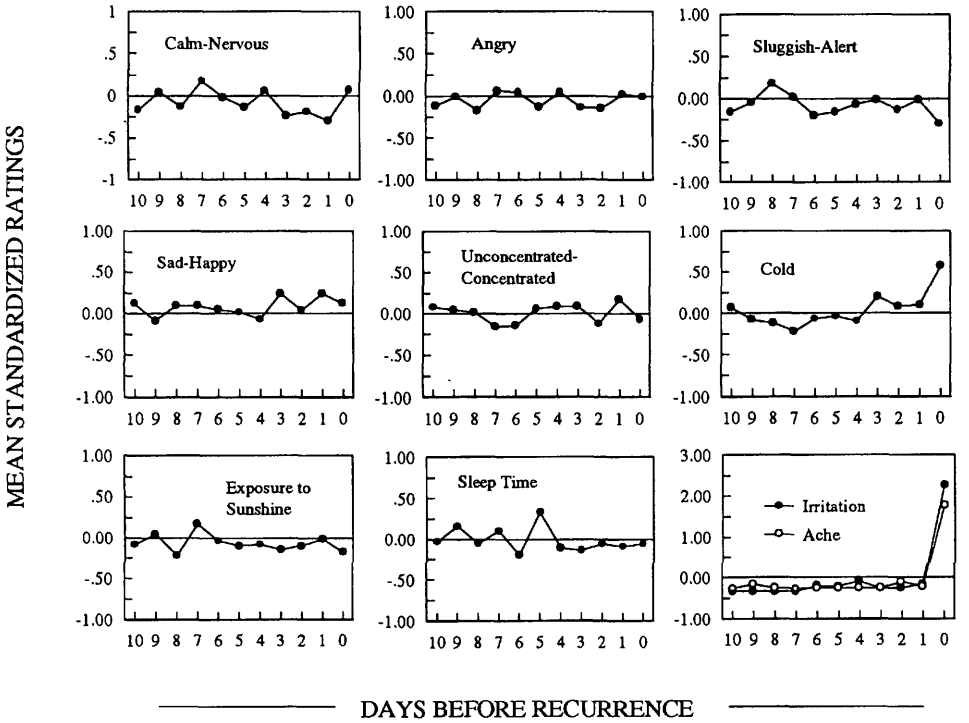

Fig. 2. Mean standardized ratings for the oral herpes group as related to number of days before recurrence.

ANOVA for sums of means showed the means to deviate significantly from zero [$F(1,34) = 4.65$; $p <$ 038].

The reported amount of sleep shows a fluctuating pattern with two marked dips, one on the 3rd and the other on the 8th day before the recurrence. This pattern is reflected by a significant fourth-order trend component [$F(1,37) = 4.32$, $p < .05$]. No significant trend component was obtained for rated common cold or reported exposure to sunshine.

Two-way repeated measures ANOVA with gender and time as independent variables yielded significant time effects for the two invisible herpes symptoms irritation [$F(10/360) = 41.61$, $p = .000$] and ache [$F(10/320) = 10.14$, $p = .000$]. Significant interaction effects were also obtained for irritation [$F(10/360) = 2.55$, $p < .007$] and ache [$F(10/320) = 3.41$, $p < .007$], indicating that females reported more irritation and ache than the males on the day of recurrence and the day before. Significant time [$F(10/360) = 2.52$, $p = .000$] and interaction [$F(10/360) = 2.64$, $p < .004$] effects were also obtained for reported amount of sleep. None of the remaining seven rating scales showed any significant time, gender, or time-by-gender effect.

In the case of the females, a significant [$F(1,22) = 11.06$, $p < .004$] fourth-order trend component was obtained for the sluggish-alert continuum, and a significant [$F(1,22) = 6.12$, $p < .03$] trend component of the same degree was obtained for the sad-happy dimension. In the case of the males, none of the mood variables exhibited any significant trend component, but the linear component for the calm-nervous scale approached significance [$F(1,14) = 4.55$, $p < .06$], as did the fourth-order trend component for the angry scale [$F(1,13) = 3.83$, $p < .08$].

