# Stress as a Precipitating Factor in Subjects With Recurrent Herpes Labialis

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The model of recurrent herpes labialis was selected to evaluate the role played by stress in increasing susceptibility to illness. Initially, 35 paid volunteers with recurrent herpes were enrolled in the project. Compared with 35 age- and sex-matched controls, this group demonstrated a familial predisposition for recurrent herpes labialis.

Eighteen subjects without confounding variables known to precipitate recurrent herpes infections completed a pretested "stress" questionnaire during a dormant and again during an active stage of infection. In the week prior to the appearance of a recurrence, this group experienced (1) increased daily hassles, (2) increased stressful life events, and (3) higher state anxiety. These findings are discussed in the broader context of stress-associated disease with some speculations concerning a possible biologic mechanism, which involves modulations of T-lymphocyte function.

The basic conceptualization of Cassel[1] that psychosocial stress not neutralized by effective support is temporally related to the onset of certain medical conditions has done much to broaden contemporary thought concerning the causation of disease. Reasearch studies that support this hypothesis are numerous. Neser[2] demonstrated that fragmentation of the family was associated with increased morbidity from stroke. The study by Medalie et al[3] of 10,000 civil servants documented that the combination of high anxiety and low spouse support was a potent risk factor for the development of angina pectoris. In a study of pregnant women, Nuckolls et al[4] demonstrated that high stress and low support were associated with a high delivery complication rate. Meyer and Haggerty[5] found that acute and chronic stress within the family was associated with increased susceptibility to streptococcal infections. Holmes[6] found that stressful life events preceded the development of tuberculosis. Finally, there are numerous studies suggesting increased morbidity and mortality during bereavement.[7-9] Clayton, however, did not find in her research a correlation be-

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tween bereavement and mortality and questions the validity of some of these studies.[10]

There are also studies suggesting that stress influences the onset and course of certain viral illnesses including the common cold[11,12] and infectious mononucleosis.[13,14] The present study focuses on another viral infection, recurrent oral herpes simplex. It has been estimated that 70 to 80 percent of the population have antibodies to herpes simplex type 1, indicating that the individual has had a primary infection in or around the mouth. About 40 percent of these individuals have recurrent oral infections.[15] The herpes virus lies dormant within the cells of the trigeminal ganglia and under certain circumstances replicates, travels down the peripheral nerve, and produces a vesicular eruption on the vermillion border of the lip.

Research studies attempting to relate psychosocial factors with recurrent oral herpes have often been anecdotal[16] or inclusive.[17,18] This study examines the temporal association between stress and recurrent herpes infections and the possibility of a familial predisposition for recurrent oral herpes as determined by detailed family history.

## Methods

### *Familial Predisposition for Recurrent Herpes Labialis*

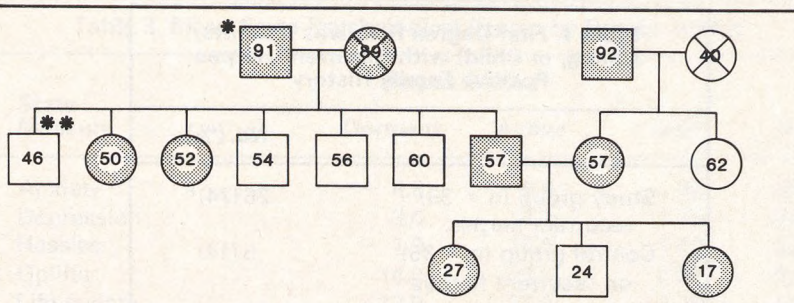
Thirty-five paid volunteers aged between 20 and 43 years with a history of having three to four recurrent episodes of oral herpes per year were interviewed. At this interview a detailed family history was obtained from all herpes subjects to identify first-degree relatives (parent, sibling, or child) with a history of recurrent oral herpes. The data obtained are based on history alone; no attempt was made to verify that lesions really were herpes simplex. However, all of these subjects showed positive antibody titers (complement fixation) to herpes simplex type 1, indicating that the subjects had had an infection with this virus. Thirty-five controls, matched for age and sex, without a history of recurrent herpes labialis were also interviewed.

