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Psychological and Immunological Predictors of Genital Herpes Recurrence

by

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ABSTRACT

Psychological and Immunological Predictors of

Genital Herpes Recurrence

Margaret E. Kemeny

A growing body of evidence indicates that psychological factors influence health status. Immunity is believed to be an important mediator in this relationship, although the immunological pathways linking psychological factors to specific diseases have not been determined. This study is a prospective investigation of psychological and other potential triggers of genital herpes simplex (HSV) recurrence, and immune mediators of these relationships.

Thirty-six patients with chronic recurrent genital HSV were interviewed and filled out questionnaires once a month for six months. Stressful life experience was assessed using the Life Experiences Survey, the Daily Hassles Scale (for chronic stressors), and measures of anticipated stressors, distress over previous life experiences, and the stresses of having genital herpes. Subjects were administered questionnaires to assess their satisfaction with progress on life goals, satisfaction with social support, negative affect (using the POMS), and feelings of defeat. Coping flexibility was assessed by interview. Three non-psychological triggers of HSV episodes were evaluated: fatigue, menses, and symptoms of other infections. Outbreaks of HSV over the six month period were medically documented. At each monthly inter-

view, nineteen of the patients had a blood sample drawn for assay of the proportion of helper-inducer and suppressor-cytotoxic T cells.

Results indicated that: 1) patients who reported more stressful life experience exibited a lower proportion of helper-inducer T cells; 2) patients who reported more depression, hostility, anxiety, or defeat displayed a lower proportion of suppressor-cytotoxic T cells; 3) social support satisfaction and coping flexibility did not have direct or moderating effects on immune measures; 4) only the infection score had a close to significant relationship to HSV recurrence rate; 5) when patients with high infection scores were removed, depressed patients and patients less satisified with their progression on life goals were found to have more HSV episodes; 6) Changes in health behaviors did not account for the relationships above; 7) anxiety predicted when recurrences took place--less anxiety was reported in the months preceding recurrences; 8) the suppressor-cytotoxic proportion was lower prior to and following HSV episodes.

Between subject analyses suggested that depression may create an immunological environment conducive to recurrent episodes of HSV.

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INTRODUCTION

Significance

A growing body of research is providing support for the ancient belief that stress and psychological processes influence health status (Cohen, 1979,1981; Elliott & Eisdorfer,1982; Weiner, 1978). Immune system functioning is believed to be an important mediator in the stress-disease relationship (Ader,1981; Jemmott & Locke, 1984). Animal studies have found that environmental conditions (such as maternal separation) and experimental stressors (e.g., crowding) can in fact depress certain aspects of immune functioning (Borysenko & Borysenko, 1982; Coe, Rosenberg, & Levine, 1984; Riley, 1981; Solomon, 1969). In human studies, experimentally induced stressors (e.g.,sleep deprivation, a simulated battle task), naturally occurring stressors (e.g., examinations, bereavement) and negative psychological states (e.g.,loneliness, power motivation) have been shown to covary with alterations in a wide variety of immune parameters (Jemmott & Locke, 1984; Palmblad, 1981).

The role of immune functioning as a mediator in the relationship between psychological factors and disease remains inferential however. No studies have yet shown that stress-induced immune changes have subsequently increased the probability of disease. These changes may fall within the normal range of immunological variability and therefore fail to alter the host's disease susceptibility (Rogers, Dubey, & Reich, 1979).

Elliott and Eisdorfer (1982) argue that to understand the relationship between stress and disease all of the processes involved in what they diagram as an X-Y-Z model must be studied. X refers to potential activators (i.e., stressors), Y to short-term physiological responses (as in changes in immunological measures or in blood pressure), and Z to long-term health consequences (such as herpes recurrences or coronary heart disease). Many studies show X-Y links (that stress and psychological factors affect short term physiological changes) and other studies show X-Z links (that stress and other psychological factors influence some disease processes). However, what is missing are studies that examine all three of these links simultaneously.

Research Goal

The overall objective of this study was to utilize recurrent genital herpes as a model to study the relationships among stress and psychosocial factors, immunological change and disease outcomes. The study was designed to determine the relationship between psychosocial factors and herpes recurrence in a sample of patients with frequent outbreaks of the disease and to determine whether changes in the proportions of helper and suppressor T cells mediate this relationship.

Recurrent genital herpes simplex virus infection (HSV) is a model system for studying the relationships between psychological processes, changes in immune factors and disease process. Recurrences of HSV do not depend on invasion of the host by infectious agents since the virus, after initial infection, remains present in the carrier at all times. Therefore the explanation for recurrence can be found only in host fac-

tors (except in the case of reinfection). There is, also, wide variability in the rate of recrudescent episodes (i.e., lesion development) both between individuals and within individuals. Some individuals have frequent outbreaks following primary infection while others have no recurrent episodes. Individuals may have long periods of relative quiescence followed by periods of frequent episodes. The factors which explain this variablity and the conditions which provoke genital herpes reactivation and recrudescence are not known, but emotional stress continues to be reported anecdotally and in medical texts (Harrison, 1977) as a causal factor. In addition, host immune status is believed to play a key role in determining the frequency, duration and timing of recurrence.

Recurrent HSV is also an excellent model for investigation because recurrences of the disease are frequent in a substantial proportion of carriers. Since many patients have frequent recurrences and the repetition of the infection does not leave the patient in a progressively deteriorating state of health, the same subject can be studied several times to determine which antecedent conditions are related to the reactivation of the virus and the recurrence of the lesions.

Review of the Literature

This review of the literature will focus on three areas. First, the relationships between stress, stress moderators (e.g., social support, coping), and disease will be reviewed with an emphasis on infectious disease. The review will focus on studies that use objective measures of health outcome rather than self-report measures. (For a comprehen-

sive review of the stress-disease literature see Elliott & Eisdorfer, 1982.) Secondly, the research on the physiological mediators linking psychological processes to disease will be reviewed emphasizing research on stress and immunity. Third, research on psychological and immunological factors which are related to herpes simplex will be described.

Psychological Factors and Disease

Life events and disease. While the relationship of stressful life experience to the etiology and progression of disease has been observed for centuries (see Zegans, 1984), research on this topic began in earnest with the development of the Schedule of Recent Experience by Holmes and Rahe (1967). This measure consists of 42 major life changes (e.g., loss of job, death of spouse, moving) that the subject checks off as having occurred or not during a specified period (often the past six months to one year). Holmes and Rahe (1967) found that the more life changes a person reported the more likely he or she would be to develop an illness of some kind during the upcoming months or years. In one of their classic studies (Holmes, Hawkins, Bowerman, Clarke, & Joffe, 1957) tuberculosis (TB) patients and controls were asked to list the life events that had occurred in their lives over the past 10-14 years. The researchers found that in TB patients the number of major life events gradually increased over time and that about one to two years prior to hospitalization there was an abrupt rise in major life change which was not apparent in the controls. A number of studies have since shown that patients report or experience more major life changes in the six month to one year period prior to the development of

a myocardial infarction (Theorell & Rahe, 1971), sudden cardiac death (Rahe & Lind, 1971), pregnancy complications (Gorsuch & Key, 1974) and illness in general (Holmes & Masuda, 1974).

Other studies have evaluated the relationship between particular stressful events and the etiology of disease. For example, Parkes and Brown (1972) has shown an increased mortality rate six months to one year following the death of a spouse. A number of studies have confirmed this finding (Ekblom, 1963), while others have not (Clayton, 1974). The evidence for a relationship between the loss of a spouse and morbidity is also mixed (Jacobs & Ostfeld, 1977). It is possible that the effects that are found are not due to the stress of the bereavement itself but to other characteristics that differentiate the bereaved individual from one who has not suffered such a loss (Rowland, 1977). For example, the bereaved group may be older and less healthy prior to the loss and therefore more likely to develop illness than the non-bereaved group. Or the bereaved spouse may have shared a harmful environment with the lost spouse which resulted in ill-health for both spouses. Also, the "unfit" may marry the unfit and therefore the coincident morbidity or mortality of both may be more likely when compared to other groups (see Jacobs & Ostfeld, 1977, and Rowland, 1977, for reviews of these methodological issues).

The life change literature has been criticized for a number of reasons (Brown & Harris, 1978; Dohrenwend & Dohrenwend, 1974; Mechanic, 1974; Minter & Kimball, 1978; Rabkin & Struening, 1976). First, the magnitude of the correlation between life change and illness is in general small (correlations are usually less than .30). And most of the

early studies were retrospective and therefore suffered from inaccuracies in the reporting of past events (Jenkins, Hurst, & Rose, 1979) and from the impact of present illness and mood on reports of past events (Bower, 1981). The reaction to serious illness can sometimes also involve a search for a "cause" for the illness and therefore distort perception of recent life experience (Brown & Harris, 1978). Also, some life events can represent presymptomatic indicators of the illness measured as outcome (Cohen, 1981), thus inflating the association between "life events" and illness. Most studies also rely on subjective measures of illness which confound true illness with "illness behavior." Illness behavior involves the way in which people perceive, interpret and respond to their physical symptoms. There is wide variability across individuals in their sensitivity to symptoms, in their tendencies to see their symptoms as serious or not, and in the likelihood that they will seek treatment for their symptoms (Cohen, 1979, 1981; Mechanic, 1974; Minter & Kimball, 1978). Studies that rely exclusively on self-report measures of illness run the risk of confounding their outcome measure with their psychological independent variable. The possibility of this type of confounding is emerging as a contested issue among major stress researchers (see a discussion of this issue between Dohrenwend, Dohrenwend, Dodson, & Shrout, 1984 and Lazarus, DeLongis, Folkman, & Gruen, 1985).

Daily hassles and disease. An alternative method for studying stressful experience has focused on the everyday stresses of daily living, called "daily hassles" (Kanner, Coyne, Schaefer, & Lazarus, 1981; Lazarus & DeLongis, 1983). In contrast to major life change, the Daily

Hassles Scale measures the chronic annoyances and ongoing problems that plague daily life such as traffic noise and financial problems. A number of studies have found a relationship between daily hassles and health and well-being (DeLongis, Coyne, Dakof, Folkman, & Lazarus, 1982; Monroe, 1983; Zarski, 1984). Evidence also suggests that daily hassles are more predictive of self-reported somatic illness than are major life changes (Lazarus & DeLongis, 1983). In a recently completed study, DeLongis (1985) had subjects complete the hassles scale, a mood rating and a health record for four consecutive days during each of five months. She found that hassles scores were significantly higher on the day preceding an illness period than during well periods.

The research on daily hassles and health suffers from the same methodological problems that plague the life event literature including low correlations with illness (only slightly higher than between life events and illness) and reliance on self-report measures of health.

In addition, recent research suggests that there may be more potential for confounding between the Daily Hassles Scale and self-report health and psychological symptom measures than between major life event scales and such measures. Lazarus, DeLongis, Folkman and Gruen (1985) and Dohrenwend and colleagues (Dohrenwend, Dohrenwend, Dodson, & Shrout, 1984; Dohrenwend & Shrout, 1985) have recently engaged in debate on this issue. Both agree that the critical question concerns the extent to which both measures (Daily Hassles and symptom outcome) reflect a third common variable--psychological disorder. Dohrenwend and colleagues (1984) found that psychological professionals rated Hassles items as more likely to be symptoms of psycho-

logical disorder than Holmes & Rahe life event items. In response, Lazarus and colleagues (1985) reanalyzed their data and found that those Hassle Scale items rated to be most confounded did not have a higher correlation with Hopkin's Symptom Checklist symptoms in comparison to the purportedly less confounded items. They reiterate their theoretical position that stress lies not in environmental input but in the person's appraisal of the relationship between input and its demands on the person as well as individual capabilities to deal with these demands. They argue that these factors cannot be studied separately if one uses a relational perspective. In response to Lazarus and colleagues, Dohrenwend and Shrout (1985) reevaluated the Hassles Scale. They suggest that the lack of differential correlations with psychological symptoms between the two categories of Hassles items stems from the fact that an item is not checked unless the subject feels that it has been at least a "somewhat severe" hassle. Thus, all items may reflect psychological disorder. They recommend that events and reactions to events be assessed separately to reduce such confounding problems; this strategy they feel would not jeopardize Lazarus's theoretical position.

Stress and infectious disease. A relationship between psychological factors and infectious processes has been observed for some time. Dubos (1965a, 1965b) believed that an infectious agent alone cannot cause disease; susceptibility or resistance to disease is also a function of host factors including prior exposure and resulting immunity, nutrition, other diseases, genetics, socioeconomic and public health factors as well as psychological factors (see Plaut & Friedman, 1981 and Friedman & Glas-

gow, 1966 for reviews of the relationship between psychological factors and infection).

A number of prospective studies have evaluated the relationship of stressful experience to infectious disease etiology. Hinkle and Plummer (1952) found that telephone company employees who displayed a greater dissatisfaction with life also had a greater number of acute respiratory infections. In a more sophisticated study, Hinkle (1974) interviewed a group of telephone operators once a week for six months and had a physician do viral and bacterial cultures and examine their nose and throat each week. Subjects were asked to keep a daily record of events. Hinkle found that events which involved feelings of sadness were most likely to be followed by an acute respiratory illness. Meyer and Haggerty (1962) studied 16 families for 12 months, recording stressful life events reported, collecting throat cultures and conducting exams every three weeks for streptococus. They found that greater family-related stress occurred during the two week period prior to infection than during the two week post-infection period.

A series of studies have been conducted which expose individuals to an infectious disease-causing agent and evaluate the role of psychosocial factors in differentiating those who develop the infection from those who do not. Jackson, Dowling, Anderson, Riff, Saporta, and Turck (1960) exposed college students to a nasal spray containing either viral material or saline and found that those who developed a cold from the virus were more likely to have the following characteristics: they believed that they would develop a cold, they believed that emotional states influence physical states or they reported more distress

about a problem at the time of the exposure to the virus. In a study of response to innoculation with rhinovirus, Totman and Kiff (1979) found that previous life events did not predict verified cold symptoms while an index of loss of opportunity for involvement in social activities over the past six months did. Also an index of change in social activities predicted viral shedding.

Stress has also been shown to be related to infectious disease progression. Boyce, Jensen, Cassel, Collier, Smith, and Ramey (1977) examined 58 children for respiratory infection five days a week for a year and completed bi-weekly throat cultures for bacteria and viruses. The families were interviewed at the end of the year period for life changes that occurred over the course of the year and for the strength of the family routines. They found that children whose families had more major life changes had more severe respiratory infections during the year with a longer duration, when age, sex and race of the child and family income were held constant. Also, contrary to their prediction, children from families with stronger routines had more severe infections. McClelland, Alexander, and Marks (1982) found that prison inmates who had more stress (aggravations, worries, obstacles) had more severe upper respiratory infections.

Social support and disease. A number of psychological factors other than stress have been shown to be related to disease etiology and progression. A factor that has received considerable recent attention is social support. Social support has been defined by House (1981) as the performance by significant others of various types of helpful functions in the service of socioemotional aid (e.g., demonstrations of love, car-

ing, esteem, empathy), instrumental aid (provision of actions or materials) or informational aid (communication of opinion or fact relevant to the problem at hand). Social support has been conceptualized as a resistance factor which buffers the adverse impact of exposure to stress (Cassel, 1976; Cobb, 1976; Kaplan, Cassel, & Gore, 1977) or as a factor with direct rather than interactive effects on the individual's emotional and physical well-being (Thoits, 1982a). Evidence supports both a direct relationship between social support and health and the buffering effect of social support (see Cohen & Syme, 1985).

A number of studies have evaluated social support in relationship to disease processes. Berkman and Syme (1979) conducted a nine year follow-up study of a stratified sample of 2229 men and 2496 women between the ages of 30 and 69 who lived in Alameda County, California. They evaluated information on four sources of social support in relationship to mortality over the nine year period: 1)marriage, 2)contacts with close friends and relatives, 3)church membership and 4)informal and formal group associations. They found that men and women in each age group who were married had lower mortality rates than those widowed, single, or divorced. This relationship was significant for men only, however. Those reporting fewer contacts with friends and relatives had significantly higher mortality rates than those reporting higher numbers of contacts. Also those belonging to a church or temple had significantly lower mortality rates than those who were not members. And finally, those who belonged to one or more formal or informal groups had lower mortality rates than indviduals who did not belong to such groups. This last finding was significant for women only.

When these support factors were combined into a social network index, the authors found that mortality rate increased as social connectedness decreased. Importantly, these findings were independent of self-reported health status at the time of the survey and high risk health behaviors such as smoking and drinking.

Gore (1978) studied unemployed men and found that those who had emotional support had lower cholesterol and uric acid levels than those without support. Those with arthritis and low social support had increased numbers of swollen joints in comparison to those with social support. Nuckolls, Cassel, and Kaplan (1972) studied the role of life stress and psychosocial assets in the etiology of pregnancy and birth complications. She found that women with a low level of psychosocial assets and high life stress had three times the complications of women with high life stress and high psychosocial assets. Hitchcock (1982) found that gallbladder patients with low social support had poorer recoveries than patients with higher social support. De Aroaujo, van Arsdel, Holmes, and Dudley (1973) studied patients with asthma and found that individuals with high stress and low social support needed more medication to control their symptoms than individuals with high stress and high social support. In the study recently completed by DeLongis (1985), the intraindividual correlation between daily measured hassles and self-reported health scores was highly variable (from -.5 to .9). Some people appeared to be highly reactive to stress, others not at all, and others seemed to be healthier during stressful periods. When she incorporated emotional support into the analysis, she found that individuals who reported low social support at the beginning of the

study were twice as likely to experience health problems when under stress as those who reported high social support.