Whereas only the females exhibited significant mood patterns, only the males displayed a significant pattern for reported amount of sleep, with very low values on the 8th and the 3rd day before the occurrence of visible symptoms and a high peak on the 6th day before the attack. Accordingly, the pat-

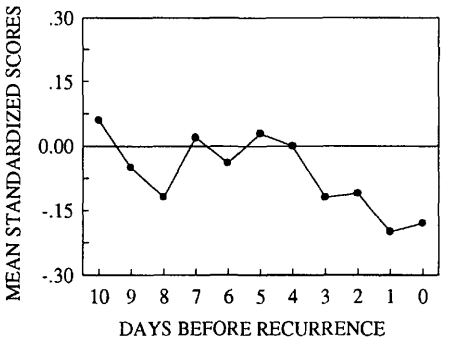

Fig. 3. Mean reported well being for the genital herpes group as related to number of days before recurrence. The means are based on individual scales constructed by averaging the five mood scales after reversing the signs of the calm-nervous and angry scores.

tern is characterized by a significant fourth-order trend component [$F(1,14) = 16.36$, $p < .002$]. One might have expected that the marked variation in rated amount of sleep would have been clearly reflected by the mood ratings, particularly perhaps by the sluggish-alert scores, but this was not the case. Neither the males nor the females exhibited any significant trend component for exposure to sunshine or reported common cold.

Herpes episodes in women were categorized by occurrence in premenstrual/menstrual ($N = 10$) or other ($N = 20$) phases. The mean standardized ratings for the two sets of data are shown in Figure 4. A significant difference was found for calm-nervous [$F(1,28) = 8.76$, $p < .01$], indicating more nervousness in the premenstrual/menstrual phases, and a significant time-by-phase interaction effect was found for the sad-happy dimension [$F(9,252) = 2.50$, $p < .01$], indicating reduced happiness at the end of the prerecurrence period and a reversed tendency at the beginning of that period for the premenstrual/menstrual phases. For the remaining three mood dimensions, however, there were no significant phase or time-by-phase effects.

Oral herpes. The standardized ratings for the oral herpes group are shown in Figure 2. The alertness data exhibit a cyclic trend, corresponding to a significant fourth-order trend component [$F(1,25) = 4.40$, $p < .05$], with nadirs on the day of recurrence and 6 days earlier. Moreover, there was a nearly significant tendency for the alertness means to fall below base line, as shown by a repeated measures ANOVA for sums of means [$F(1,27) = 3.02$, $p < .09$]. None of the four remaining mood variables exhibited any significant trend component.

Among the remaining variables, reported common cold exhibited by far the most pronounced trend. This trend has a J-shaped form, reflected by a significant quadratic trend component [$F(1,27) = 5.87$, $p < .03$], with a high value on the day of visible symptoms.

There is no indication that exposure to sunshine was a triggering factor because the scores tend to fall below base line throughout the prerecurrence period.

In an attempt to determine whether the enhanced occurrence of the common cold at the end of the prerecurrence period accounts for the pattern found for rated alertness, the following control analysis was performed. All of the herpes episodes that had been preceded by at least 10 days without any reported common cold, excluding the day of recurrence, were identified. Twenty-eight episodes, provided by 20 subjects, were found. These episodes were analyzed in the same way as before. The cyclic trend remained, the corresponding fourth-order trend component approaching significance [$F(1,18) = 3.41$, $p < .09$]. A repeated measures ANOVA for sums of means did not show the means to deviate from base line in either direction [$F(1,18) = 0.74$, $p < .40$].

DISCUSSION

Genital herpes. The results for the whole genital herpes group showed that recurrence of genital HSV infection was preceded by significant mood changes over a period of 10 days. Specifically, this group exhibited a reduced and decreasing level of reported well being, with a temporary improvement in the middle of the period. The overall decreasing trend was significantly represented by the calm-nervous scale and the cyclic form of the trend by the sluggish-alert scale.