### *The Role of Stress*

Eighteen of the above-mentioned 35 subjects completed a stress questionnaire at two points in time. (The other 17 subjects reported confounding variables, such as a concomitant febrile illness, sunburn, trauma of menses, and were omitted from the psychosocial part of the analysis.) Time 1 was selected at random, when the subject had no lesion and the herpes virus was inactive. Time 2 was within three days of the first appearance of the vesicular eruption, ie, during an active lesion.

The multifaceted stress questionnaire was developed from components that have been tested and validated in previous research endeavors. The questionnaire was designed to assess the following major areas: stressful life events,[19] global support,[20] daily hassles and uplifts,[21] anxiety and tension,[22] coping ability,[23] personality type,[24] depression,[25] and well-being.[26] The subjects were asked to relate what had been happening and how they had been feeling during the week prior to the appearance of a recurrent infection.

The stressful life events part of the questionnaire was assessed using a 12-item abbreviated scale modified after the list of events employed by the Dohrenwends.[19] This modified version has been used in other studies and found to correlate well with the longer version. The global support scale contained two items and was validated against utilization rates in a family practice center by Blake et al.[20] The separate abbreviated scales measuring daily hassles and uplifts were developed from the scales provided by Kanner et al.[21] Each scale contained 10 items selected by several independent judges as the hassles and uplifts most relevant for the target population. The entire nine-item anxiety and tension scale from the Profile of Mood States (POMS)[22] was the measure selected to detect state anxiety. This measure has been shown in the literature to be sensitive to change. The six-item measure of coping ability was developed for a study of stress and air traffic controllers.[23] This scale was shown to have good psychometric properties, especially internal consistency reliability, in a sample of over 400 air traffic controllers. The six-item measure of type A behavior used in this study was derived from the longer version developed by Jenkins and colleagues.[24] This abbreviated scale was used in the National Health Survey of 1978. The measure of




Sample pedigree of a family in which individuals from three generations have a history of recurrent herpes labialis.

* Shaded individuals have recurrent herpes.

** Age of living individuals or age of death.

Figure 1. Sample pedigree of a family in which individuals from three generations have a history of recurrent herpes labialis.

depression selected for the study was a two-item scale of depression modified from a brief scale (the Ware scale) developed by Brook et al.[25] The Ware scale was used in a large insurance survey, where its reliability and validity were well-documented. The final scale included in the questionnaire was the 10-item scale of well-being developed by Bradburn.[26] This scale has been used in numerous studies, including the National Health Survey, and its reliability and validity have been well-established.

### *Design and Analysis*

To determine whether a familial predisposition exists for recurrent oral herpes, a chi-square statistic for independent groups was used to compare the rate of recurrent herpes among first-degree relatives for the study group and for the controls.

Scores on the stress questionnaire were categorized in two ways. Variables that reflected "trait" measures and those designated as "state" measures were analyzed separately. Each score was tested for significant change between the dormant and active stage by means of a paired *t* test. One-tailed tests of significance were employed because of the predicted directionality of the differences. For psychological scores found to differ significantly, the individual items making up the scale were also examined to insure that the changes noted were due not to isolated outliers but to consistent changes across the scale's items.