Drawing conclusions from the social support and health literature is difficult because each study uses a different method for defining and measuring social support. Studies focus on structural factors such as marriage, on support network, on differing dimensions of support (e.g., receiving information, feeling cared about), on what individuals receive from others, and on individual ratings of satisfaction with support. There are few studies which compare various measures of support to one another or compare various measures in their ability to predict health outcomes. Also, there is very little knowledge of the construct validity of these scales. Therefore the question of what is actually being measured with these scales is largely unknown. Also, the majority of studies use self-report measures of health which are potentially confounded with the social support dimensions (see Thoits, 1983). The studies summarized above however primarily depend on verified health outcomes. While they suggest that various forms of social support can have both interactive and direct effects on a variety of health outcomes and on mortality rates, the mechanisms involved are far from understood.

Coping and disease. The way in which an individual copes with a stressful experience has also been shown to be related to a number of disease processes. Coping has been defined in numerous ways including "efforts, both action-oriented and intrapsychic, to manage (that is, master, tolerate, reduce, minimize) environmental and internal demands, and conflicts among them, which tax or exceed a person's resources"

(Cohen & Lazarus, 1979, p. 219). Coping is believed to serve two primary functions: "problem-solving" (dealing directly with the environmental demand) and "emotion-regulating" (modifying the distress resulting from the demand). Five modes of coping have been defined by Cohen and Lazarus (1979,1983) including direct action (concrete acts such as confrontation), inhibition of action (avoiding action such as restraining oneself from yelling at another), intrapsychic (for example, reappraising a situation or defenses such as denial), turning to others for support, and seeking information. The way in which an individual copes can be measured as either a disposition, if the individual is expected to use a particular mode across a variety of different types of situations, or as a process if the intent is to measure what the individual actually does in a particular situation.

The way a person copes has been studied in relation to a number of health outcomes. Aldrich and Mendkoff (1963) found that the way in which elderly individuals responded to being moved influenced the death rate subsequent to the move. Those who responded philosophically showed the lowest death rate, while those who responded with anger showed a somewhat higher death rate. Those who responded with denial or depression or who were psychotic before or after the move had the highest death rate. In a similar study, Janoff-Bulman and Marshall (1982) found that elderly individuals who reported positive well-being in response to their situation had a higher death rate three years later in comparison to those who reported strong negative evaluations of their situation. Both studies suggest that angry or negative responses in the aged may result in a longer life. Other studies have found consis-

tent results (Derogatis, Abeloff, & Melisaratos, 1979; Lieberman & Tobin, 1983).

Studies have been conducted on the relationship between coping and health outcomes in patients with a particular disease. For example, Weisman and Worden (1975) found that patients with terminal cancer who responded to their situation with withdrawal, alienation and depression had shorter survival rates than did those who used their social relationships as a coping strategy. Rogentine, van Kammen and Fox (1979) found that patients with malignant melanoma who believed that little adjustment was necessary to cope with their new diagnosis were more likely to relapse when compared to those who perceived that more adjustment was required.

A number of studies have been conducted looking at a particular dimension of coping--whether or not individuals actively seek out information relevant to their condition or treatment (vigilant coping) or avoid this information. For example, Cohen and Lazarus (1973) evaluated patients' coping strategies prior to hernia, cholecystectomy or thyroid surgery in relationship to their recovery from this elective procedure. They measured avoidance/vigilance by means of a structured interview to assess how the patients handled the anticipation of surgery. They found that patients who were vigilant (sought information about their surgery, possible outcomes,etc.) had a slower and more complicated recovery when compared to patients who were avoidant immediately prior to surgery. These findings were later replicated (Cohen, 1975). Summarizing the studies in this area, Cohen and Lazarus (1983) suggest that active participatory coping strategies are, in gener-

al, associated with more difficulty during a hospital stay, e.g., in the short run, but with better long-term rehabilitation after a serious illness (that is, in the long run). A meta-analysis of 26 studies that have looked at the relationship between avoidant and vigilant coping and health outcomes is consistent with this summary (Mullen & Suls, 1982). Thus, avoidant strategies may be adaptive in situations such as waiting for surgery or when initially adjusting to a severe illness or injury (Cohen & Lazarus, 1979).

Affect and disease. The effects of stressors, moderated by appraisal and coping processes, are believed to result in affective changes which influence physiology and disease outcomes (see Lazarus & Folkman, 1984). Zegans (1984) suggests that "The emotions may serve as the organism's bridge between the meaning (or significance of stressful events) and changes in physiological function." Despite the importance that is placed on the role of affect as the final link in the chain from stress to disease, only a few studies have evaluated the relationship of affect (e.g., mood and emotional states) to health outcomes. Jacobs, Spilken, and Norman (1969) studied two groups of college students, those who had had an upper respiratory infection (URI) in the previous 2 weeks and those who had not had a URI over the past year. They found that the ill group had had more life changes involving role crisis, and also experienced more personal failure, depression, hostility and anxiety than controls. Patients with necrotizing ulcerative ginivitis report more life events in the previous year and evidence more anxiety, emotional disturbance and depressive symptoms than do control subjects matched for age, sex and dental hygiene (Cohen-Cole, Cogen, Stevens,

Kirk, Gaitan, Hain, & Freeman, 1981). Depression as measured on the Minnesota Multiphasic Personality Inventory (MMPI) or by other indicators has been found to be predictive of longer recovery from brucellosis, TB and influenza (Calden, Dupertuis, Hokanson, & Lewis, 1960; Imboden, Canter, Cluff, & Trever, 1959; Imboden, Canter, & Cluff, 1961). Anxiety, on the other hand, has not been consistently related to recovery from illness (see Cohen & Lazarus, 1979). Emotional lability in general has been found to predict length of hospitalization for asthma and tuberculosis (Dirks, Jones, & Kinsman, 1977). Interestingly, patients with asthma were hospitalized more often if they were either high or low on emotional lability than if they had moderate levels of emotional lability. Emotional expressiveness in patients with irreversible diffuse obstructive pulmonary syndrome was associated with increases in respiratory symptoms and physiological decompensation (Dudley, Verhey, Masuda, Martin & Holmes, 1969).

Clearly, the relationship of mood and emotional state to disease outcomes represents an underresearched area. Most studies have evaluated forms of emotional disorders such as depression and anxiety rather than more normal variations in mood or emotional states (see Ekman, 1984, for a discussion of the factors which discriminate emotional pathology from mood, emotion and emotion-related traits). There are few patterns that emerge from the studies in this area, although depression does appear to be related to a variety of outcomes including incidence of URI, ulcerative gingivitis, and recovery from a variety of illnesses. However, the possibility that the disease processes themselves caused depressive affect is an important alternative hypothesis which cannot be ruled out in many of these studies.

Helplessness, hopelessness, and disease. Both feelings of helplessness and hopelessness have been found to be related to health outcomes. Helplessness has been defined as the reaction to stressful circumstances in which the individual feels there is little that can be done to alleviate the problem and that what might be attempted will probably end in failure (Gatchel & Baum, 1983). Hopelessness has been defined as feelings of frustration, despair and futility; the individual may feel responsible for a particular negative situation but feel that nothing can be done to undo the failure (Schmale, 1972). The underlying issue in helplessness is a sense of inability to handle a situation; the issue in hopelessness is a negative future orientation. An interest in these constructs lead Engel and Schmale (Engel & Schmale, 1967; Schmale & Engel, 1967) to the formulation of the giving up-given up complex and the testing of its relationship to health outcomes. They define this complex as a disruption of key relationships, a loss of motivation because no solution to life problems appears available, plus the recall of past experiences in which a similar reaction took place. Schmale (1972) reports evidence in support of the hypothesis that this giving up-given up complex is "permissive" of disease. For example, Schmale and Iker (1971) conducted a study where they were able to predict who would show cancerous changes at the time of cone biopsy for cervical cancer based on "high hopelessness potential" and/or recent feelings of hopelessness. Derogatis, Abeloff and Melisartos (1979) have found that feelings of helplessness and hopelessness were related to decreased survival time in patients with metastatic breast cancer.

All studies that attempt to use psychological factors such as depression and hopelessness as predictors of the results of diagnostic procedures for cancer, for example, suffer from a major alternative hypothesis--that the pre-cancerous individuals are more hopeless because they know, prior to the biopsy results, that they are more likely to have malignant disease based on their family history, subtle messages of risk from their doctor, etc. Also, many cancers have an impact on mood state so that the patients with underlying disease may already be experiencing changes in mood state such as depression. This problem is not solved by studying individuals prospectively because of the long lag time between the onset of a carcinogenic process and the actual manifestation of the disease (see Fox, 1981, for a discussion of these issues).

The phenomenon of "learned helplessness" has been discussed widely in relationship to disease state. Learned helplessness results from repeated exposures to uncontrollable events which condition the individual to expect outcomes to be noncontingent on responses (Seligman, 1975). Learned helplessness paradigms have been found to lead to passivity in dogs (Overmeier & Seligman, 1968), motivational loss, emotional disturbance and cognitive impairment in humans (Rodin & Langer, 1977), changes in skin conductance in humans (Gatchel & Proctor, 1976), and have been associated with the development of ulcers, weight loss and decreases in brain norepinephrine (see Gatchel & Baum, 1983).

Investigators have also evaluated the effects on health of psychological characteristics that can be conceived of as the opposite of helplessness or hopelessness, for example, "coherence" (Antonovsky, 1979)

and "hardiness" (Kobasa, 1979). Antonovsky defines the "sense of coherence" as a global orientation which includes a pervasive feeling of confidence that the environment is predictable and the feeling that there is a high probability that things will work out as well as can reasonably be expected. In other words, the individual feels the opposite of helpless and hopeless in relation to his or her environment. In an initial exploration into the relationship between a number of psychological factors and health, Antonovsky (1979) studied 389 Israelis in seven neighborhood health centers and measured their health as well as their self-esteem, social support, personal resources, and coping strategies. He found that a particular type of coping strategy had the highest correlation with health and seemed to mediate the relationship between other resources and health. These coping items were consistent with the definition of coherence and led to the formulation of the concept of the sense of coherence.

Kobasa (1979, 1982) studied a psychological characteristic she termed "hardiness" which consists of a sense of control over what happens in life, a feeling of meaningfulness and committment to self, a view of change as a challenge and an internal locus of control. She compared two groups of individuals: a group of male executives above the median in the number of major life events experienced over a three year period and below the median in a self-reported measure of illness and a comparable group of executives who were also above the median in exposure to life events but <u>above</u> the median in self-reported illness. She found the high stress/low illness group to have significantly higher scores on her hardiness scales in comparison to the high stress/high

illness group. Subsequent research has found conflicting results (Kobasa, 1982a; Kobasa, Maddi, & Kahn, 1982; Kobasa & Puccetti, 1983).

Greer and Morris (1979) found that a "fighting spirit" and optimism were associated with fewer recurrences of cancer in a prospective study of patients with breast cancer.

Psychological traits and disease. Studies have evaluated various psychological traits or characteristics in relation to disease. For example, Kasl, Evans, and Niederman (1979) studied 1400 cadets entering West Point and classified each as either immune to mononucleosis based on the presence of Epstein Barr Virus (EBV) antibody in the blood stream, or susceptible to mononucleosis. Two thirds of the cadets were found to be immune. There was a greater incidence of mononucleosis among those who seroconverted during training (i.e., developed antibody to EBV) if the cadet reported his father to be an overachiever, or if the cadet's academic performance was poor and he was highly motivated to have a military career. The interaction between motivation and performance also predicted who would seroconvert and how long those who developed mononuceosis stayed in the hospital. Canter, (1972) found that individuals who were more psychologically vulnerable (high emotional distress, hypochondriasis and morale-loss and low ego-strength) had more symptoms of febrile disease after exposure to an aerosal with an infectious agent, and had more hours of fever. In a similar study Canter, Cluff, and Imboden (1972) found that psychological vulnerability predicted hypersensitivity reactions (including physical evidence and reported symptoms) to a variety of viruses. Greenfield, Roessler, and Crosley (1959) found that length of recovery from mono-

nucleosis (defined using immunological test results such as a white blood cell count) was negatively correlated with ego strength and psychological health measured six months after recovery.

In the study described earlier by Totman and Kiff (1979), introverts on the Eysenck Personality Inventory had more cold symptoms and viral shedding than extroverts after exposure to rhinovirsuses. In a further study on this cold unit, Broadbent, Broadbent, Phillpotts, and Wallace (1984) found more virus shedding in response to rhinovirus innoculation in introverts than in extroverts and more nasal secretion after infection with either rhinovirus or influenza virus in subjects with high levels of obsessive symptoms. Also, interestingly, subjects who were housed with others taking a beneficial medication for their symptoms had less secretions than those who were not housed with individuals on a successful medication. Also, in subjects treated with interferon, extroversion interacted with the beneficial effects of the drug. Specifically, there was no main effect for interferon on clinical symptoms; when extroversion was controlled for, however, interferon had a significant effect on symptoms suggesting that controlling for between subject variability in this way revealed the beneficial effects.

A series of studies were conducted on the relationship between inhibited power motivation, power-related stress and upper respiratory infection (URI). Power motivation was defined by using a thought sampling technique called the Exercise of Imagination which involves writing stories in response to pictures. The stories are scored in a standardized way for the desire to have an impact on others through influence, persuasion, helping others or attacking. The need for power is com-

pared to the need for affiliation which is also measured using this thought sampling technique. Activity inhibition is scored from the number of "nots" expressed during the story-telling as a indicator of self-control or restraint. The power motivation measure and the activity inhibition score are used together to measure inhibited power motivation. Power-related stresses include events that block or challenge expression of the need for power.

McClelland, Floor, Davidson, and Saron (1980) found that college students above average in inhibited power motivation and who reported above average numbers of power-related stresses had more severe upper respiratory infections. Jemmott, Borysenko, Borysenko, McClelland, Chapman, Meyer, and Benson, 1982 found that first year dental students above average in inhibited power motivation had more severe and a greater incidence of self-reported URIs subsequent to a high stress period than subsequent to a low stress period. Other students not high on these qualities did not show this difference. McClelland and others (1982) found that state prison inmates above average in power motivation and self-reported power-related stresses reported more URIs. But those higher in inhibited power motivation and power-related stress did not have any more URIs. The authors conjecture that the differences between these findings and the findings on students may be a function of the structure of the inmate's situation. Inmates are required to inhibit many of their activities in prison and, as a result, the prison environment may be more distressing for those who are incapable of this kind of inhibition. Thus, inhibited power motivation may not have the negative effects it does in other groups.

It is very difficult to interpret the body of reseach on inhibited power motivation. It seems that each aspect of this configuration of characteristics can be interpreted in multiple ways. The measure of power motivation involves a number of different processes including the motivation to attack and the motivation to help. The justification for including these different processes under the umbrella of power motivation is unclear. The inference that the number of "nots" expressed during the description of a story is a valid indicator of the process of inhibition also remains untested. The determination that a particular stressful situation is a power-related stress is made by the investigator and not the subject, when in fact the event under question may be viewed by each participant quite differently. The strength of this approach lies in combining a measure of stress with a measure of vulnerability to the particular issues that the stressor may raise (see Gruen, Folkman, & Lazarus, 1985, for a discussion of stress vulnerability). However, much more work on validity and other instrument development issues must be addressed before this particular set of data is interpretable.

Physiological Moderators of the Stress-Disease Relationship

Stress and psychological factors have been linked to a number of physiological systems including the central and autonomic nervous system, the cardiovascular system, the pulmonary system, the endocrine system and the immune system (Elliott & Eisdorfer, 1982). The pathway that is usually hypothesized to link psychological processes to infectious disease outcomes begins with stimulation of the central nervous system,

which leads to changes in hormonal patterns resulting in shifts in the immune system's ability to protect the host from infectious organisms. This review will discuss the relationship of psychological factors to each of these three systems.

Nervous system responses to psychological factors. Psychological factors have been shown to influence both the central nervous system (CNS) and the autonomic nervous system (ANS). A number of neurotransmitters (substances that transmit neuronal signals via synapses) and neuromodulators (substances that act on neuronal communication but not via the synapse) have been shown to be influenced by exposure to stressful conditions, for example. Whole brain norepinephrine is depleted in response to stress in animals, particularly novel stress (Zigmond & Harvey, 1970). A few studies have shown that brain epinephrine is also decreased in response to stress (Saavedra, Kvetnansky, & Kopin, 1979). Serotonin, on the other hand, is elevated in response to stress (Elliott & Eisdorfer, 1982). The endogenous morphine-like peptides called endorphins have also been found to be affected by stress. Changes in brain endorphins parallel changes in pain threshold (Madden, Akil, Patrick, & Barchas, 1977).

The ANS has long been recognized to respond to emotional arousal (Ax, 1953; Cannon, 1926,1932; Schacter & Singer, 1962). There is debate however concerning the extent to which each emotion is accompanied by a distinct pattern of ANS activity. William James (1884) proposed that each emotion had a different ANS pattern. His thinking was supported by the research of Ax (1953) on ANS responses during the experience of fear and anger and by other research (Funkenstein,

1956), although these early studies have been strongly criticized for methodological reasons. Cannon (1926) claimed that all emotions were accompanied by a general undifferentiated arousal. Cannon's thinking was supported by Schacter and Singer (1962) who found that subjects' experience of differentiated emotions was a function of a general physiological arousal and different cognitions. The differing cognitions led to differing emotional interpretations of a generalized arousal. Despite research that contradicts Schacter & Singer's results (Maslach, 1979) their perspective is shared by a majority of psychologists.