No significant trend components for mood were found for men. Women showed significant fourth-order trend components for the sluggish-alert and sad-happy continua. This may be because the females were superior to the males in rating their mood states. Another reason may be that mood indeed is more strongly related to recurrence of genital herpes in females than in males. A menstrual cycle effect was not found. It is true that, for the calm-nervous and the sad-happy dimensions, the attacks in the menstrual/premenstrual phases were preceded by more pronounced trends in rated mood

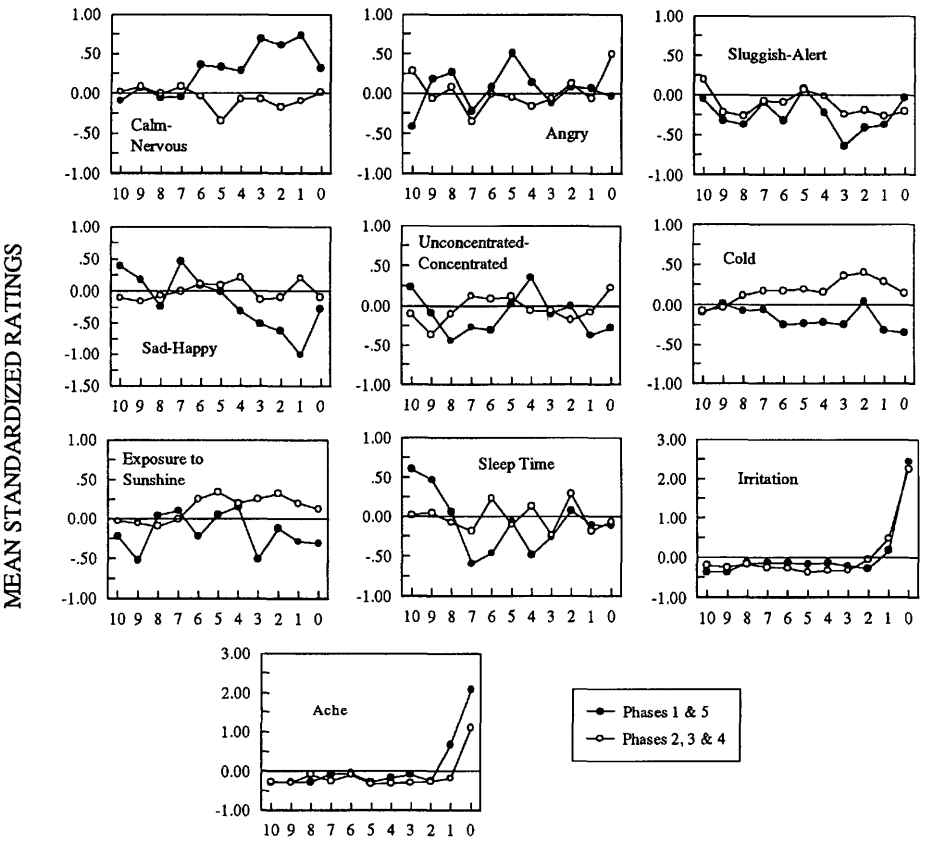

Fig. 4. Mean standardized ratings for episodes occurring in the premenstrual or the menstrual phase of the menstrual cycle (phases 1 and 5) and in either of the remaining phases (phases 2, 3, and 4) as related to number of days before recurrence.

than were the attacks in the phases in the middle of the menstrual cycle, but the attacks were not overrepresented in the menstrual/premenstrual phases. Moreover, in the case of the alertness scale, which showed the most pronounced trend in the whole female group with a highly significant fourth-order trend component, the premenstrual/menstrual phases and the phases in the middle of the menstrual cycle displayed very similar patterns, as revealed by visual inspection of the alertness graph in Figure 4.