## Results

### *Familial Predisposition*

Figure 1 is a sample pedigree showing multiple individuals in each of three generations with recurrent herpes labialis. Further evidence of a familial predisposition is derived from a comparison of the rate of recurrent herpes among first-degree relatives for subjects with and without a history of recurrent herpes. Twenty-six of 35 subjects (74 percent) with a history of recurrent herpes reported that a first-degree relative also had recurrent herpes, whereas only 5 of the 35 individuals (14 percent) in the control group (without a history of recurrent herpes) gave a history of having a first-degree relative with recurrent herpes (Table 1). The highly significant chi-square value ($\chi^2 = 25.5$, $P < .001$) suggests that the large differences observed are unlikely to be due to chance alone. This finding of a familial predisposition for recurrent oral herpes has not been previously described.

| Table 1. First-Degree Relatives (Parents, Sibling, or Child) with Recurrent Herpes Positive Family History | |
|---|---|
| | **No. (%)** |
| Study group (n = 35) recurrent herpes | 26 (74)* |
| Control group (n = 35) no recurrent herpes | 5 (14) |
| *$\chi^2 = 25.5$, $P < .001$, n = 70 | |

**Table 2. Mean Trait Psychological Scores by Herpes Status**

| Trait Measures | Herpes Status: Dormant | Active | *t* test* | P |
|---|---|---|---|---|
| Type A behavior | 90.4 | 91.2 | −0.17 | .43 |
| Global support | 4.4 | 4.4 | .00 | .50 |
| Coping resources | 13.8 | 13.4 | .38 | .35 |
| Spouse support | 23.1 | 23.2 | −0.16 | .43 |
| Coping with stress | 5.8 | 5.6 | .27 | .39 |

*Paired *t* tests, one-tailed (n = 18)

### *Stress*

The major hypothesis to be tested, that of the possible relationship between psychosocial factors and recurrent herpes, emphasized the distinction between state and trait behavioral measures. Trait measures were conceptualized as remaining relatively stable over time, reflecting the subject's typical mode of response. State measures are considered to be more transient and to be influenced more by environmental circumstances. It was hypothesized that trait measures such as coping ability, personality type, and global support would not likely demonstrate a significant change when compared with the dormant vs active stages.

Personality type, coping ability, and measures of support did not differ significantly at the two times during which they were assessed (Table 2). Type A personality, characterized by the traits of hard-driving competitiveness, time urgency, and job involvement, was clearly unchanged at the two stages compared. Also unchanged were two measures of support: a global measure encompassing family, friends, and co-workers, and a measure specifically describing the degree and extent of spouse or significant other support.

The final two trait measures were designed to assess coping ability. One measure assessed the availability of coping resources, while the other, the subject's perceived ability to cope with stressful occurrences. Neither coping measure was found to change significantly between the dormant stage and the week prior to the appearance of a recurrent lesion.

These consistent findings suggest that changes in the background level of support, coping ability, and type A behavior are unlikely candidates for explaining the timing and occurrence of a recurrent herpes lesion.

**Table 3. Mean State Psychological Scores by Herpes Status**

| State Measure | Herpes Status: Dormant | Active | *t* test* | P |
|---|---|---|---|---|
| Anxiety | − 4.8 | 9.6 | −1.99 | .03 |
| Depression | 3.6 | 4.2 | −1.16 | .13 |
| Hassles | − 7.9 | 10.8 | −1.80 | .04 |
| Uplifts | 14.0 | 14.6 | −0.59 | .28 |
| Life events | −10.9 | 17.2 | −2.75 | .01 |
| Profile of mood | | | | |
| States anxiety | − 8.4 | 14.6 | −3.90 | .01 |
| Positive well-being | 3.0 | 3.6 | −1.34 | .09 |
| Negative well-being | 2.0 | 2.2 | −0.52 | .30 |
| Affective balance | 1.0 | 1.4 | −0.55 | .29 |

*Paired *t* test, one-tailed (n = 18)

The more likely candidates hypothesized to be sensitive to change were the state measures. Four psychological state measures that differed between the dormant stage and the week prior to the appearance of a recurrent lesion were (1) an increased level of stressful life events, (2) elevated levels of anxiety as measured by two separate anxiety scales (one a brief global anxiety measure developed by Brook et al[25] and the other an anxiety scale from the Profile of Mood States Inventory), and (3) increased daily hassles and frustrations (Table 3). No significant changes were noted for the measure of depression or for positive affects such as daily uplifts or general feelings of well-being, as measured by Bradburn's scale of well-being.[26] As can be seen from Table 3, the negative and positive affects reported for the Bradburn scale were nearly identical for the two stages examined.