Recent evidence however suggests that different emotions may in fact produce different patterns of ANS activity (Ekman et al., 1983). Ekman and colleagues asked subjects to complete two tasks while wired to psychophysiological monitoring equipment. First, they were asked to move their facial muscles in prescribed ways that were consistent with expressions signalling six different emotions. Subjects were not told the nature of the expression they were expected to perform (e.g., they were told to move particular muscles and not told that these would form an expression of sadness). Secondly, subjects were asked to remember and relive a situation that made them feel each of the six different emotions. The researchers found, in contrast to previous research, that skin temperature and heart rate differentiated the emotions. Not only did the positive and negative emotions show different heart rate and skin temperature patterns but different negative emotions (e.g., anger versus disgust) showed distinct autonomic patterns. They explain their ability to find different patterns of ANS activity in response to different emotions on the basis of aspects of their design: they looked at

multiple emotions and multiple measures of ANS; they chose subjects who were not embarrassed by the tasks expected of them (actors and individuals who worked in the Ekman lab and were accustomed to having their faces filmed) under the assumption that previous negative findings may have resulted from the overlay of the ANS effects of embarrassment on top of experimental effects; they insured that blends of emotions did not occur by asking subjects to report their emotional reaction to the instructions and eliminating cases of emotion blends in the emotion re-experience task; and they eliminated cases where the subjects could not make the requested facial display in the facial movement task. This study's findings have recently been replicated.

Endocrine responses to psychological factors. Since Selye and Cannon contributed their pioneering research on the physiological effects of stress, numerous hormonal responses to stressful experience have been discovered in both animals and humans. As early as 1911, Cannon (1926) showed that the catecholamines (hormones secreted by the adrenal medulla) respond to external challenge, coordinating the "fight or flight" response. While these responses and their mobilization are adaptive, Cannon demonstrated that a threshold level for stress exists beyond which physiological homeostatic mechanisms fail and the organism dies.

Selye (1956) found that animals exposed to stressors of all kinds, both physical and psychological, responded with what he termed the "morphological triad" consisting of ulcers in the stomach lining, a shrinking of the thymus gland and a swelling of the adrenal glands. Adrenal swelling was used as an indirect measure of cortisol response

since cortisol could not be quantified directly at that time. This triad occurred in a stage that Selye called the "alarm reaction." If the stress continued the organism would move into the stage of "resistance," and finally into the stage of "exhaustion." These three stages were called the General Adaptation Syndrome. Selye argued that the morphological triad was a "non-specific" physiological response to all types of stress, both physical and psychological.

Mason (1975a,1975b) conducted a series of studies to test an alternative view, that hormones respond differently depending on the characteristics of the stimulus. Mason found that the pituitary-adrenal cortical system was not always stimulated by noxious agents, and that a psychological reaction of emotional arousal seemed a necessary requirement. In a study using heat stress as a stimulus, for example, Mason heated the environment of the animal slowly in order to reduce novelty and extreme or sudden temperature changes. Even when resulting temperatures were comparable to those used in prior stress research, Mason did not find changes in adrenal cortical hormone levels. Thus, he did not find this hormonal response to a great diversity of stimuli, but rather to a single category of stimuli common to many situations--factors which elicit emotional arousal. In contrast to Selye's findings of a specific hormonal response to a variety of types of stimuli, Mason found that hormonal response depended on whether or not the animal was emotionally aroused.

In addition, Mason substantiated that psychological stimuli including novelty, unpredictable events, suspenseful anticipation, involvement and effort caused an increase in plasma and urinary

17-hydroxycorticosteroids (17-OHCS), a metabolite of cortisol, as well as changes in other hormones. His body of research supports the notion that there are multi-hormonal responses to specific types of stimuli which demonstate interdependence (Mason, 1975a, 1975b).

Our understanding of the relationship between psychological factors and hormonal responses is most complete with respect to the adrenal cortical system and related metabolites such as plasma and urinary 17-OHCS (Rose, 1980). In general, subjects tend to show adrenal cortical activation when they are exposed to important changes in their environment including the anticipation of events (Rose, 1980). The following stresses are examples of situations that have been shown to result in increased cortisol excretion: crying in infancy, a stormy post-natal birth, surgery, anticipation of surgery, surgical preparation, admission to the hospital, emotionality in anticipation of exams, exhaustive exercise, anticipation of exhaustive exercise and relocation. While other hormones (e.g., the catecholamines) may respond to positive events, cortisol tends to respond to predominantly negative events (Rose, 1980). Researchers have also found individual differences in cortisol response to stressful situations depending on such factors as level of denial. For example, successful defenses in patients awaiting breast biopsy have been associated with lower levels of 17-OHCS (Katz, Weiner, Gallagher, & Hellman, 1970). Similar findings were reported in a study of soldiers flying combat missions (Bourne, Rose, & Mason, 1967). Thus it is not necessarily the objective nature of the stimuli that determines the cortisol response but the individual's perception of it as threatening or challenging. If an individual can screen him- or

herself from realizing the impact of a potentially stressful event then a cortisol response may not be elicited (Rose,1980). Also, the cortisol response to a stressor does not continue indefinitely. Research has shown that it can undergo rapid extinction upon re-exposure (Rose, 1980).

The second most fully understood hormonal response is that of the catecholamines, epinephrine and norepinephrine, secreted from the adrenal medulla. The catecholamines respond to a variety of stressors in parallel to cortisol but may not extinguish as rapidly on re-exposure. The evidence suggests that the catecholamines may be responding to attention or vigilance which may continue after the "stressful" aspects of a situation have diminished (Rose,1980). The catecholamines can also respond to intensely pleasurable situations (Rose, 1980). It was once thought that epinephrine responded to fear and anxiety and norepinephrine was associated with aggression and anger (Ax, 1953; Funkenstein, 1956). These data have not been confirmed, however, and it is generally recognized that both are secreted in response to a variety of affective states including pleasant states, but that the threshold for norepinephrine release in response to psychological stimuli is higher than for epinephrine (Frankenhauser, 1975). In a series of laboratory studies, Frankenhauser (1971, 1975) found that both epinephrine and norepinephrine rose when subjects performed mental work under mild conditions of external control, or when shocked or when engaged in heavy work. However when subjects were given control of their environment, epinephrine decreased but norepinephrine remained high. This evidence suggests that norepinephrine is elevated in any condition which

demands attention but that epinephrine may not be activated unless other factors are present such as lack of personal control. Recent evidence also suggests that Type As (who are characterized by an underlying hostility) have an increased norepinephrine response to challenges such as puzzle-solving (Friedman, Byers, Diamant, & Rosenman, 1979; Glass, 1977).

Other hormones have also been studied in response to stress. For example, growth hormone responds to stress but does not seem to be as responsive as cortisol (Rose & Hurst, 1975). In other words, it may require a somewhat higher threshold of stimulus intensity. Prolactin also responds to stress (Boyd & Reichlin, 1978). Testosterone diminishes during stress (Kreuz, Rose, & Jennings, 1972) but the response may depend on the nature of the stressful situation. For example, Bernstein, Gordon, Rose, and Peterson (1978) found that following aggressive encounters, victorious monkeys showed a brief rise in testosterone while defeated monkeys showed a prolonged fall. Overall, there is increasing evidence that psychological factors do not act on a single hormone but on groups of hormones in patterns that are orchestrated into hierarchies (Mason, 1968, 1974).

Overview of immunology. This section will begin with an overview of the basic concepts in immunology and measures used to assess immunological change and then discuss psychological factors and immunity. The overall function of the immune system is to protect the host from viral, bacterial and other types of disease-carrying organisms. This system is not localized in any one area of the body as are most other physiological systems (e.g., the cardiovascular system, the nervous

system). Instead it consists of organs throughout the body (e.g., the bone marrow, the thymus gland, the spleen, the lymph nodes) and cells that circulate through the blood and lymph system. These cells and their function can be divided into two groups: those comprising "natural" immunity and those comprising "acquired" immunity. Immunological cells which are capable of interacting with any foreign organism are considered to be part of natural immunity; those that can only interact with organisms that match the chemical structure and binding characteristics of the immunological cell itself are part of acquired immunity. In both cases, immunity is an aggressive reaction which involves destruction of foreign molecules, called "antigens," which are recognized as foreign and therefore different from host cells and tissue (Roitt, 1985).

The two primary components of natural immunity are macrophages and polymorphonuclear leukocytes (PMNs). Both are white blood cells capable of engulfing and phagocytizing (digesting) foreign organisms (such as bacteria and viruses) nonspecifically. They are considered the first line of defense against these organisms because of their ability to bind nonspecifically, thus not requiring time for the expansion of the numbers of specific immune cells. A newly discovered type of natural immunity is the "natural killer cell" which is capable of killing virally infected cells.

The natural immune system is usually not capable of completely holding back the spread of viral or bacterial particles and thus the acquired immune system is required. This system includes two aspects--cellular immunity and humoral immunity. The humoral immune system consists primarily of B lymphocytes--white blood cells which originate in

the bone marrow, and when mature, travel throughout the blood and lymph system. When a B cell comes in contact with a foreign organism for which it is specific, it transforms itself into a "factory" producing a type of protein molecule called antibody. There are five classes of antibody (IgG, IgM, IgA, IgE, IgD) which serve a variety of functions including the neutralization of invaders and the promotion of phagocytosis of foreign particles by macrophages.

The cellular immune system consists primarily of T lymphocytes which are white blood cells that originate in the bone marrow and then migrate to the thymus where they mature and then circulate through the body. T lymphocytes, like B lymphocytes, can interact only with foreign organisms for which they are specifically matched. Once in contact with a "compatible" foreign organism some types of T cells can kill (lyse) the cell while others synthesize and secrete substances called lymphokines which regulate other aspects of the immune response. There are three primary types of T cells. First, cytotoxic T cells can directly kill cells that have been infected with foreign organisms. Second, helper T cells can help B cells to produce antibody and can stimulate precursors of cytotoxic T cells to mature. Third, suppressor T cells suppress the promotion of antibody production and the maturation of cytotoxic cells.

The process from recognition of an antigen to destruction of the foreign organism is somewhat different for cell-mediated and humoral immunity. In cell-mediated immunity, macrophages process the antigen and present it on their surface so that it can be recognized by circulating T-cells that match it. In response to antigen presentation by the

macrophage, T-cells become activated and proliferate, producing cytotoxic T cells specific to the antigen and memory cells which accelerate future responses to the same antigen. Activated T-cells also elaborate lymphokines which attract other cells to engage in the fray. In humoral immunity, macrophages present antigen to matching helper T-cells. These helper cells then activate B cells, causing them to differentiate into cells which produce antibody specific to the antigen. Antibody can then coat the foreign organism rendering the antigen immobilized. Among other activities, antibody can attach to target cells and allow them to be killed by effector cells (antibody-dependent cell-mediated cytotoxicity). While helper cells activate this whole process in response to antigen presentation, suppressor T-cells antagonize helper cells and limit antibody production (see Roitt, 1980; Stites, Stobo, Fundenberg, & Wells, 1984)

Measurement of immunity.. A major goal of clinical immunology is the assessment of the adequacy of immune function as a measure of how well the individual is capable of fighting off infection and disease. To do this the researcher can assay blood samples to assess numbers or functions of cell types. Quantitative assays measure the numbers of the various constituents that are available to fight off an infection (for example, how much antibody is available). Assessments can be made of the total number of white blood cells found in a blood sample (which would include macrophages, PMNs, B cells and all T cell sub-sets). Or more specifically, one could count the total number of lymphocytes, the number of T cells, the number of B cells or the number of T cell subsets (e.g., the number of helper and suppressor T cells) in the sam-

ple. Also the "titer" or amount of a specific type of antibody (for example, IgA) can be quantified.

Alternatively, the functioning of the cells could be assayed. This can be accomplished in a number of ways. For example, a lymphocyte can be exposed to an foreign organism that is capable of stimulating an immune response (the antigen) and the tendency for those cells to transform themselves in response can be determined. For example, lymphocytes can be exposed to a herpes simplex antigen and the degree of transformation (measured by DNA synthesis in the cell) can be quantified. Or the lymphocyte can be exposed to a mitogen (substance that causes DNA synthesis in lymphocytes even without the presence of a specific antigen) and the degree of transformation can be quantified. Commonly used mitogens are Concanavalin A (ConA) and Phytohaemagglutinin (PHA) which stimulate T cells to proliferate and pokeweed which stimulates both T and B cells. also, a cytotoxicity assay can assess how well a particular cell type can kill a virally-infected cell. There are a number of other methods for assessing the functional capability of immunological cells (see Grieco & Meriney, 1983).

Various tests measuring the competence of the immune system are used in studies of the effects of stress on immunity. It is readily apparent that no one test fully measures immune competence or is the "best" measure. Each test has advantages and disadavantages for different research questions and diseases. Many are required for an adequate test of the relationship between stress and immunity.

Immunological responses to psychological factors. The evidence suggesting a link between psychological factors and immunity falls into four

primary categories: 1) anatomical and physiological studies showing that structural and functional links exist between the nervous system and the immune system, and between the nervous system, the endocrine system and the immune system; 2) animal studies that experimentally manipulate stress and evaluate the effect on immunity, 3) human studies that experimentally manipulate stress level or correlate psychological processes with various measures of immunity; and 4) studies showing that the immune system can be experimentally conditioned.

1. Anatomical and Physiological Links

There are a number of physiological pathways through which the experience of stressful events might be capable of acting on immune functioning. The existence of these pathways does not prove that they are in fact functional, i.e., that under stressful conditions these pathways are activated. But their existence does provide a picture of the ways in which stressors may be capable of triggering immune changes.

First, evidence indicates that what happens in the brain is capable of affecting aspects of the immune system directly. In a series of studies, Marvin Stein (1980) has shown that lesions in various parts of the brain, particularly the hypothalamus, result in changes in various aspects of immunity. For example, bilateral anterior hypothalamic lesions protected against lethal anaphylaxis in guinea pigs; anterior lesions diminished delayed hypersensitivity reactions and significantly lowered titers of antibody in response to picrul chloride. In addition, evidence now suggests that the thymus gland is innervated by the brain stem and spinal cord in mice (Bullock & Moore (1981).

The second area of evidence combines data indicating a CNS effect on hormonal secretion with data that hormones influence immune function. There are two primary pathways from the brain to the immune system via the endocrine system. In the first, stressful and other experiences are processed by the cortex and the limbic system relays emotional information to the hypothalamus which regulates homeostasis. Hypothalamic neurosecretory cells are then stimulated to release neuropeptides which travel to the pituitary gland causing release of adrenocorticotropic hormone (ACTH). ACTH causes the release of corticosteroids from the cortex of the adrenal gland. The second pathway links the hypothalamus to activation of the sympathetic nervous system. This activation results in secretions of catecholamines from the adrenal medulla. Both the corticosteroids released from the activation of the first pathway and the catecholamines released from the second have effects on immunity.

Cortisol has profound effects on immunity. Administration of corticosteroids causes a depletion of the precursors to macrophages (Parillo & Fauci, 1979) as well as changes in macrophage function. Steroids can also inhibit antibody synthesis and reduce the production of antibody (Gisler, 1971). Steroids have also been found to result in a general circulating lymphocytopenia (depletion of lymphocytes) which is thought to result from a redistribution of lymphocytes out of the circulation to other places like the bone marrow (Parillo & Fauci, 1979). Endogeneous cortisol levels are correlated with lymphocyte "traffic" (Abo, Kawate, Ito, & Kumagai, 1981; Thompson, McMahon, & Nugents, 1980). In other words, cortisol causes lymphocytes to redistribute out of the circula-

tion where they are needed to kill off invading organisms and into such locations as the bone marrow where they cannot protect the organism from foreign material. Corticosterone has also been found to decrease the tissue mass of the spleen in animals (Riley, 1981). Overall, it seems that steroids have a greater effect on lymphocyte "traffic" thanon function.

The catecholamines have also been found to influence immunity. They can decrease such immunological responses as anaphylaxis and delayed hypersensitivity (Schmutzler & Freundt, 1975). The administration of physiological doses of epinephrine can, in 15 minutes, result in the release of T cell sub-sets at two to four times their normal number. Suppressor T cell numbers are increased and helper T cells are decreased (Crary, Borysenko, Sutherland, Kutz, Borysenko, & Benson, 1983).

Other hormones influence immunity as well. Growth hormone has been shown to reverse steroid-caused immune suppression (Gisler, 1974). Testosterone can also suppress immunity (Wyle & Kent, 1977). Estrogen has been shown to cause thymic involution and other immunological effects (Ahlqvist, 1981).

Neuropeptides, hormones and neurotransmitters appear to be capable of influencing cells of the immune system because there are receptor sites on lymphoid cells which have been shown to be responsive to these substances. For example, lymphocytes appear to have receptors for neuropeptides like B-endorphin and the enkephalins and for hormones including the glucocorticoids, the catecholamines, and growth hormone (see Locke & Hornig-Rohan, 1983). In addition, lymphocytes

have been shown to have adrenergic and cholinergic receptors (Bourne, Lichenstein, Melmon, Henney, Weinstein, & Shearer, 1974; Pochet, Delespesse, Gausset, & Collet, 1979). More recently, Blalock (1984, 1985) has presented a body of evidence suggesting that the central nervous system and the immune system may be capable of communicating because CNS factors such as neurotransmitters and immune factors such as lymphokines share similar characteristics, each system can respond to the factors produced by the other, and the cells in each system have receptor sites for the substances produced by the other system.

2. Animal Studies on Stress and Immunity

A number of animal studies, beginning with the pioneering work of Solomon and Amkraut in the 1960's (Solomon, 1969), have been conducted which expose animals (predominantly mice and rats) to experimental stressors and determine whether or not their immunological responses differ from control animals who are not exposed to a stressor (see Riley, 1981, and Borysenko & Borysenko, 1982, for reviews). The stressors include overcrowding, chronic loud noise, acceleration, ether anesthesia, restraint, shock, confinement and others. These stressors have been found to cause a number of immunological changes including involution of the thymus, diminished lymphocyte response to mitogen, decreased lymphocyte cytotoxity, reduced numbers of suppressor T cells, decreased antibody response, etc.