The findings discussed above support the results from previous studies pointing to a relationship between negative mood states and recurrence of genital HSV infection (10, 13, 14). In the same vein, the findings suggest that previous failures to clearly relate recurrences of genital herpes to negative mood states (21, 22) are attributable to insensitive methods. Our more specific findings may provide a detailed picture of the relationship.

The only nonpsychological variable that exhibited a significant pattern was reported amount of sleep. Whereas the females displayed more marked trends than the males in the case of the mood variables, the males showed a more pronounced trend than the

females for sleep. This significant trend, with its extremely low levels on the 8th and the 3rd day before the recurrence, is compatible with the common belief that sleep deprivation is a risk factor for recurring HSV infection. If true, a probable mediator is a depression of the immune system (23). For the females, however, the reported amount of sleep was never markedly reduced during the prerecurrence period. This may mean that the females did not experience any severe sleep deprivation or that sleep deprivation, for some reason, is not a major risk factor in females. It could be speculated that immune system changes facilitating or responding to recurrences are related to release of somnogenic immune peptides (e.g., monokines and cytokines) that may interfere with sleep regulation. Conceivably, women are more resistant to one or several somnogenic immune peptides.

An interesting possibility is that the reduced emotional well being and amount of sleep at the beginning of the prerecurrence period is associated with prodromal processes at the ganglion level, in accordance with the ganglion trigger theory, whereas the reduced well being and amount of sleep at the end of the prerecurrence period is associated with prodromal processes at the skin level, in agreement with the skin trigger theory. According to the skin trigger theory, a precipitating factor would operate for a few days just before the attack, because inoculation of virus into the skin causes lesions in humans 2 to 3 days later (24). This prediction conforms nicely with the low levels of reported emotional well being for some days just before the recurrence, as well as the marked dip in reported amount of sleep for the males in this period. Unfortunately, the starting-time of the hypothetical prodromal process at the ganglion level cannot be determined very exactly, mainly because of varying estimates of the speed with which the virus is transported in the nerve; the estimates range approximately from 2 mm/hour to 10 mm/hour (25, 26). Thus, a test of the hypothesis that the decreased emotional well being and amount of sleep at the beginning of the prerecurrence period are linked to prodromal processes at the ganglion level must await a more exact determination of the rate of viral transport.

Oral herpes. The results obtained for the oral herpes group differed from those obtained for the genital herpes group, even though this was not clearly revealed by two-way ANOVA. First of all, whereas the common cold did not seem to be a precipitating factor in the case of genital herpes, it apparently was the most critical factor in the case of oral herpes, with a dramatic increase at the end of the prerecurrence period. The fact that the common cold turned out to be a significant precipitating factor for oral herpes did not, of course, come as a surprise. It was perhaps also to be expected from clinical experience that genital herpes would appear as less affected by the common cold than would oral herpes. As far as we know, however, such a difference has previously never been demonstrated systematically. The difference may, in fact, be of some significance in understanding the role of the immune system in recurring HSV infection. It suggests, for example, that the relationship between the common cold and oral HSV infection recurrence is not mediated by a general depression of the immune system but rather by local immunological or other changes.

No significant findings were obtained for reported exposure to sunshine. This negative outcome was somewhat unexpected in view of the fact that administration of ultraviolet light over a healed recurrent site has been able to trigger infections (27) and the fact that many people suffering from oral herpes believe exposure to sunshine to be a serious risk factor and thus try to avoid such exposure. This fear may be unwarranted or exaggerated.

In contrast to the genital herpes subjects, the subjects suffering from oral herpes did not show any overall reduction in reported emotional well being during the prerecurrence period. On the whole, the mood state appeared as rather unimportant in the recurrence of oral herpes, the sluggish-alert scale being the only mood scale showing a significant time-lag relation to recurrence. One reason for this may be that the influence of the mood on the recurrence tendency was masked to a large extent by effects of the common cold. This may also have been true in the study by Luborsky et al. (15) mentioned in the introduction.