Thus, it appears that despite the presence of positive coping skills, support, and moderate levels of positive reinforcement, the concomitant presence of negative, stress-provoking circumstances continues to be associated with an increased likelihood of recurrent herpes lesions. In addition, increased confidence in the validity of the findings comes from the replicability of the measures used. That two distinct but moderately correlated anxiety measures both exhibited similar associations with changes in herpes states suggests the finding is not measure specific. The consistent pattern of no association for both the trait measures and the positive affective measures also increases confidence in the findings despite the relatively small sample size involved. This finding may be an indication of the robustness of the associations examined or of sample selection bias.

The stressful life events scale and the anxiety scale from the Profile of Mood States (POMS) inventory were then subjected to further item analyses. These analyses were undertaken to (1) identify the major components of the scale that accounted for the association with herpes states, and (2) to insure that the changes were consistent across the items of the scale and not just due to a few isolated outlier items. Table 4 lists the nature of the stressful life events that these subjects experienced in rank order of frequency. Interestingly, the two most prominent types of stressful life events cited by the respondents in the week prior to the onset of the herpes lesion were interpersonal problems and work-related difficulties. Given this pattern and frequency of events, the associations noted for increased hassles and anxiety are consistent with these findings.

The final analysis examined whether the items making up the anxiety scale were consistent discriminators of dormant and active herpes states.

Table 5 lists the individual items from the POMS anxiety scale. This scale is designed to portray the mood state of the individual during the week prior to the development of a recurrent herpetic lesion. As can be seen from Table 5, all nine anxiety items are consistently higher for the active stage. In fact, six of the nine adjectives—tense, on edge, panicky, uneasy, restless, and anxious—were found to have statistically significant differences in this sample. The remaining three items also exhibited strong trends in the predicted direction.

These results, combined with the descriptive life events findings, indicate that the major associations noted are internally consistent, thereby increasing confidence in their potential validity from these data. It appears that negative affects and stressful life events are associated with recurrent herpes despite the concomitant presence of support systems and adequate coping styles. The true test of the validity of these findings, however, can only be assessed through independent replication using a larger sample size.

**Table 4. Stressful Life Events Associated with Recurrent Oral Herpes Simplex in Rank Order of Frequency**

| Major Areas of Stress | Events |
|---|---|
| Relationship problems | Major problem with spouse or significant other |
| | Personal problem with other family members or friends |
| | Termination of close relationship |
| Job | Job Change |
| | Problem with people at work |
| Health | Worry over physical or mental health of anyone |
| Persons moving into or out of house | |
| Financial problems | |
| Residential move | |
| Death of a family member | |

## Discussion

Obtaining histories on familial reported recurrences is not as reliable as firsthand documentation. A systematic detection bias is possible, as herpes patients are more likely than control patients to have discussed cold scores with their family members. Nevertheless, the difference between the study group and the control group may, in fact, reflect a real genetic difference. There is no previous suggestion in the medical literature that there is a familial predisposition for having recurrent oral herpes simplex, and there is no mention of a genetic trait for recurrent herpes in the current editions of standard dermatology textbooks by Fitzpatrick, Pillsbury, or Demis. It is unlikely that this finding represents reinfection through transmission of the infectious agent within the family, as person-to-person transmission occurs only during the primary infection with herpes simplex and is not the etiology of recurrent infections.

There are at least two plausible explanations for these findings. A recent study demonstrated that different, naturally occurring HSV-2 isolates had varying effects on the immune system of healthy controls. This variation suggests that differences among strains may influence whether an individual will develop recurrent infections.[27] On the other hand, one might speculate that this represents a genetic trait controlled by the D-DR region of the short arm of the sixth chromosome that influences the regulation of the cellular immune system.