A number of conclusions can be drawn from the animal stress studies. Both major and minor stressors of various types influence a wide range of immunological outcomes. The timing of administration of both stressor and immunological challenge is crucial, however. For ex-

ample, acute stress may suppress immune competence while chronic stress may enhance it. Stress may cause immediate impairment of immune function but this change may be followed by recovery and then by immunological "overshooting" which results in immune enhancement. For example, Monjan and Collector (1977) found that a chronic auditory stress in mice caused a 50% decrease in lymphocyte cytotoxicity and response to mitogen during the first two weeks of exposure to the stimuli. Two weeks later these levels were increased above the levels at baseline.

Recent evidence suggests that different shock paradigms may have different immunological effects mediated by different pathways. In a series of studies (see Shavit, Terman, Martin, Lewis, Liebeskind, & Gale, 1985 for a review) rats were exposed to footshock stress of a prolonged, intermittent nature or a brief continuous nature with the same overall amount of stress exposure. Intermittent stress resulted in analgesia apparently mediated by endogenous opioids and decreases in natural killer (NK) cell activity. Brief and continuous stress resulted in analgesia that was not mediated by opioids and did not result in decreased NK cell activity.

The effect on immune function or immunologically-related disease also seems to depend on the relationship between the timing of stress onset and of the viral or other challenge to the immune system. For example, if stress is applied prior to or immediately subsequent to immunization with an antigen, it can be immunosuppressive but if stress is applied several days after immunization it is not immuno-suppressive (Solomon, 1974). These findings help to explain early contradictory

data showing that stress and stress-related hormones inhibited tumor growth. For example, if steroids are injected seven days after implantation of a tumor then the steroid administration promotes tumor growth. However, steroid injection seven days before implantation retards growth. These findings may result from an initial immune suppression which then rebounds and overshoots resulting in immune enhancement and the retardation of tumors (Monjan & Collector, 1977).

A few animal studies have examined factors other than stress in relationship to immune functioning or immunologically-related diseases. For example, Sklar and Anisman (1979) found that whether or not mice had control over the stressor they were exposed to determined how they responded to injected cancer cells. Mice who could escape electric shock had slower growing tumors than mice who were exposed to the same amount of stress but were "yoked" to other mice so they could not determine their own response to the stress. Those who had control and a third group of mice who experienced no shock had similar rates of tumor growth. Laudenslager and Ryan (1983) used such a paradigm to directly study control in relationship to immunity. They found PHA and ConA stimulation of lymphocytes was suppressed in rats exposed to inescapable, uncontrollable electric shock but not in rats who received the same shock but could terminate it.

Some studies have looked at the relationship between in spontaneous behavior in response to stress and immunologically-related phenomena. For example, Amkraut and Solomon (1972) found that female BALB/C mice developed smaller murine virus sarcomas if they spontaneously showed fighting behavior in comparison to nonfighting female mice.

Coe, Rosenberg and Levine (1984) developed a model for evaluating the buffering effects of social support on stress-induced immune changes. They separated infant squirrel monkeys from their mothers and placed them in cages alone. This separation led to a protest reaction and agitation as well as immunological and hormonal changes. If the infant monkeys were placed with other juvenile monkeys immediately following the separation then smaller immunological changes resulted and they returned to baseline faster. Studies of the effect on immunity of maternal and peer separation in monkeys have also been conducted by Laudenslager, Reite and Harbeck (1982) and by Reite, Harbeck and Hoffman (1981).

There are a number of methodological problems that plague these animal studies and reduce their generalizability to human responses to stress. Recently, Riley concluded that the normal animal housing environments in laboratories were themselves extremely stressful (e.g., constant loud noise, blood drawing), causing immunological changes without further stressors added (Riley, 1981). Because of these inadequate baseline conditions it is difficult to determine the effect of stressors over and above the background level that exists. Riley developed a set of standards for animal stress studies to reduce background stress levels and found that corticosterone levels were 10 to 20 times lower in the protected facilities than in the regular housing facilities. He also advocated the use of mild stressors such as rotation which do not have physical as well as "psychological" effects. He advocates this type of stress experiment because the stressor can also be controlled and reproduced and variations can result in graded levels of change in cortisol and immune function.

Other methodological problems in animal stress research include the fact that much of the stress research is conducted on corticosteroid-sensitive animals like the mouse and rat. Steroids easily produce lymphoid depletion in these animals. Humans are, however, steroid-resistant and therefore the results may not be generalizable (Parillo & Fauci, 1979). Also, the types of stressors used in animal studies have little relevance to the types of stressors humans normally experience; for example, the animal stressors are usually physical and quite severe (see research on maternal and peer separation above for exceptions). And, rodent strains have been bred to develop special characteristics while humans are highly outbred; this difference complicates generalizability since genetics play a major role in disease production and immune function.

3. Human Studies in Stress and Immunity

There have been approximately 30 studies that have evaluated the relationship of psychological factors and stress to immune functioning in humans. Their methodologies involve either experimentally inducing a stressful situation or evaluating the effects of naturally occurring stressors.

Three studies investigated the effects of an experimentally induced stressful situation on subsequent immunological impairment. Palmblad, Cantell, Strander, Froberg, Karlsson, Levi, Gronstrom, and Unger (1976) exposed eight females to a 77 hour vigil involving the performance of a simulated battle task (firing rifles, battle noise) and found that the subjects had a heightened lymphocyte ability to produce interferon in response to Sendai virus during vigil exposure and afterwards.

Phagocytosis was reduced but returned to a level higher than baseline after the stress exposure. Palmblad, Blomback, Egberg, Froberg, Karlsson, and Levi (1977) later conducted a study of 16 females exposed to the 77 hour vigil and found that blood coagulation factors and fibrinogen decreased significantly during the vigil as compared to baseline levels and levels after the vigil. The coagulation factors did not return to normal after five days while the fibrinogen did. In a further study, Palmblad, Bjorn, Wasserman, and Akerstedt (1979) assessed the influence of 48 hours of sleep deprivation in addition to a number of vigilance tasks on in vitro DNA synthesis of blood lymphocytes and on granulocyte adhesiveness in 12 young males. After sleep deprivation, all subjects showed marked reduction of DNA synthesis after stimulation with PHA. This level returned to baseline after 5 days. Changes were not found in other immunological measures. In all three studies immunological changes were accompanied by changes in catecholamine and cortisol levels.

All three of Palmblad's studies involve a combination of physical and psychological stressors, resulting in interpretation problems similar to those found in the animal studies in this area. All subjects not only participated in psychologically stressful tasks, but were kept awake, disrupting their sleep cycle, and were exposed to disruptions in normal eating patterns and patterns of social interaction, etc. It is impossible to determine which aspect of the study produced the immunological changes.

Three studies have assessed the effects of a particular set of stressful experiences (spaceflight and splashdown) on immunity. In a

study of the Apollo spaceflight, Fischer, Daniels, Levin, Kimzey, Cobb, and Ritzman (1972) found higher lymphocyte counts following splashdown compared to pre-flight levels. But lymphocyte response to PHA was unchanged. Kimzey, Johnson, Ritzman, and Mengel (1976) studied Skylab 3 astronauts before flight, during flight and postflight and evaluated blood and immunological functions. They found only subtle changes, and even the most significant change, a reduction in circulating red blood cells, did not have a negative effect on the astronauts' cardiovascular or exercise responses. Kimzey (1975) also studied the effects of splashdown. He found that there was a higher white blood cell count at recovery from splashdown in comparison to to pre-flight levels; in contrast, T cell response to PHA was normal just prior to flight and during flight and decreased 1-2 hours after splashdown to return to normal three days later. As with the Palmblad studies it is unclear whether the immunological changes resulted from the physical effects of spaceflight and splashdown or the psychological effects or both. For example, recent research on Spacelab 1 suggests that decreased stimulation of lymphocytes by PHA in astronauts after spaceflight may be due to the effects of weightlessness (Cogli & Tschopp, 1985).

Two studies have evaluated the effects of bereavement on immunity. In a classic study, Bartrop, Lockhurst, Lazarus, Kiloh, and Penny (1977) studied 26 bereaved spouses 1-3 weeks after bereavement and again 6 weeks after the initial assessment. The spouses died of injury (following a train wreck) or illness. Lymphocyte response to ConA and PHA were significantly reduced at six weeks though not at two weeks

when compared to hospital staff controls matched for age, sex and race. There were no differences in T and B cell numbers, autoantibodies, or delayed hypersensitivity or in cortisol, prolactin, growth hormone or thyroid hormones between bereaved and controls. In a similar study Schleifer, Keller, Camerino, Thornton, and Stein (1983) compared individuals one month prior to bereavement with the same individuals 5-7 weeks after bereavement. Subjects were men whose wives had terminal breast cancer. They found a post-bereavement reduction in T cell response to PHA and ConA and a reduced B cell response to pokeweed mitogen. They did not find differences in white blood cell count, lymphocyte count, or T and B cell count. The reductions returned to pre-bereavement levels for most but not all men within one year.

Both studies suffer from similar methodological problems. First, they had no measures of the extent of stressfulness of the bereavement for each subject. The actual death of a spouse could be extremely stressful for some and a major relief from a protracted stressful period for others. Small effects may be found because of individual differences in perception of the stressful experience, with only those perceiving the event as stressful displaying immunological changes. Also, it is unclear if the changes found resulted from the stress of the bereavement or the potentially dramatic change in life style and health habits that is coincident with bereavement, for example, difficulty sleeping, eating poorly, drinking more, etc. Also, as pointed out by Jemmott and Locke (1984), these studies are conservative tests of the relationship between acute stress and immunological change since subjects were also suffering throughout the period from the chronic stresses of a dy-

ing spouse (except in the Bartrop and colleagues' subjects whose spouses died in a train wreck). These studies do however point to differences in immunological changes over time in response to stress, i.e., that stress-induced immunological changes may not occur immediately following a major stress but only after a particular time period has passed. These changes over time may result from the changing psychological response of the subject (for example, from denial to experiencing the loss) or from a physiological process that takes some time to be initiated.

In a series of studies Kiecolt-Glaser and colleagues have studied immunological responses to medical student examination stress. The basic model involves an immunological assessment of medical students one month prior to final exams, immediately prior to the exams and, in some studies, during the first week back from summer vacation. In one study (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985) they examined B lymphocyte response to the Epstein Barr virus in students seropositive for EBV. They found these responses elevated on the first day of exams compared with the other periods. These immunological changes paralleled changes in psychiatric symptoms. They also evaluated the interactive effects of loneliness as measured at the beginning of the study and found that the lymphocyte response during the low stress period was lower for the lonely students but there were no differences during the high stress period. In another study, Kiecolt-Glaser, Garner, Speicher, Penn, Holliday, and Glaser (1984) studied natural killer cell activity (NKCA), plasma IgA, IgG, IgM and salivary IgA using the above design. They found that NKCA declined from the

pre-exam to the exam period. Those with high stress scores (measured using the Holmes and Rahe Schedule of Recent Experience) and high loneliness scores had significantly decreased NKCA. Plasma IgA increased from the first to second time period while the other antibody measures did not change. They mention that IgA has a much shorter half-life than IgG and IgM so this antibody may be the best candidate to be most reactive to stress. In a similar study (Glaser et al, 1985), NK cell lysis, percentages of NK cells and production of interferon by mitogen-stimulated lymphocytes were decreased during the examination period.

These researchers (Kiecolt-Glaser, Glaser, Strain, Stout, Tarr, Holliday, & Speicher, 1985) also tested for possible stress-ameliorating effects using a relaxation intervention. They again studied medical student exam stress and found a decreased proportion of helper T cells and a decreased helper/suppressor T cell ratio in students immediately prior to exams. Using three nutritional assays, they were able to determine that these stress effects were not mediated by changes in nutritional status. They then randomly assigned students to either a relaxation group or a control intervention and found that the frequency of performing the relaxation exercises was correlated with increased helper T cells.

Kiecolt-Glaser, Glaser, Williger, Stout, Messick, Sheppard, Ricker, Romisher, Briner, Bonnell, and Donnenberg (1985) have also evaluated the effect of stress on the immune systems of the elderly. Subjects were from 60 to 88 years old, residing in an independent living facility and had no identifiable medical or immunological problem. Subjects were

assigned to either relaxation training three times a week for a month, a social contact control group for the same time period or no contact following the initial interview. Immunological assessments were made at baseline, at the end of the intervention period and one month following the intervention. They found that the relaxation group had a significantly enhanced level of natural killer cell activity and lowered herpes simplex-1 antibody levels which were mostly maintained at the follow-up assay. The other subjects did not show reliable changes in these measures of immunity. The researchers did not find changes in response to pokeweed mitogen or to PHA. It is unclear if subjects were monitored for changes in medication levels which may have changed as a result of the intervention and may have caused the immunological changes.

The set of studies by Kiecolt-Glaser and colleagues, despite some methodological problems, represents the strongest evidence to date for a relationship between stressful experience and immunity, particularly given the intervention effects found.

Dorian, Keystone, Garfinkel, and Brown (1982) also studied academic stress but in psychiatry residents undergoing oral fellowship exams. The residents' immune responses were studied two weeks prior to exams and two weeks after the exams and compared to psychiatrists and residents not taking the exam who were matched for age and sex. The exam group had higher B, T and white blood cell counts and lower lymphocyte response to mitogens ConA and PHA and lower plaque forming cell responses in the two week period prior to the exam period as compared to controls. After the exam the only difference between the groups was a higher lymphocyte response to PHA in the exam group.

However, cortisol levels were lower in the stress group in comparison to the control group before and after the exams.

Jemmott and colleagues have conducted a number of studies on academic pressure and lymphocyte response. In one study (Jemmott, Borysenko, Borysenko, McClelland, Chapman, Meyer, & Benson, 1983), the authors studied salivary secretion of IgA during high stress versus low stress periods of the school year. They found IgA secretion to be lower during the high stress than low stress periods. They also found that the subjects' own ratings of the stressfulness of the program at each time point was correlated with the immunological measure.

A number of studies have focused on the relationship between immunity and major life changes in general rather than a specific event. For example, Greene, Betts, Ochitill, Iker, and Douglas (1978) studied life change, mood and immunological changes in 33 subjects innoculated with the A/Victoria/75H3N2 virus. The more life change the subjects reported over the past year the lower their lymphocyte cytotoxicity. They also found a marginally significant relationship between life change and lymphocyte response to mitogen. In addition, they found that subjects who were higher in life change and also higher on the Profile of Mood States (POMS) vigor scale had lower lymphocyte cytotoxicity and hemagglutination-inhibition antibody titer. In a similar study, Locke and Heisel (1977) asked 124 subjects undergoing swine flu immunization to report on life change over the past month and year and mood state using the POMS. They found no relationship between these variables and antibody response two weeks after immunization. A similar lack of findings was reported by Locke, Hurst, Heissel, Kraus, & Williams,

1979) between life change stress over the past month and year and serum antibody titers two weeks after swine flu immunization. However they did find that the life change stress experienced during the two week period from immunization to assay was related to antibody response, with the moderately stressed individuals having a significantly greater antibody response than those experiencing either low or high life change stress.

In another study of antibody reponse to a viral immunization, Roessler, Cate, Lester, and Couch (1979) studied individuals who received immunization from the A/USSR/92/77 virus, and were then given the same immunization again a month later along with two other immunizations. Blood samples were drawn at each time period as well as three weeks following the second batch of immunizations. Then four months later subjects filled out a life change questionnaire for the past year. Life change stress was not related to antibody titer for any of the viruses. However the authors found that life change stress was negatively correlated with the "strength" of the antibody response to one of the viruses (B/Hong Kong).

In sum, measures of recent life change (over the past few weeks) seemed more highly correlated with antibody titer than life changes that took place some time ago. Jemmott and Locke (1984) suggest that antibody titer may be more affected by recent stresses than by past or accumulated stresses.

A number of studies have attempted to look at psychological factors other than stressful life experience, such as loneliness, coping, power motivation, psychiatric symptoms, and psychological vulnerability

either alone or as they interact with stressful experience in predicting immunological changes. McClelland and his colleagues have conducted several studies on inhibited power motivation and immune competence. McClelland and others (1978) found that subjects who display a high need for power and who are exposed to a lot of power-related stressors have a lower white blood cell count and a lower natural killer cell response than subjects who do not have these experiences. In a similar study (McClelland, Floor, Davidson, & Saron, 1980), they found that subjects high in inhibited power motivation who also reported themselves to be exposed to more power-related stressors had lower levels of secretory IgA. These subjects also experienced more upper respiratory infections. In a study of prison inmates, McClelland, Alexander, and Marks (1982) found that prisoners high in power motivation, who reported power-related stresses and were low in activity inhibition had lower secretory IgA levels. In a study of the same psychological variables, Jemmott, Borysenko, Borysenko, McClelland, Chapman, Meyer, and Benson (1983) studied academic stress in dental students. They evaluated a series of exam periods (high stress) and non-exam periods (low stress). They found that IgA secretion decreased from the first low stress period to the high stress period and then returned to baseline at the final low stress period. But for subjects high in inhibited power motivation, IgA did not return to baseline at the final low stress period but continued to decline. There is certainly some consistency in this body of research, however as mentioned previously, it is unclear what psychological dimensions are being assessed by the measure of inhibited power motivation.