It is not clear why the oral herpes subjects experienced invisible and visible symptoms on the same day, whereas the genital herpes subjects tended to experience the invisible symptoms 1 day before the visible ones.

In contrast to the corresponding data for the genital herpes subjects, neither the mood data nor the sleep time data for the oral herpes subjects supports the skin trigger theory. On the other hand, the results for reported common cold does so.

General conclusions. The results of the present study seem to indicate that reduced emotional well being tends to be associated with triggering events in recurrent herpes, at least in the case of genital herpes. Considering the great similarity between genital and oral herpes, it seems most probable that

this association is not restricted to genital herpes, even though the sluggish-alert dimension was the only mood dimension exhibiting a significant time-lag relation to the recurrence of oral herpes. As already mentioned, the failure to link the recurrence of oral herpes to any other mood dimension may have been because of a masking effect of the common cold. Specifically, the present study suggests that reduced alertness is particularly strongly related to recurrence of herpes.

It cannot be immediately concluded, however, that reduced perceived well being actually caused recurrences. Alternatively, the apparent reduction in perceived well being may have been caused by some associated, unknown triggering factor, such as increased levels of prostaglandins (28).

The hypothesis that certain mood states tend to cause herpes recurrences would be strengthened if the mood states preceding recurrences could be shown to correlate with corresponding external events. A lesson to be learned from the present study is that unstructured diary notes are not very useful for establishing such correlations because of coding difficulties and the risk of obtaining a large number of blanks or no diary notes at all. Nevertheless, the present diary notes were not completely useless but suggested that the mood preceding genital herpes tended to be in agreement with corresponding daily events. The use of a structured daily record form, such as that used by Evans and Edgerton in a study on life events and mood as predictors of the common cold (29), seems thus to be a promising approach for future research.

It should be noted, however, that associations between reported mood states preceding herpes and daily events do not prove the existence of a causal relationship between mood and recurrence of herpes, because mood has a tendency to affect a person's perception of and reactions to daily events rather than being caused by these events and to affect, or even create, the daily events. Ideally, only more dramatic events, such as a divorce or fear of losing one's job, should be considered to disentangle the causal relationship between mood and external events.

Strong support for a causal relationship between mood and recurring herpes would exist if: a) the ganglion trigger theory could be considered true; and b) it could be shown that the start of the prodromal process at the ganglion level tends to be preceded by a marked mood change. As stated above, however, the start of the hypothetical prodromal process cannot yet be determined sufficiently for such purposes. At present, the strongest support for interpreting the findings now discussed in terms of a causal psychosomatic relationship is perhaps the demonstration by Rasmussen and his co-workers (30) of increased susceptibility to HSV in mice subjected to avoidance learning, stress, and restraint.

Let us assume, at least for the sake of discussion, that reduced well being indeed did cause the recurrences. What, then, may have mediated this relationship? As pointed out by several previous authors (10, 31), one possible link between mood and herpes recurrences is the excretion of catecholamines. It is well established that adrenaline has an immunosuppressive effect, probably by stimulating the production of cyclic AMP in various types of cells of the immune system (32, 33). Moreover, adrenaline levels have been directly linked to recurrence of herpes (34). Not only adrenaline but also noradrenaline has been related to herpes infection (35).

Among other types of hormones that might operate as mediators between mental states and recurrences of herpes are corticosteroids and endorphines. Corticosteroids have been shown both to be produced in excess in negative mood states (36–38) and to deplete T lymphocytes (39), which play a major role in destroying virus-infected cells. Recently, endorphins have also been associated with the immune system (40). However, our present knowledge about endorphins as related to mood states and immunological reactions remains rather meager.

In future research, the abovementioned and other possible mediators between mood states and recurring herpes should be investigated systematically. A promising approach would be to extend the present one by correlating daily data on various hypothetical mediators with daily mood and life events during prerecurrence periods. Although such an approach would require much work both by patients and by researchers, it would no doubt be worthwhile.

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