Although it is generally agreed that psychosocial factors appear to be temporally related to the onset of recurrent herpes labialis, documentation for this assertion is sparse and inconclusive. Many years ago, Rasmussen and co-workers[28] demonstrated increased susceptibility to herpes simplex in mice subjected to avoidance learning, stress, and restraint. Heilig and Hoff[29] and Schneck[30] claim to have induced recurrent herpes simplex by suggestive therapy. In an early study, Katcher et al[17] reported that nursing students with a high "unhappy factor" score on the Clyde Mood

**Table 5. Mean Profile of Mood States Anxiety Scores by Herpes Status**

| Items | Herpes Status | | | |
|---|---|---|---|---|
| | Dormant | Active | *t* test* | P |
| Tense | 1.2 | 2.2 | 3.31 | .01 |
| Shaky | 0.4 | 0.7 | 1.32 | .10 |
| On edge | 0.7 | 1.9 | 3.47 | .01 |
| Panicky | 0.3 | 0.7 | 1.80 | .04 |
| Relaxed | 2.6 | 2.3 | −1.23 | .12 |
| Uneasy | 0.7 | 1.4 | 1.91 | .04 |
| Restless | 0.8 | 1.6 | 2.85 | .01 |
| Nervous | 1.0 | 1.5 | 1.64 | .06 |
| Anxious | 0.8 | 1.9 | 3.82 | .01 |

*Paired *t* test, one-tailed (n = 18)

Scale and a low "social asset" score were at high risk for experiencing recurrent herpes. In a later project, he was not able to demonstrate a correlation between psychosocial factors and the precipitation of a recurrent infection.[18] Recurrent oral herpes is a multifactorial process in which stressful life events and situations seem to be, in certain individuals, a very important factor.

Many of the subjects in this study report that soon (24 to 48 hours) after a disturbing experience they developed a recurrent cold sore. The responses on the stress questionnaire, developed as an instrument to help quantitate psychosocial factors, confirmed that during the week prior to the appearance of the active lesion subjects experienced increasing numbers of stressful life events when compared with the dormant period. In addition, subjects scored highly on the tension-anxiety scale of the Profile of Mood States. This study design might be criticized because of the increased likelihood of retrospective response bias, ie, subjects were asked to recall what happened to them and how they felt one week prior to the appearance of the lesion. Nevertheless, simple memory decay for recall over this brief period of time is likely to be small.

How the psychosocial environment influences the biologic susceptibility to recurrent herpes infections is not fully understood. There is increasing evidence suggesting that psychological factors affect the cellular immune system.[31] Stressors that influence immunity include bereavement,[32,33] sleep deprivation,[34] examination stress,[35,36] and stressful life events.[37] In a subgroup of ten subjects in this study in which immunologic tests were performed, there was a dominance of adherent suppressor cells, which blunted T-lymphocyte blastogenesis, zero to three days after the appearance of a recurrent lesion.[38]

Sheridan et al[39] demonstrated a significant fall in the helper cell–suppressor cell ratio during recurrence of herpes simplex virus type 2. Hersey et al[40] have shown that ultraviolet light reverses helper-to-suppressor cell ratios; a sunburn is a known precipitant of recurrent herpes labialis. Finally, Crary et al[41] report that the administration of epinephrine decreases lymphocyte function in healthy human subjects.

The following attractive but speculative hypothesis is offered: Certain psychosocial experiences are capable of activating the neuroendocrine system. Among other results there is an outpouring of catecholamines from the adrenal medulla. This, in turn, modulates the cellular immune system and allows the dormant herpes virus to replicate, travel down the peripheral nerve, and produce the vesicular eruption. This hypothesis is currently being tested with an independent sample of subjects followed prospectively. The results of the present study will, therefore, be subjected

to replication and the findings correlated with changes in the cellular immune system.

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