Locke, Kraus, Leserman, Hurst, Heisel, & Williams (1984) studied 114 undergraduates and the relationship of life change stress and psychiatric symptoms to natural killer cell activity. They found that students reporting large numbers of life changes over the past year but reporting few psychiatric symptoms displayed significantly more natural killer cell activity than students exposed to a similar degree of stress but reporting more symptoms. They contend that the high stress, low symptom group was displaying "good coping" and that the high stress, high symptom group was displaying poor coping because the stress resulted in psychiatric complaints. The researchers also measured life changes over the past month which did not correlate with natural killer cell activity. There are multiple problems with this study including the fact that they measured life change one week, the blood assay was completed two weeks later, and symptoms were assessed at both time points. They then used the life change score two weeks prior to the assay with no measurement of the stresses that took place during the interim period. NKCA is a quite variable assay (responding to walking up a flight of stairs, Targan, Britvan, & Dorey, 1981) so this discrepancy could be a problem. Also they found that symptoms two weeks prior to the assay were more strongly related to NKCA than symptoms measured at the time of the assay. Given the wide variability in the assay, this suggests the correlation may be spurious or that they are measuring the effects of other factors. Also the inference of coping styles from the tendency to report psychiatric symptoms is unjustified. Instead, the high stress, low symptom students could be deniers or repressors or could represent other types of patients. An alternative

hypothesis might be that deniers under stress have diminished NKCA which rebounds two weeks later to display enhanced activity.

A few studies have evaluated depression in relationship to immunity. Schleiffer, Keller and Meyerson (1984) found depressed PHA, ConA and Pokeweed mitogen (PWM) response and fewer T and B cells in patients with major depressive disorder when compared to age and sex matched healthy controls. Percentages of T and B cells did not differ between the groups. In a follow-up study, these researchers ambulatory patients with major depressive disorders. They found no difference in these patients and controls in response to mitogens. Suspecting that their earlier findings with hospitalized patients may have resulted from the effects of hospitalization rather than depression, they also compared hospitalized schizophrenics with controls and found no differences in mitogen responses. In addition, they found no immunological differences between patients hospitalized for elective herniorrhaphy and controls. They conclude that their findings relating mitogen response to major depressive disorder in hospitalized patients was probably a function of the severity of the depression and not the result of hospitalization (see Stein, Keller and Schleiffer, 1985, for a review of this and other research on depression, endocrine function and immunity).

Van Dyke (1985) studied fourteen patients with major depressive disorders and nine patients with Cushing's Disease (a disease involving elevated cortisol levels). They found that depressed patients had lower NK cell activity levels when compared to normal matched controls. No differences were found in ConA, PHA, and PWM responses. Depressed patients also had increased cortisol levels. Cushing's patients had low-

er NK cell activity levels when compared to controls. In addition, this group of researchers studied 15 women who had lost their husbands and eight matched controls. The bereaved were more depressed and increased levels of depression were correlated with decreased levels of NK cell activity although the correlation was not significant. They found no relationship between bereavement or depression and mitogen response.

Cappel, Gregoire, Thiry, & Sprecher (1978) found a decreased PHA response in psychotically depressed patients during the acute phase of their depression when compared to remission. However they found that these decreased levels did not differ from those of controls, so the findings are difficult to interpret. Kronfol, Silva, Greden, Dembinski, Gardner, & Carroll (1983) found melancholic psychiatric patients to have lower PHA and PWM responses in comparison to controls and an unmatched group of psychiatric patients who were not melancholic. No studies have evaluated fluctuations in affect and immunity in a normal population, however.

A few studies have focused on a patient population and immunological changes that may be correlated with disease state. For example, Pettingale and colleagues (Pettingale, Greet, & Tee, 1977; Pettingale, Merrett, & Tee, 1977) studied 160 women prior to breast biopsy and found that changes in emotional state correlated with changes in IgA level. Patients with increased levels of IgA prior to mastectomy had a slightly (but significantly) improved prognosis one year after the biopsy, based on a clinical rating.

Levy, Herberman, Maluish, Schlien, & Lippman (1985) conducted a study of patients with stage I or II breast cancer five to seven days

following either mastectomy or lumpectomy. They found that patients who showed a high level of natural killer cell activity (NKCA) had fewer lymph nodes positive for cancer than patients in the low NKCA group. Also, observer-rated adjustment, social support and fatigue (measured with the POMS fatigue scale) together predicted NKCA. The authors suggest that their findings may support their hypothesis that resignation could lead to decreases in NKCA and that this immune change could lead to a poorer prognosis (based on lymph node results). Since the low NKCA group had almost no positive nodes and the high NKCA group had an average of about three positive nodes, a more parsinomious interpretation of the data would be that patients with metastases have lower NKCA as a result of the tumor load and are also more fatigued as a result of their cancer in comparison to women with no metastases post surgery. While the fact that women rated as more adjusted had less NKCA is an interesting finding, they found no relationship between adjustment and nodal status.

In summary of the human studies in the area of psychological factors and immunity, it appears that both stresses of daily living (exams) and major life changes (death of a spouse) are correlated with immune changes. However recent stressors appear to be more likely to be related to immune changes than life changes measured over a period of time. Most of these data are correlational; however the fact that the immune measures that appear to be responsive to stress (e.g., NKCA, HSV-1 antibody titer) can also be changed through interventions such as relaxation lend weight to the correlational data. An ambiguity is added to the data, however, considering that many of the relationships

found between stress and immunity may be confounded with either physical stress (e.g., the battle task, splashdown) or possible stress-induced changes in health behavior (e.g., during bereavement or the examination periods).

The role played by psychological moderators of the stress and immune change relationship is largely unexplored except that loneliness appears to compound stress effects, a finding consistent with the social support literature. While a number of studies have evaluated the relationship of inhibited power motivation to immunity, it is not yet clear what this combination of variables measures.

To summarize the immune measures most responsive to stress, it seems that both NKCA and IgA are responsive to minor variations in stress level. Lymphocyte response to mitogen sometimes responds to major stressors such as bereavement and sometimes does not. Also quantitative counts of major cell types (e,g., T and B cells) have a variable relationship to stressful experience. T cell subsets have been found to be responsive to stress, so it is possible that counts which combine many different cell types (e.g., a lymphocyte count) obscure differential effects of stress on sub-types, for example, helper versus suppressor T cells. There are no clearcut pathways that link stress to immunity. Some studies that have found stress effects on immunity have not found accompanying changes in cortisol and catecholamines while others have. Clearly, changes in these hormones are not the only pathway linking psychological factors and immunity.

4. Studies Demonstrating Conditioning Effects on Immunity

Ader and Cohen (1981) have conducted a series of studies demonstrating behaviorally conditioned immune suppression in mice. In their paradigm, saccharin (the conditioned stimulus) is paired with cyclophosphamide (the unconditioned stimulus), a substance which produces gastrointestinal distress and immune suppression. After pairing, subsequent exposure to saccharin causes a decrease in antibody titer to sheep red blood cells. These findings have been replicated by Rogers, Reich, Strom (1976) and by Wayner, Flannery, and Singer, (1978). Ader has shown that the conditioning effect is not due to a change in steroid levels (Ader, 1981). He has also demonstrated that the conditioned immune suppression is clinically significant (Ader & Cohen, 1982). Specifically, Ader and Cohen conditioned immune suppression in NZB x NZW mice and found that these immune changes retarded age-dependent onset of systemic lupus erythematosus (both progression and survival). This research suggests that delayed onset of autoimmune disease may be possible through immunological conditioning (see Ader & Cohen, 1985, for a review of the conditioning research).

Smith and McDaniel (1983) have generalized the conditioning paradigm to humans and demonstrated that a delayed hypersensitivity response to the tuberculosis skin test can be conditioned to be diminished by providing the expectation that the subjects will not have the response.

The conditioning data provide an interesting and important addition to the stress-immunity literature. The conditioning paradigm is not equivalent to the stress paradigm. The majority of the stress research rests on the theoretical position enunciated by Lazarus (1966). Lazarus

argues that stressors have an impact on physiology only if the environmental stimulus is perceived and then appraised as threatening. This threat appraisal results in an emotional response which leads to physiological changes. For a conditioned immune effect to occur the stimulus must only be perceived; it does not have to be appraised as positive or negative in any way. In other words, conditioning occurs as a direct link from the sensory perception of the stimulus to physiological changes which result in an immunological change.

Psychological and Immunological Predictors of Recurrence

Genital herpes is a sexually transmitted disease that is estimated by the United States Department of Health and Human Services to be carried by at least five million Americans (Tummon, Dudley, & Walters, 1981). While accurate estimates of current and past prevalence are not available it is suspected that genital herpes has become increasingly prevalent over the past 20 years (Tummon et al., 1981). It is the second most prevalent venereal disease (after gonorrhea) with at least 100,000 new cases each year (Klein, 1976).

Genital herpes is caused by the herpes simplex virus (HSV). Two biologically and immunologically distinct types of HSV exist--HSV Type 1 and HSV Type 2. Type 1 was generally found in oral herpes (labialis) and Type 2 in genital herpes but it is now recognized that genital infections can be due to either type with no distinguishing clinical characteristics. Taken together, HSV-1 and HSV-2 are among the most prevalent infectious agents in humans (Klein, 1976).

Genital herpes is a major medical problem in the United States today for a number of reasons. First, an association has been noted between genital herpes and cervical cancer although no adequate prospective serological studies have been undertaken in this area (Tummon et al., 1981). Second, genital herpes in pregnant women has been associated with an increased incidence of spontaneous abortions (Tummon et al., 1981) and with the risk of infection to the newborn infant with devastating consequences (Rosenthal, 1979). Third, genital herpes can, in rare cases, lead to herpes encephalitis, an infection of the brain. Fourth, contracting HSV can have profound psychological effects (Bierman, 1985). A survey of 3,148 people with genital herpes reported that having the disease caused many individuals significant emotional problems resulting in sexual abstinence, isolation, changes in self-esteem, and depression (American Social Health Association, 1981). Finally, there is currently no cure for genital herpes and the potential for immunization against the virus is unclear. A number of treatments to shorten the clinical course of HSV recrudescence have been tested but have failed to show efficacy until the recent development of Acyclovir (Bierman, 1984). Acyclovir has been shown to reduce the intensity of outbreaks and prevent their reoccurrence (Corey, Adams, Brown, & Holmes, 1983; Whittington & Cates, 1984). It is yet too early to determine whether this drug is being positively viewed by patients with herpes since the medication is expensive, among other factors.

Pathophysiology of genital herpes. The herpes virus is transmitted through physical contact. Once the virus has contact with the skin or mucous membrane it attaches itself to the outer wall of the host's cells

with which it fuses. Upon entry into the cell, the virus is transported to the nucleus and the cell's genetic code is replaced by the virus's code. Viral replication can then begin, borrowing the host's cellular "machinery." New viral particles are then transmitted to other host cells. The immune system responds to the invading virus particles and limits viral growth (Hamilton, 1979). As cells die over time in response to viral invasion and immunological attack, cellular death and tissue destruction are manifested as herpes lesions.

The HSV is capable of remaining in the body and avoiding total destruction from immune defenses because, after a period of viral replication and lesion development, it will ascend from the genital area through peripheral nerves along an intra-axonal pathway to a cluster of sensory and autonomic nerve cells at the base of the spine called the sacral ganglia. In the case of oral herpes, viral particles are transported to the trigeminal ganglia. In their travels along the nerve and while remaining in the ganglia the HSV particles are protected from the host's immune system. The virus then remains dormant in the ganglia until viral replication begins again and a recurrence of the herpes infection is initiated. There are a number of factors which have been suggested to "activate" a herpes recurrence, including sunlight, a cold or infection, heat, trauma to the skin, the menstrual cycle, food allergies, and emotional stress (Hill,1985). However, these suggested activators have not been systematically studied and the relationship between them and lesion formation is based largely on anecdotal evidence.

Physiological processes underlying HSV recurrence. The subsequent development of an outbreak of genital herpes lesions, after the primary

infection, takes place in three stages. First the virus must be "reactivated" in the sacral ganglia. A "recurrence" can then begin, indicated by the presence of viral particles in the nerve pathways or at the original site of the lesions. "Recrudescence" of the infection may then result indicated by the formation of lesions in the genital area usually at the original lesion site but sometimes elsewhere. Reactivation of the virus from the ganglia can either be followed by recrudescent disease or an asymptomatic state (Blyth & Hill, 1984). In other words, viral particles can be detected at the local level but in insufficient numbers to cause lesion development.

The physiological basis for HSV reactivation, recurrence and recrudescence remains unclear. The virus may remain dormant in the sacral ganglia for the rest of the life of the individual after initial exposure or the individual may experience further outbreaks. Outbreaks can occur very infrequently or as often as four times per month with some patients reporting continual recrudescent disease for extended periods of time. In one study, 50-80% of patients had an outbreak within three months of the primary infection (Guinan, MacCalman, Kern, Overall, & Spruance, 1981). In another, 16 of 27 patients had a recurrence within two months of the first outbreak (Rosenthal, 1979). While the reasons for the wide variability in viral reactivation and lesion development are unknown, there are two primary hypotheses explaining the reactivation process. The "static state" hypothesis suggests that viral multiplication is reversibly interrupted once HSV is harbored in the cells of the sacral ganglia. Inciting factors then trigger viral multiplication and HSV travels down the sensory pathway to the skin or

mucous membrane resulting in a recurrent infection (Klein, 1976). One suggested explanatation for reactivation is the "nerve trigger theory" suggesting that some form of nervous stimulation to the sacral ganglia causes the latent virus to come out of its dormant state and travel down to the site of the original lesions (Hamilton, 1979).

The "dynamic state" hypothesis holds that viral multiplication continues at a slow pace throughout the "latent" state in the ganglia but that this minute amount of replication is insufficient to allow recrudescence of genital herpes unless the individual's immune system becomes deficient and permits unchecked multiplication (Blyth & Hill, 1984). Thus, viral shedding may be constantly occurring but particles will not be able to invade cells once they reach the skin unless local immunological control is insufficient to protect the host's cells from invasion. In this case the "trigger" may be at the local or skin level ("skin trigger theory") causing a local immunological defect permissive of viral replication.

A third possibility exists. Since reactivation of the virus from the ganglia can either be followed by recrudescent disease or an asymptomatic state, a two stage process may be involved. Viral multiplication may be inhibited at the sacral ganglia but, as a result of nervous or other inciting factors, viral multiplication may be stimulated and a low level of viral particles may begin to travel to the site of the original lesions. Recrudescence will not result however unless this neuronal stimulation is coupled with a local immunological depression which results in rapid increase in viral numbers.

The data in support of these possibilities are contradictory. One way to test the validity of the dynamic state theory is to determine if a transient immunological deficiency precedes HSV recrudescence. Otherwise healthy individuals develop recurrences on a frequent basis suggesting that generalized immmunosuppression is not the basis for recrudescent disease. And to date, HSV recrudescence has not yet been consistently associated with any particular immunological change detected in the peripheral blood (see Rouse, 1985 for a review). Specifically, the humoral immune system is believed to be uninvolved in HSV recurrence because levels of antibody to HSV do not fluctuate before or after a recurrence. Recrudescence as a result of a deficiency in cellular immunity is a favored hypothesis but the evidence is not impressive. A number of studies have indirectly indicated that cellular immunity may play a role in HSV outbreaks. First, protective immunity to HSV can be bestowed on an organism by adoptive transfer of immune lymphocytes. Second, infection can be enhanced by suppression of immune functioning via drugs or neonatal thymectomy. Third, patients with compromised cell-mediated immunity are more prone to severe, and in some cases, fatal HSV infections. However direct tests of an association between an aspect of cellular immunity and HSV outbreaks have not found consistent results (Hill, 1985; Rouse, 1985). Recent evidence suggests that an imbalance between HSV specific lymphocyte transformation and the elaboration of lymphokines may be associated in time with HSV recurrence (Gange et al., 1975; O'Reilly, Chibbaro, Anger, & Lopez, 1977; Sheridan,Donnenberg, Aurelian, & Elpern, 1982; Shillitoe, Wilton, & Lehner, 1977). Specifically, leukocyte inhibition factor, ma-

crophage inhibition factor, and possibly immune interferon do not appear to be produced in proportion to the generally heightened lymphocyte transformation response during outbreaks. However, other researchers attempting to replicate these findings have not been able to do so (Russel, Kaiser, & Lao, 1976). Other research has found recurrence to coincide with an imbalance in the ratio of helper to suppressor T cells indicating increased levels of suppressor cells (Sheridan et al., 1982).

The development of recrudescent disease from the ineffective functioning of a natural component of immunity (e.g., natural killer cell activity or macrophage function) has been hypothesized (Lopez, Kirkpatrick, Read, Fitzgerald, Pitt, Pahwa, Ching, & Smithwick, 1983), and diminished NK cell activity has been associated with increased susceptibility to HSV infection(Lopez et al., 1983) but the data remain inconclusive. One problem with this body of research is that blood samples are usually drawn during recrudescence and compared to periods when lesions are not detectable. Differences in immunological function found may be the result of exposure to virus particles and not the cause of viral shedding. Patients with recurrent herpes have not been tracked over a long period of time measuring frequently and sequentially for immune deficits in order to determine the link between these deficits and subsequent recurrence (Rouse, 1985).

The data on HSV reactivation and recrudescence suggest three possible pathways through which psychological changes could influence the timing of HSV outbreaks. First, nervous stimulation as a result of stressful or emotional experience could directly activate viral shedding

since the latent virus is housed in nerve clusters including autonomic nerve cells (Static State-Nerve Trigger Theory).

Second, stress or psychological processes could cause a local immunological depression which then could result in a failure to protect host cells from invasion by constantly shed viral particles (Dynamic State-Skin Trigger Theory).

Third, stress could activate the latent virus in the ganglia and cause viral shedding. Stress could simultaneously produce a local immunological depression causing this low level of viral shedding to increase and result in cellular invasion and lesion development. In other words, it is possible that lesions will not develop unless there are sufficient "triggers" at both the nerve and local level. And psychological factors could function as triggers at either level or both.

Psychological factors and HSV recurrence. The evidence linking psychological factors to HSV recurrence is sparse and inconclusive. Seven studies describing case histories of patients with herpes (five with herpes of the lip (RHL) and two with genital herpes) suggest that such factors as hostility, separation anxiety, generalized emotional stress, guilt and repressed sexual feelings are linked with recurrences (Blank & Brody, 1950; Chang, 1975; Guinan, 1981; Konstantin, 1961; Lieb, 1979; Schneck, 1947; Ullman, 1947). These studies are fraught with methodological problems including reliance on the retrospective report of the patient, inadequate definition of psychological terms, and lack of adequate controls. For example, a study that is often reported in the literature as supportive of the relationship between stress and herpes recurrence is based on the case of a 24 year old soldier who re-

quested treatment for depression and suicidal preoccupation (Schneck, 1947). This patient reported to his therapist that he had had 40 episodes of herpes of the lip over the previous 10 years and that most occurred if tension and feelings of hostility mounted in the absence of adequate outlets. This case report is based wholly on the retrospective recollections of the patient; no attempt is made to corroborate his recollections.

The "best" of the case history reports involved the selection of 10 patients with extensive previous medical care for recurrent herpes of the lip who reported no obvious cause (e.g., sunburn, menstrual period) for their recurrent outbreaks (Blank & Brody, 1950). These six males and four females were interviewed for their dermatological history and then seen weekly for about an hour in psychoanalytically-oriented psychotherapy. The number of sessions per patient ranged from two to fifty. Psychological tests were also administered. The authors report "strikingly" consistent patterns among nine of the ten patients. For example, these patients were pleased to participate in the therapeutic sessions, tended to be passive, obedient and anxious to please, developed a rapid "positive transference" to the therapist, and exhibited a hysterical character structure "inclining to sexualize all nonsexual relations." The authors do not report on the way in which these judgments were made about the patients. In addition, the authors reported that the therapeutic relationship had a positive impact on HSV recurrence with patients reporting that their herpes had disappeared or diminished, to recur (in two cases) when therapy appointments were broken.

Interestingly, two case reports suggest that herpes recurrence can be induced by hypnosis. One case study reports on the hypnotherapy of a 27 year old soldier who had suffered "hysterical blindness" following the explosion of a shell near him during World War II (Ullman, 1947). After successfully treating the blindness with hypnotherapy the author and his colleagues began to experiment with the patient's response to hypnotic suggestion. At one session the hypnotherapist suggested that in the next 24 hours fever blisters would form on the patient's lower lip in a specified area. The therapist suggested at the same time that the patient appeared rundown and debilitated and that he might be catching a cold. Twenty-four hours later, multiple small blisters appeared on the patient's lip in the suggested location. A skin consultant confirmed the diagnosis as HSV. The author feels that adding the component of the induction concerning the unpleasant feelings was an essential addition to the direct suggestion that blisters would appear. The second hypnosis study was conducted on three patients who had herpes labialis (Schneck, 1947). They were reminded under hypnosis of an unpleasant affective experience while at the same time suggesting that they feel the itching associated with herpetic lesions. In all patients herpes developed in one or two days. These interesting reports have not been confirmed under controlled laboratory conditions so the findings remain speculative.

Two studies report on the effect of psychoactive drugs on HSV recurrence. Lieb (1979) found that administration of Lithium for the treatment of depression and anxiety in two patients (one with herpes of the lip and one with genital herpes) caused recurrences to disappear,

to reappear when treatment was discontinued. Chang (1975) reported the observation that daily doses of chlorpromazine influenced recurrence rate in six of eight patients with recurrent genital herpes. Recurrence rate was reduced by three and one half times and episodes were milder and briefer during treatment. When the drug was discontinued, herpes recurred with the same clinical severity as pre-treatment. Speculating on the mechanism involved, Chang discounted the drug's sedative effect because trifluoperazine or diazepam did not have a similar effect. He also observed that the anti-serotonin effect of thorazine could not explain its effect on recurrence because reserpine was ineffective in reducing recurrences. Obviously, other factors timed with medication administration could have caused the changes in recurrence rate since there were no control groups employed. Also, it is unclear whether or not recurrences were verified or whether the subjects' self-report was relied on entirely.

One set of animal studies indicates that avoidance learning and restraint increases susceptibility to innoculated HSV virus (Rasmussen,1957). The author found that mice who were involved in 14 or 21 days of avoidance learning were significantly more susceptible to HSV by innoculation than control animals who went through identical experiences except without shock. Similar results were found when mice were confined with loosely wrapped copper screen as the stressor. It is unclear how physically traumatic both stressors were and how this physical trauma might have contributed to lowered resistance. If the physical effects were removed, it remains to be seen whether a "psychological" stress effect on HSV susceptibility would have been found.

Two epidemiological studies were conducted in this area (Halonen, Rimon, Arhonka, & Jantti, 1974; Ship, Morris, Durocher, & Burket 1960). Halonen and colleagues attempted to test for the possible role of HSV in determining psychiatric disorder. Although not mentioned in the article, this research could also be used to evaluate the reverse effect--the relevance of psychiatric disorder in predicting HSV. Serum specimens were collected from patients and healthy personnel in three psychiatric hospitals. A total of 174 HSV-1 antibody tests were administered. HSV antibody titers were higher in each psychiatric group measured in comparison to the medical personnel group. The highest levels were found in psychotic depressives. Because neither measles nor rubella antibody titers were increased in the depressed patients, the authors rule out a general change in circulating antibody in psychiatric patients. Although the authors found it tempting to state that HSV caused psychotic depression, they had no causal evidence based on this study. The other differences between medical personnel and psychiatric patients (frequency of illness, institutionalization, sanitary conditions, demographics) could certainly play a role in explaining a difference in HSV prevalence between the two groups.

In the second epidemiological study (Ship et al., 1960) 343 medical and dental students as well as 242 medical and psychiatric patients were interviewed and examined for recurrent herpes of the lip as well as recurrent aphthous ulcers (canker sores or RAU). Approximately 41% of the student sample reported a history of RHL with 41% of the students and 59.8% of the patients reporting occasional or frequent recurrences. Findings relevant to psychological or social factors associated with RHL

included the fact that RHL history was different for different religious groups with the highest prevalence for Catholics, then Protestants, and lowest for Jews. Based on the Cornell Medical Index, no differences in emotional factors were found between subjects with RHL and those without it. There were no consistent patterns of emotional make-up correlated with severity of the disease.

A series of cross-sectional studies have evaluated the relationship between psychological factors and herpes simplex. Taylor (1979) compared four groups of women: those with genital HSV who had a high recurrence rate, those with genital HSV who had a low recurrence rate, those with chronic vaginitis and those with neither HSV nor chronic vaginitis. Women with HSV did not report more recent stressful events than did women with chronic vaginitis or controls. However the women with a high recurrence rate reported experiencing more recent stressful events than the women with low numbers of recurrences. Watson (1984) studied 51 subjects with genital HSV and found that the number of recent life experiences reported over the past year correlated with the number of recurrences retrospectively reported over the past year. Of those subjects who reported high recent stress, those with an internal locus of control experienced significantly fewer recurrences than did those subjects with an external locus of control. VanderPlate and Kerrick (1985) studied 52 patients with genital HSV and administered a battery of tests including the Schedule of Recent Experience and measures of state and trait anxiety and depression. The number of recurrences the subjects reported over the past year and the average number of recurrences per year were not significantly correlated with

anxiety, stress or depression. These studies rely exclusively on the retrospective recall of recurrence rate by the subjects which may be confounded with the psychological state of the subject when they fill out the questionnaires. In other words, subjects may have difficulty accurately recalling the number of recurrences that took place over the previous year, and the extent and nature of their inaccuracies may be partly a function of their psychological state. For example, anxious subjects may be more likely to inflate the number of recurrences as well as the number of stressful life experiences that took place over a period of time when compared to non-anxious patients.

Three studies tested whether increased stress or negative mood occurred prior to the development of HSV outbreaks. Schmidt, Zizanski, Ellner, Kumer, & Arno (1985) studied 18 patients with recurrent herpes labialis who did not evidence factors that might precipitate recurrence other than emotional stress (in other words, they did not have recurrences that appeared to be caused by illness, sunburn or the menstrual cycle). They were administered a series of questionnaires at two time points: one was a random time point during which no recurrence took place, and the second was within the first three days of lesion formation. The questionnaires measured life events, daily hassles, social support, anxiety, coping ability, personality, depression and well-being. At the time of the recurrence the subjects were asked to fill out the questionnaires to describe their stress, etc., during the week preceding the outbreak. The authors found that subjects reported that more life events, daily hassles and anxiety occurred in the week prior to the outbreak than in the other random week. They

found no differences in the other variables measured. While the authors claim that their data support a relationship between these psychological factors and increased susceptibility to recurrence, serious methodological flaws do not justify this interpretation of the data. This study is a retrospective evaluation of the relationship between psychological factors and recurrence. Once the subjects have had a recurrence, they are asked to recall their feelings, etc., over the previous week. Thus, this study suffers from the problems of other retrospective studies (e.g., influence of current state on recollection of previous events) that have been discussed elsewhere (see Jenkins, et al., 1979). It is quite possible that if subjects believe that stress activates their recurrences they will report that they were stressed the week before a recurrence in order to support this belief.

Goldmeier and Johnson (1982) studied 58 individuals with genital HSV and recorded prospectively their recurrence rate via clinic follow-up and mailed questionnaire. All subjects were administered the General Health Questionnaire prior to the beginning of the study. The researchers compared the subjects who had a recurrence before 28 weeks (50% of the sample) with the subjects who did not have a recurrence in this time period. Subjects who did not experience a recurrence had significantly lower scores on the questionnaire in comparison to the recurrence group, suggesting that the recurrence group had more symptoms of anxiety and depression and more obsessive symptoms. The authors do not report whether they examined individual scales (e.g., anxiety) within the questionnaire or whether the questionnaire items included symptoms that may be health-oriented and indicative of poor health rather than exclusively psychological symptoms.

The strength of the assertion that psychological factors are linked to HSV reccurrence must rest heavily on the prospective studies conducted by the Friedman, Katcher and Luborsky group (Katcher, Honori, Brightman, Luborsky, & Ship, 1973; Friedman, Katcher, & Brightman, 1977; Luborsky, Mintz, Brightman, & Katcher, 1976). In their studies, 49 nursing students with RHL were followed over a three year period. The Clyde Mood Scale, a "social assets" scale measuring social class and aspects of individual personal history such as success in school and relations with parents, the Johns Hopkins Symptom Index, the Cornell Medical Index and other scales were administered at the beginning of the study. Subjects were asked to fill out the mood scale and the Johns Hopkins scale as they "usually feel" in order to reflect "trait" rather than "state" characteristics. They were also examined for RHL, and given a medical history and a blood test. Each subject was asked to report the presence of RHL and associated symptoms (e.g., fever) on a daily calendar form which was collected bi-weekly. They were also paid to have their recurrences verified by the medical personnel.

A report of the data from the first year (Katcher et al., 1973) indicated that one-third of the variance in RHL was predicted by a combination of the psychological and social variables measured. Specifically, incidence of documented and student-reported RHL had a significant positive independent correlation with the unhappy factor on the Clyde Mood Scale and a significant negative independent correlation with the social assets score. When all psychological and social variables were combined in a regression analysis, they accounted for 41% of the

variance in documented RHL. Only social assets was a significant predictor, however. When HSV antibody titer was included as a predictor, psychological variables added 19% to the variance accounted for by antibody titer but only antibody titer was significant. When both antibody titer and severity of history of RHL were added to psychosocial factors, the latter factors accounted for 14% of the variance with the "Duncan's Index" and history of RHL the only significant predictors. The authors never mention what the Duncan's Index measures however.

When the entire three year period was examined, Friedman and colleagues (1977) reported that 39% of the variance in 3 year incidence rate of RHL was accounted for by a combination of history of RHL, number of upper respiratory infection (URI) episodes in the three year period, antibody titer, social assets and mood. All five of these variables accounted for significant variance. URI had the strongest correlation with RHL episodes(r =.27). In contrast to the one year data, social assets had a positive rather than a negative correlation with RHL incidence. Subjects who experienced more unpleasant moods experienced more RHL episodes but the strength of the association was weak and of little predictive value according to the authors (r =-.11). It seems that the authors are too ready to discount the impact of psychological variables in favor of factors such as previous history and antibody titer. It does not seem useful to include in a regression such variables as previous history and antibody titer since these factors cannot be seen as causes but are highly correlated with recurrence rate for other reasons (e.g., most patients with past frequent recurrences are likely to have frequent recurrences in the future but that does not

mean that both past and future rates are not influenced by psychological factors). Therefore the results suggesting such a high degree of variance accounted for by psychosocial factors alone is important. Unfortunately the authors do not discuss the details of the social assets scale and why it might have reversed its relationship to recurrence rate during the two study periods. It would have been helpful if the researchers had distinguished the various aspects of social assets measured since the different aspects might have very different relationships to the outcome (e.g., social class versus relationship with parents).

These authors also studied the correlation of daily ratings of mood and appearance of HSV over a three month period (Luborsky et al., 1976). They asked student nurses with RHL to fill out the Clyde Mood Scale daily upon arising for three months. Each nurse was also checked daily for cold sores and HSV in mouth secretions. Students also kept a daily calendar of cold sores, illness, and life events during this period.

The mood scores were transformed to standard scores for the four day period prior to and the four day period following each recurrence. One hundred statistical tests were necessary to correlate mood with recurrence. Five of these tests reached significance. Since this number was not greater than would be expected by chance the authors concluded that no systematic relationship existed between mood and RHL. It is unfortunate that the authors only studied mood upon arising when it would be unlikely that much variation in mood would be detected. Also a multivariate test rather than a series of $\underline{t}$ tests would have had more power to detect a relationship between state and RHL.

A recent study (Glaser et al., 1985) has shown that herpes virus antibody titer is increased in medical students immediately prior to final exams compared to levels one month prior to exams; loneliness was also correlated with antibody levels. The authors suggest that this increased HSV antibody level during the stressful exam period in latently infected medical students reflected modulation in the cellular immune response's control of the latent virus. The researchers did not measure herpes recurrence. As described earlier, these researchers (Kiecolt-Glaser et al., 1985) also found changes in HSV-1 antibody titer in response to a relaxation intervention in elderly patients.

In summary, there is only one study reported in the literature using a prospective design that attempts to test the relationship of psychosocial factors to genital herpes recurrence. This study found that an overall measure of psychological symptoms such as anxiety, depression and obsessivness predicted the likelihood of a recrudescent episode in the upcoming seven month period (Goldmeier & Johnson, 1982). The prospective study of herpes of the lip indicates that trait unhappy mood may be predictive of recurrence rate. In both cases, a trait-like affect variable was found to be predictive of recurrence rate. The only prospective examination of state variables such as mood or stress level as predictors of outbreaks did not find a relationship between state mood and recurrence (Luborsky et al., 1979). The other designs used, while suggesting that such factors as anxiety, depression, social relationships and exam stress may be predictive of herpes recurrences, are unable to substantiate such a relationship because of methodological inadequacies.

Statement of the Problem

The research aimed at showing a relationship among psychological factors, immune function and disease outcomes suffers from five primary problems. First, although studies have been conducted showing that stress, coping, mood, social support and other psychological factors are predictive of disease outcomes and other studies have shown that stress is associated with changes in immune competence no studies have measured psychological factors, immunity and disease outcomes in the same group of subjects to determine if changes in immunity are in fact mediators in the stress-disease relationship.

A second weakness of the stress, immunity and disease research is the potential confounding of results by unstudied indirect effects of stress, such as stress-induced health habit changes. In other words, when individuals are under stress they may modify their health habits (sleep less, eat a less balanced diet, smoke or drink more, exercise less); these health habit changes may then alter immune function and disease state (see Bistrian, Blackburn, & Serimshaw, 1975, for immunological effects of severe nutritional deficits, Tennenbaum, Ruppert, & Pierre, 1969, for effects of alcohol on immunity in rats, Targan, Britvan & Dorey, 1981, for effects of exercise on immunity, Hinkle and Wolff, 1957, and Hinkle, 1974, for stress effects on sleep and diet). A significant relationship between stress and immune change could then be mistakenly construed as a direct effect of stress rather than an indirect effect (see Weiner, 1977, for a discussion of this issue). Stress and health habits may also interact in producing health damage as suggested by a recent experimental study of the effects of stress combined with

smoking on heart rate (MacDougall, Dembroski, Slaats, Herd, & Elliot, 1983). Human studies of stressful effects on immune function have not, in general, incorporated measures of these potentially confounding factors (see Kiecolt-Glaser et al., 1984 for an exception).

A third weakness of studies in this area is a failure to measure important psychosocial moderators in the relationship between stress and immune alterations. Coping and social support are two factors which have been found to play an important role in mediating the relationship between stress and disease outcomes (e.g., Cobb, 1976; Berkman & Syme, 1979; Cohen, 1975) It is not yet known whether these factors can also moderate the relationship between stress and immune function, indicating a biological pathway underlying their effects on disease outcomes.

Also, affect is rarely measured directly despite current models of stress and disease which posit that the combination of stressful experience, the appraisal of stress, methods of coping and personal resources may result in an emotional state which then causes physiological changes (Lazarus & Folkman, 1984). If affect is conceptualized as the "final link" in the chain from environmental conditions to physiological change, then affect should have a strong relationship to physiological change. In other words, stressful experience may not result in a physiological change unless it is accompanied by changes in affect. Therefore, the affective state of the individual should be more highly correlated with changes in immunity than would be exposure to stressful circumstances. Only one study has directly tested the relationship between affect and immunity in a normal population. Van Dyke (1985) did not find a sig-

nificant correlation between depression and changes in immunity in a small sample of bereaved individuals. Other affects have not been measured in relationship to immunity.

Although subjects are often asked to report their level of "stress," "upset," "worry," "tension," etc. in reaction to situations, these more vague and global adjectives may combine a number of different affective states with differential effects on physiological outcomes. This question of the "specificity" of relationships between different affective states and immunity must be tested in order to determine whether arousal in general influences various aspects of immunity or whether different affects have differential effects. This question is similar to (and contingent upon) the question of the level of specificity of autonomic responses to emotional stimuli (Schacter & Singer, 1962; Ekman, Levenson, & Friesen, 1983) and of specificity of hormonal responses to affective and other stimuli (Selye, 1956; Mason, 1975a). For example, affects such as sadness and dysphoria may have one effect on the nervous and hormonal system and consequently on immunity while anger, frustration and anxiety may have other effects. If so, the correlation between global upset and immunity may be found to be small because the upset measure combines affects which have different relationships to immunity.

Fourth, many studies examining stress effects on either the immune system or on disease focus on differing stress levels between groups of individuals and then compare these groups for differences in immune function or health status. This kind of "between subjects" design is appropriate for studies which intend to determine the kinds of life conditions which increase the risk of developing a particular major

disease that only strikes a proportion of the population (e.g., myocardial infarction, cancer). In contemplating the etiology of common infectious diseases (which most people develop at one time or another) or the progression of a disease state, a "within subjects" approach involving multiple measurements of the same group of people over time may be more appropriate. DeLongis (1985) makes the point that what has been assumed to be error in inter-individual studies of stress and illness may be meaningful variation if a within-subjects approach is used since individuals probably vary in the extent to which fluctuations in health status are tied to stress. In a within subjects approach the research question then focuses on fluctuations in stress level and resulting changes in immune function, health status or disease progression. The question is one of timing--why this infection at this time rather than at another time? What psychological and other factors differentiate the pre-disease state from the pre-healthy state?

The between-subjects versus within-subjects choice can also be viewed as a choice between predicting physiological and health phenomenon with trait or with state variables. While both trait characteristics of individuals (for example, the Type A behavior pattern) and the fluctuating state of the individual (for example, as a result of exposure to stressful experiences) may be important predictors of health variables, the nature of the specific question may determine the focus on one or the other. For example, questions of the timing of physiological and health changes may require the testing of state variables, or state variables in interaction with trait variables, while the question of overall disease susceptibility may require the testing of less transient phenom-

enon such as individual characteristics or chronic exposure to stressful circumstances.

In order to design studies using a within-subjects perspective, measures must be taken in the same group of people over time and also the measures chosen must be responsive to fluctuations in state. Data should be analyzed using these psychological factors as "within subjects factors" and not exclusively as "grouping factors." For example, many current studies evaluate stress as a within subjects factor (i.e., it is measured more than once in the same group of individuals) but assume that stress moderators (such as social support, coping, etc.) are grouping factors and thus measure them only once during the course of the study. By constructing the study designs in this way they are in essence conceptualizing these factors as traits or dispositional characteristics of the subjects. The variability in sense of support or in coping strategy, for example, is then considered unimportant to the question being asked. In such a study, Kiecolt-Glaser and others (1984) found that a high stress period is more likely to lead to an immune depression in students who categorized themselves as lonely at the beginning of a study period. There are three different stress periods measured but loneliness is measured only at the beginning of the study. Some subjects may be very consistent in their sense of loneliness over time while others may vary with changes in environmental conditions and relationships. Greater precision and a stronger relationship between psychological factors and immunity may be found if shifts in these psychological measures over time are considered in relation to changes in exposure to stressors.

In summary, human studies in psychoneuroimmunology are needed which measure psychological factors, potential immune mediators and disease outcome over time in the same group of individuals. In addition, an attempt should be made to determine if changes in health habits as a result of stress are responsible for these immune changes. And finally, potential psychosocial moderators of the stress-immune function relationship (i.e., coping, social support) as well as specific affects should be assessed.

Hypotheses

The three primary goals of the dissertation were 1) to specify the relationship of selected psychosocial factors to genital herpes recurrence[1] in a sample of patients who have frequent outbreaks of the disease, 2) to determine if changes in the proportion of helper and suppressor T cells mediate the relationship of psychological factors to recrudescence, and 3) to determine if stress-induced changes in immunity and/or HSV recrudescence are a result of changes in health habits. The psychosocial variables were chosen based on the theoretical and research literature which links stress and its mediators to disease. It was assumed that it is not an environmental event itself that adversely affects health status but more importantly, the individual's perception of the event, the way in which he or she copes with it, the individual's social support network, and the affective state that results

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[1] Despite some authors preference for discriminating recurrence (viral shedding but not neccessarily lesion formation) from recrudescence (lesion formation) the terms are both used in most texts to refer to the outbreak of lesions. Therefore the terms will be used interchangably.

from the combination of these factors.

The psychosocial variables in this study are hypothesized to have either direct effects on HSV recurrence rate, compounding effects, or interactive effects. Direct effects involve a direct relationship between the variable and outcome, e.g., stress is hypothesized to predict outbreaks. Compounding effects involve effects over and above the effects of another variable, e.g., negative moods are hypothesized to affect outbreaks even when controlling for stress level. Interactive effects involve the moderation of the relationship between two other variables, e.g., stress is hypothesized to predict recurrence rate only at low levels of social support. Social support therefore interacts with stress in predicting outcome. The specific hypotheses for each type of effect will be detailed below.

1. Stress was hypothesized to have direct effects on HSV recurrence rate. Specifically, the greater the perceived stress over a month period, the greater the likelihood of a recrudescent episode in the subsequent month period. Perceived stress was defined by the reaction to current major life changes, current chronic annoying situations of daily living or "daily hassles," the residual effect of past stressful situations, the effect of anticipating stressful situations expected to occur in the future, and/or a lack of satisfaction with one's progression on important life goals.

2. Negative affective states were hypothesized to have compounding effects on recurrence rate over and above the effects of stress. In addition to direct effects on recurrence rate, when the presence of one of the negative states is combined with the presence of a high level of

perceived stress, the ability to predict recurrence will be enhanced. Negative affective states include anxiety, hostility, depression and a state termed "defeat." Defeat is defined as the presence of depression coupled with the presence of a sense of helplessness in relation to environmental events. While many researchers conceptualize helplessness as a trait-like variable (such as self-esteem) and therefore expect it to be relatively stable over time within individuals, defeat is conceptualized here as a state variable, like mood, which should fluctuate over time (in relationship to the contingencies of the environment as Seligman, 1975, proposed). Fluctuations in feelings of defeat (as well as the other negative affects) are hypothesized to predict fluctuations in HSV outbreaks.

3. Social support satisfaction and coping flexibility were hypothesized to interact with stress in predicting recurrence rate. Perceived stress is hypothesized to best predict outbreaks at low levels of social support satisfaction and at low levels of coping flexibility. At high levels of social support satisfaction or coping flexibility, stress will not significantly predict outbreaks. In other words, coping flexibility and social support satisfaction will act as buffers of stressful effects on HSV recrudescence.

Social support satisfaction is defined as a high level of satisfaction with the social support available along five dimensions of support across five referent groups. This variable is not a measure of contact with supportive others but rather it is a measure of a global sense of satisfaction with the support the individual perceives is available from his or her network.

Coping flexibility refers to the number of different coping modes used to handle stressful life situations. The more coping modes used, the greater the degree of coping flexibility. Recently, researchers have suggested that it is not specific modes of coping which may protect the individual from the negative effects of health but a large coping repertoire which allows for flexible adaptation to different types of stressful situations (Cohen, Horowitz, Lazarus, Moos, Robins, Rose, and Rutter(1982).

4. The proportion of helper and suppressor T cells are hypothesized to mediate the relationship between the above psychological factors and recrudescence. Specifically, the above psychosocial variables will be significantly related to the proportion of helper and suppressor T cells. The proportion of helper and suppressor T cells will be significantly related to recurrence rate. And the proportion of helper and suppressor T cells will act as an intermediary between the psychosocial variables and recurrence rate.

5. Health habits will not mediate the relationship between psychosocial variables and recurrence rate. Therefore, the psychosocial variables specified above will be predictive of HSV recurrence irrespective of changes in health habits.

While it is hypothesized that all of the psychosocial factors measured including stress level, depression, anxiety, hostility, defeat, social support satisfaction and coping flexibility will have effects on the two types of T cells and on recrudescence, exploratory analyses will be conducted to determine if there are differential relationships between the various psychosocial variables and the outcome measures (e.g., if

anxiety and hostility differ in their relationships to the immune measures).

METHODS

Design

This study is a prospective investigation of the relationship between stress, coping, social support, and affect and genital herpes recurrence. It also investigates the role of helper and suppressor T cells as mediators in the stress-recurrence relationship. Subjects were interviewed and filled out questionnaires once a month for six months. The interviews and questionnaires assessed perceived stress, coping, social support, and affect as well as possible non-psychological predictors of recurrence including infection, fatigue, the menstrual cycle and health habits engaged in during the previous month period. Herpes recurrences over the six month period were documented by a physician or nurse-practitioner. At the monthly interview, a sub-sample of the subjects had a blood sample drawn for immunological assay. Data analyses determined the ability of the psychosocial and non-psychosocial variables to predict herpes recurrences during the six month period and whether these relationships were mediated by changes in the proportions of helper and suppressor T cells.

Subjects

The subject pool included 6 male and 30 female patients with documented genital herpes who met the following criteria:

1. over the age of 18
2. heterosexual
3. English speaking
4. carriers of HSV for six months or more
5. free from immuno-deficiency diseases (e.g., Acquired Immune Deficiency Syndrome), chronic infection (e.g., mononucleosis), autoimmune disease, or another venereal disease
6. not under treatment with radiation, chemotherapy or corticosteroids
7. not taking oral Acyclovir
8. two episodes of HSV in the previous six month period.

A dermatologist, Dr. Marcus Conant, affiliated with the University of California San Francisco (UCSF) Medical Center whose practice contains a large group of HSV patients, sent a letter to all his current and past genital HSV patients stating that a study would be conducted on psychological factors and herpes. The letter asked patients to return an enclosed card if they were willing to be contacted by a researcher about participation. In addition, the PRN clinic (an Oakland, California clinic specializing in HSV) also sent a similar letter to their patients. Additional subjects were solicited through local newspapers (the Bay Guardian, UCSF Synapse, University of California, Berkeley (UCB) Daily Cal, San Francisco State University student paper). Individuals who might be interested in participating in a study of stress and

herpes were requested to phone the researcher for more information. Presentations were also made to two local herpes support groups to solicit potential subjects.

At the time of the initial phone contact the overall nature of the study was described. It was then determined if each individual met the selection criteria above. Those who met selection criteria were informed that the study would look at whether or not stress and other psychological factors had anything to do with when individuals had herpes outbreaks. They were also told that the study would examine the relationship of health habits like exercise to recurrence rate. The design of the study was explained, i.e., coming in every month for six months to fill out questionnaires and be interviewed and coming in to participating physicians when recurrences occurred. They were also informed that a subgroup of the subjects who could come in for interviews at certain times (Monday or Wednesday afternoon or evenings) would have a blood sample drawn each month to study their immune systems. Interest in participation was then requested. Those who agreed to participate were scheduled for the initial interview.

Of the 49 subjects who agreed to participate in the study, 36 subjects participated in the entire study (seven did not come to the first appointment, one moved out of the area, three dropped out of the study because of lack of time or scheduling difficulties, and two dropped out for unknown reasons.) Nineteen subjects who could schedule the monthly interviews during times when blood drawing was possible (Monday and Wednesday afternoon or evening) formed the immunology sub-group. Each of these subjects had blood samples drawn by a phle-

botomist at the monthly interviews. These samples were used for immunological analysis.

Measures

The measures used in this study are grouped into the following four categories: measures of stress, measures of stress moderators, measures of non-psychological predictors of outcome, and measures of outcome.

The stress scales were selected to measure stress level over the past month as a result of events from three different time periods: current (i.e., over the past month) major life changes, chronic ongoing problems of daily living, and herpes-specific stressors; past stressful situations; and the anticipation of future stressful situations. In this way, the effect of past, current and future events and situations on the individual's stress level over the past month could be determined. In addition, assessment was made of the subjects' perceived satisfaction with progress on their major life goals. It was hypothesized that rather than being stressed only because of past, present or future events, individuals might be stressed because the events or transitions they had anticipated or hoped would occur have not yet taken place. For example, subjects may view having children as a major life goal and may be upset because they have not yet had children. Thus, satisfaction with the subjects' progress on major life goals was assessed to tap this stress dimension.

Stress moderators are those variables that are expected either to buffer the effects of stress on the outcome measures or to compound

these effects. Coping flexibility and social support satisfaction were conceptualized as stress buffers; negative affects and the sense of defeat were conceptualized as stress compounders.

It is possible that stress may exert its effect on recurrence and immunological functioning by changing the individual's health behaviors which then have an impact on outcome; this effect would demonstrate an indirect pathway rather than a direct psychobiological pathway. Thus, health habits are conceptualized as potential confounding factors in the relationship between stress and outcome. In addition, psychological factors may not have an effect on recurrence rate for individuals whose recurrences are determined by the menstrual cycle, infection, or fatigue. Thus, predictors of outcome including health behaviors, the menstrual cycle, infection, and fatigue were measured in addition to psychosocial predictors.

The disease outcome measure in this study was the frequency of genital herpes recurrences. In addition, changes in the proportions of helper and suppressor T cells were measured as potential outcomes of stress and as mediators in the relationship between stress and herpes recurrence.

Measures of Stress

Life Experiences Survey. Sarason's Life Experiences Survey (LES) measures major life changes that have occurred and the subject's assessment of the effect of these changes (Sarason, Johnson, & Siegel, 1978). See Appendix A for a copy of the scale. The survey consists of 57 life change events (e.g., fired from job, failing an exam, death

of a friend). The subjects indicate which events have occurred over the past month, rate each event as "good" or "bad," and rate the effect of the event on their life on a 7 point scale. (The original four point scale was converted to a seven point scale so that all questionnaires could use the same type of Likert scaling.) The Life Experiences Score consists of a summation of these effect ratings.

The LES has been found to be predictive of both psychological and health outcomes including anxiety, depression, myocardial infarction, and self-reported health status (see Sarason, Levine, & Sarason, 1982). The reliability of the scale is adequate for the previous six month period (Jenkins et al., 1979).

Daily Hassles Scale. The Daily Hassles Scale (Kanner, Coyne, Schaefer, & Lazarus, 1981) is a report of the chronic annoyances that have occurred in the subject's life (see Appendix B). It was devised to measure more minor chronic and ongoing problems of daily living in contrast to major life changes. The scale contains 117 items that range from minor annoyances (traffic noise, household tasks) to major problems or concerns (financial problems, problems with children). The subject indicates whether or not the hassle occurred in his or her life over the past month and then rates on a 7 point scale how much of a problem each hassle has been. The Daily Hassles Score consists of a summation of these ratings.

The Daily Hassles Scale has been shown to be a better predictor of self-reported health status and psychological symptoms than life event scales (Delongis, Coyne, Dakof, Folkman, & Lazarus, 1982; Kanner et al., 1981).

Residual Stress Scale. The Residual Stress Scale (see Appendix C) was developed for the purposes of this study to measure residual effects of previous life experiences. For example, an individual may have lost his or her job six months ago but may still be feeling stressed as a result of that loss despite the fact that the event took place some time ago. This scale measures the current level of stress resulting from past life experiences.

The LES covering the past six months was completed at the first appointment. Each subsequent month, subjects were given a record of the events they reported had occurred over the past six months and were asked to report on their current level of distress (upset and worry) over these past events using a seven point scale. Each month the record of past events was updated with the events that had taken place during the course of the study.

Anticipated Life Stress Scale. This scale (see Appendix D) was developed for this study because of an interest in the effects of anticipating upcoming events. Often significant anxiety arises as one prepares for a situation, such as the medical board exams, but the event and its accompanying stress would not be discernable on a life event checklist of past experience. This scale measures current distress (upset and worry) over upcoming events that are anticipated to occur in the subsequent six month period.

Subjects reported any anticipated life events expected to occur in the subsequent six month period and, on a seven point scale, the level of upset or worry they currently felt in anticipation of these events. Subjects were asked to include events that they expected

would occur as well as events that they were worried might occur (e.g., business going bankrupt).

Herpes Stress Scale. The Herpes Stress Scale (see Appendix E) was developed for this study to measure stress as a result of situations that can be particularly difficult for individuals with genital herpes. The questionnaire contains six situations; the subject was asked to rate on a seven point scale his/her level of distress (upset and worry) over the past month in relation to each situation. These areas were sexual relationships, body image, worry over transmission of the disease, pressure from partner, fear of a recurrence, and worry about future health consequences of herpes. These items were selected based on pilot testing of the protocol. All pilot subjects had genital herpes and many had worked in counseling with others with herpes. They mentioned these six situations as potentially stressful for individuals with herpes.

Satisfaction with Progression on Life Goals. This instrument (see Appendix F) was developed for this study to measure the level of satisfaction each subject felt with the progress he or she had been making on important life goals. It was intended to complement measures of the presence of life changes by including the effect of the absence of changes that are hoped for or important to the subject.

The Values and Commitments Inventory (Buhler, 1968) was administered at the first appointment. Subjects were asked to look through this list of 69 life goals and choose the five goals from the inventory that were most important to them at that point in time. At all monthly interviews, subjects were asked to rate their satisfaction with their

progress in accomplishing each goal over the past month on a scale from 1 to 7 from "not at all satisfied" to "extremely satisfied." An overall low level of satisfaction with progress on these life goals would be considered a measure of life stress.

Measures of Stress Moderators

Coping flexibility interview. The coping flexibility interview (see Appendix G) was designed to study the coping processes used to handle stressful situations. The interview was based on the structured interview format developed by Cohen (Cohen, 1975; Cohen & Lazarus, 1973) to ascertain the processes a person actually uses to cope with a situation rather than a disposition to use one or another style of coping. This structured format has been used to study coping in a number of different contexts (e.g., Cohen, 1975; Cohen & Lazarus, 1973; Cohen, Reese, Kaplan & Riggio, 1985; Shaw, 1985) and the ratings from tapes or transcripts have demonstrated high interrater reliability and good predictive validity.

A coping interview was conducted at each appointment. The subject was asked to describe two stressful situations that had occurred over the past month, how they felt in reaction to the situations and how they handled the situation. Subjects were given an opportunity to respond to the open-ended question about the way they handled the situation and were then asked a series of specific questions to capture the five "modes of coping" described by Cohen and Lazarus (1979,1983) as well as six additional "sub-modes." A detailed coding manual (see Appendix H) was developed to describe each mode of coping. The pres-

ence or absence of each mode was determined for each of the two situations based on detailed notes taken during the interview. No attempt was made to rate the extent to which each mode was used in relation to each situation because coding ratings were not made from a full transcript of the interview.

Flexibility of coping was assessed by deriving the number of different modes used by each subject across both situations. The interviewer and another coder[2] coded the coping interviews for evidence of these modes of coping. The two coders also both coded a random subsample of the coping interviews in order to test the reliability of the coding judgements.

Social Interaction Scale: Satisfaction Subscale. The Satisfaction Subscale of the Social Interaction Scale (Beck, Kemeny & DiClemente, 1981) measures level of satisfaction with social support of five types (the giving of assistance, feeling cared about, feeling valued, feeling a part of a group or partnership and the giving of information) available to the subject from five different groups of people in the individual's support network (see Appendix I). The five groups are spouse/partner, relatives, friends, coworkers or fellow students, supervisors or professors. The scale measures the individuals' global reactions or overall sense of satisfaction with support available rather than the number of contacts initiated or the availability of support. Satisfaction was measured because individuals vary in their needs for contact. Thus, level of support availability or contact may not be as predictive of the negative affective states that could result in physiological changes as

[2] Elizabeth Chesterman, Health Psychology, UCSF.

could the overall level of satisfaction with support available, which can be seen as a result of the fit between support availability and individual support needs.

This scale has shown high levels of internal consistency. In a test of the scale's construct validity, it was found that social support satisfaction buffered the effects of health professional student examination stress on depressive symptoms (Beck, Kemeny, & DiClemente, 1981).

Profile of Mood States. The Profile of Mood States (POMS) was administered to measure anxiety, depression and hostility (McNair, Lorr, & Droppleman, 1971). The subjects rated how much they had been feeling each of a list of 65 affects (e.g., angry, tense, cheerful) over the past month on a five point scale from "not at all" to "extremely." The sub-scales of Tension-Anxiety, Depression--Dejection, and Anger-Hostility were used in this study.

The POMS shows predictive validity in a broad spectrum of clinical change studies (Imber, 1975). The scale has high internal consistency (.74 to .92) and test-retest coeficients of .61 to .69 based on a one month interval (McNair & Garr, 1982).

Emotion reexperience scores. An additional measure of affect was developed for the purposes of this study. The design of this measure was based on the assumption that the ability to re-experience a specific emotion as one is discussing a past experience that provoked that emotion may be an indicator of the presence of the mood state consistent with that emotion. For example, in Type A research, a chronic state of

hostility can be inferred from the presence of non-verbal indicators of anger when discussing a past situation that caused the subject to feel angry (Rosenman & Chesney, 1980). "Hostile" individuals are defined as those who manifest angry behavior when recalling past angry situations; individuals who are not hostile do not re-experience (and express non-verbally) anger when discussing past anger-provoking events. Thus, hostile individuals are assumed to have a low threshold for the re-experience of angry feelings.

During the coping interview, subjects were asked to specify the emotions they felt during the stressful situations they described. The subjects were then asked to rate on an 8 point scale the intensity with which they experienced each emotion during the experience and the intensity of each emotion they felt as they described each experience during the interview. This procedure utilized the format devised by Ekman and colleagues (1983) and used in previous emotion research. Specifically, the subjects were asked "Sometimes when you describe an emotional experience you begin to have the feelings again. Did that happen now? Did you begin to feel the sadness (etc.) again? On a scale from 0 to 8 how much did you feel the sadness again as you told me about it if 0 is the least sadness you've ever felt and 8 is the most sadness you've ever felt?" Re-experience intensity ratings were gathered for the primary emotions experienced as well as any secondary emotions experienced. The emotions of sadness, happiness, and anger and the experience of helplessness were of interest in this study. If sadness, anger and helplessness were not mentioned while discussing either of the two stressful situations, the subject was asked to describe

an experience during the past month that made him or her feel each of the feelings. In addition, all subjects were asked to discuss a situation that made them feel happy. The ability to easily re-experience sadness as well as difficulty re-experiencing happiness were used as indicators of depression. The ability to easily re-experience anger was used as an indicator of hostility. The ability to easily re-experience feelings of helplessness was used as one indicator of defeat. As mentioned previously, defeat was conceptualized as a state that could fluctuate in response to life circumstances and involved depressive affect and feelings of helplessness.

Pearlin's Mastery Scale. Pearlin's Mastery Scale (Pearlin & Schooler, 1979) was administered as a second measure of helplessness (the absence of mastery). (See Appendix J.) This scale consists of seven sentences describing feelings of helplessness or hopelessness. The original sentence structure of the scale was changed slightly so that month to month fluctuations in mastery or helplessness/hopelessness could be detected. The subject was asked to rate on a 7 point scale how true each of the seven statements was for him or her over the past month.

Measures of Non-Psychological Predictors of Recurrence

Health status. Certain illnesses such as upper respiratory infections have been shown to predict herpes recurrences (Katcher et al., 1973). Therefore the relationship between infection and recrudescence was examined in this study. It was also considered that stress may only have

a relationship to recurrence in those subjects whose recurrences are not determined by other illnesses.

Health status was measured using the symptom status scale of the Duke-UNC Health Profile (Parkerson, Gehlbach, Wagner, James, Clapp, & Muhlbaier, 1981) which is a list of 28 symptoms suggestive of the presence of illness (see Appendix K.) Each subject indicated on a 3 point scale (not at all, sometimes, alot) how much trouble they have had with each of the symptoms over the past month. The resulting score is a weighted sum of the ratings on each item which is then divided by the maximum possible score. An infection score (indicated in Appendix K) was computed which included only those symptoms that are likely to indicate the presence of an infection (e.g., difficulty breathing, fever).

The Health Profile shows moderate test-retest reliability and adequate levels of construct, convergent and discriminant validity (Parkerson et al., 1981).

It may be that the relationship between stress or mood and recurrences is a result of the menstrual cycle's effect on both mood and recurrences or that stress only has an impact on recurrence rate for individuals whose recurrences are not determined by their menstrual period. To test the effect of the menstrual cycle on recurrence rate, female subjects were asked to monitor their menstrual cycle and report monthly on the dates of their menstrual period.

Fatigue is considered to be a predictor of recurrence. The POMS Fatigue subscale was used in this study to test the relationship between fatigue and recurrence rate.

Health habits interview. Individuals under stress have been shown to change their health habits (e.g., diet, drinking, exercise). (See Hinkle, 1974; Hinkle & Wolff, 1957.) These changes may then influence immune status and herpes recurrence rate, confounding the study of the direct effects of stress on immunity and recurrence. Therefore changes in health habits were assessed during the interview (See Appendix L). The subjects were asked to describe for the past month the average number of hours slept per night, amount and type of exercise engaged in, amount of alcohol consumed and cigarettes smoked. They were also asked to rate their level of sexual activity on a 5 point scale since sexual activity may also activate herpes recurrences. The following variables were then computed for each month: the average number of hours slept, the average number of hours of exercise of any kind, the average number of hours of light exercise (e.g., floor exercises, walking), the average number of hours of heavy exercise (e.g., running, swimming), the average number of glasses of alcohol consumed, the average number of cigarettes smoked, and the average level of sexual activity.

Outcome Measures

Immunological status. A blood sample was taken at each appointment for assessment of immunological status on a sub-sample of 19 of the subjects. (Cost precluded obtaining assays on a larger number of subjects.) The blood was then assayed to determine the proportion of helper-inducer T cells and suppressor-cytotoxic T cells. These assays were chosen because they measure two components of the immune system

which are essential to the adequate regulation of immune functions important to viral control. The helper-inducer T cell assay assesses the proportion of lymphocytes which display markers indicating the ability to either activate B cells to produce antibody or stimulate precursors of cytotoxic T cells to mature. The suppressor-cytotoxic assay quantifies the proportion of lymphocytes which display markers indicating they serve either a suppressive function by suppressing promotion of antibody and the maturation of cytotoxic cells or that serve a cytotoxic function by killing virally-infected cells. (For simplicity, and following convention, the helper-inducer T cells will be referred to as helper T cells; the suppressor-cytotoxic T cells will be referred to as suppressor T cells.) The helper/suppressor T cell ratio and the proportion of helper T cells have recently been shown to be responsive to medical student examination stress suggesting that these cells may be be capable of reacting to the stresses of everyday life (Kiecolt-Glaser et al., 1985). Also, the ratio as well as the number of suppressor T cells has been shown to change during HSV episodes (Sheridan et al., 1982). The assay of helper and suppressor T cells was carried out in the Clinical Immunology Laboratory at UCSF under the direction of Conrad Casavant, Ph.D., Assistant Director, Immunology Laboratory, and Associate Clinical Professor of Laboratory Medicine. The assay was conducted using monoclonal antibodies and an indirect immunofluorescent technique. Fluorescing cells were counted and analyzed by technologists using an epiillumination fluorescent microscope.

Frequency of genital herpes recurrences. Subjects were asked to go to one of the study physicians[3] for verification of genital herpes recur-

rences that occurred during the course of the study. At the visit the physician examined the lesions and determined whether they were clinically typical of genital herpes, clinically suggestive of herpes, or not clinically typical or suggestive of herpes. Subjects were also asked each month to report on the recurrences that took place during the previous month since subjects were not always able to have outbreaks documented.

Procedure

Each consenting patient was interviewed by the researcher once a month for six months at approximately the same time of day and, as much as possible, at equal intervals between appointments. The interviews took place at either the University of California San Francisco campus or the University of California Berkeley campus, depending on the preference of the patient, and lasted one hour.

Appointment Number One

The following data were collected at the first appointment only.

1. demographics, age, marital status, history of HSV, frequency of recurrences over the past six months, perception of the etiology of HSV recurrences, current disease state, and medical regimens used.

2. the Values and Commitments Inventory (Buhler, 1968) was administered as a measure of the highest priority life goals for the subject at that point in time (and was subsequently used in the Goal Progres-

[3] Participating physicians and clinics included Dr. Marcus Conant, UCSF dermatologist, Dr. Edward Becker, dermatologist in private practice, and the PRN Clinic in Oakland which served only herpes-related problems.

sion Scale).

3. The Life Experiences Survey (Sarason et al., 1978) filled out to cover the past six months (to be used in the Residual Stress Measure).

Appointment Number One Through Six

The following data were collected at every appointment in reference to the previous month. Some of the questionnaires described below were sent to the subject prior to each interview to fill out at home in order to reduce the amount of time each subject spent in the interview.

1. The measures of stress (the Life Experiences Scale, the Daily Hassles Scale, the Residual Stress Scale, the Anticipated Life Stress Scale, the Goal Progression Scale, and the Herpes Stress Scale).

2. The measures of stress moderators (the Coping Interview, the Social Interaction Scale, the Profile of Mood States, the Emotion Reexperience scores, and The Mastery Scale).

3. The measures of non-psychological predictors of recurrence (the health habits interview, the Duke-UNC Health Profile, the POMS Fatigue sub-scale, the dates of the menstrual cycle)

The nineteen immunological subjects had a blood sample drawn by a phlebotomist at the time of each monthly interview.

Subjects were asked to return to one of the participating physicians or clinics for documentation of HSV outbreaks when they developed during the six month study period. This process involved a brief physical examination to verify the presence of herpes lesions.

RESULTS

Overall Data Analysis Plan

The data analyses were focused around four primary questions: 1) What are the relationships between the psychosocial variables and the immunological variables? 2) What are the relationships between psychosocial variables and herpes recurrence? 3) What are the relationships between the immune measures and recurrences and among psychological measures, immune measures and recurrences? 4) Do changes in health-related behaviors mediate the relationship between psychological factors and immune and recurrence outcomes?

Two primary approaches were used to answer these questions. The first is a between subjects approach which asks questions of the format: Do subjects who are more stressed over the course of the six month study period demonstrate a more depressed immune system when compared to individuals who are not so stressed over the study period? The second method uses a within subjects approach which asks questions of the format: Are subjects' immune systems more depressed during high stress months as compared to low stress months?

Each predictor variable is hypothesized to have a particular type of relationship to the outcomes studied. There are four types of relationships hypothesized--direct effects on outcome, compounding effects, interactive effects, and mediating effects. Direct effects are significant relationships between predictor and outcome, e.g., increased stress is

predicted to be correlated with decreased immunity. Compounding effects are effects over and above the effects of another variable, e.g., defeat is predicted to have a significant relationship to immunity even when the effects due to stress are removed statistically. Interactive effects involve variables that are hypothesized to moderate the effects of another variable on outcome, e.g., stress is hypothesized to affect immunity when social support is at a low level and not at high social support levels. Thus, social support has an interactive effect with stress on outcome. Mediating effects are effects that act as intermediaries between another variable and outcome, e.g., stress is predicted to affect HSV recurrence because stress depresses immunity and depressed immunity increases the probability of recurrence. Immune change is therefore the mediator in this relationship.

Stress, negative affect and defeat are hypothesized to have direct effects on immunity and HSV outcome. Negative affect and defeat are also hypothesized to influence these outcomes over and above the effect of stress. Social support and coping flexibility are hypothesized to have interactive effects with stress on outcome. Stress is expected to have the greatest effect on outcome when social support and coping flexibility are at a low level. Helper and suppressor T cell changes are hypothesized to mediate the relationship between psychological factors and HSV recurrence. Health habits are hypothesized <u>not</u> to mediate the relationship between psychological factors and outcome.

Between Subjects Approach

In the between subjects approach, the four types of hypothesized relationships will be tested using hierarchical and simultaneous multiple regression correlation (MRC). In hierarchical MRC independent variables are entered into the regression equation in a specified order. The unique effect of each independent variable on the dependent variable can then be tested while excluding the variance shared with other independent variables entered earlier in the equation. In simultaneous MRC, no specified ordering is chosen for variable entry into the regression equation. The unique effect of each independent variable can be tested while excluding the variance shared with all other independent variables in the equation. In both hierarchical and simultaneous MRC, the semi-partial correlation (sr) is a representation of the unique effect of the variable on outcome.

Direct effects will be tested at the first step in a hierarchical MRC (or, equivalently, with a Pearson correlation coefficient). A significant simple correlation is expected between outcome and each of the variables with hypothesized direct effects. Compounding effects will be tested using simultaneous MRC. It is expected that the variable with hypothesized compounding effects over stress will have a significant relationship to outcome even when stress is included in the equation and therefore the variance attributable to stress is excluded. This procedure is equivalent to including the compounding variable as a second step in a hierarchical MRC after stress but has the added advantage of providing the unique effects of stress over the compounding variable. In this way, the two variables can be compared to one another in their relationship to outcome.

Interactive effects will be tested at the third step of a hierarchical MRC. For example, stress will be entered at the first step, social support will be entered at the second step, and the interaction between stress and social support will be entered at the third step. It is hypothesized that this interaction third step will be significant. If an interaction is suggested, then the direction of the interaction will be tested.

Mediating effects will be tested using simultaneous MRC including the mediating variable as well as the variable being mediated. For example, the number of helper T cells and stress level will be entered into an MRC equation predicting HSV recurrence. It is hypothesized that while the simple correlation between helper T cells and recurrence and between stress and recurrence would be significant, their semi-partial correlations (when both are in the equation) would not be significant; the semi-partial correlations of one or both of the independent variables should be greatly reduced relative to the simple correlations also. A greatly diminished semi-partial correlation would suggest that much of the variance accounted for in the outcome is shared between the two variables, indicating mediating effects. If, instead, both variables maintain high correlations with recurrence (relative to the simple correlation) it would indicate that the variance that stress accounts for in HSV recurrence is separate from the variance that helper T cells account for in recurrence suggesting that no mediation occurs.

Each of the psychosocial predictor variables entered into the MRCs for the between subjects analyses was the average of the subject's values on that variable over the six month study period. For example,

the social support variable that was used in the between subject's analyses for a given subject was the average of that subject's six monthly values for social support satisfaction. If data were unavailable on a given variable for a month period then the subjects' values for the remaining five months were averaged.

Within Subjects Approach

There are no accepted methods for analyzing the relationship between two variables that are measured over time (unless the number of measurement periods is quite large and a time series approach is appropriate). Therefore the following approaches were devised to analyze these data.

First, a correlated t-test procedure was performed. For each subject the month in which the subject reports the maximum stress is located as well as the month in which the minimum stress is reported. These two months are compared in terms of outcome. For example, are there fewer helper T cells measured at the highest stress month in comparison to the lowest stress month? Are there more HSV recurrences in the month following the high stress month?[4] This type of analysis is carried out for each of the psychosocial variables predicted to have a

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[4] A month long follow-up period is used for all within subjects analyses involving HSV recrudescence as the dependent variable. Thus, stress averaged by the subject over the previous month is used as a predictor of outbreaks in the following month. The relationship between life changes that occur during the month and recurrences that occur during the same month cannot be evaluated since the reporting of events takes place at the end of the month after the subject is aware of whether or not they have had a recurrence. This report of events could be confounded by the recurrence information. Therefore the stress assessment provided at one interview is used as a predictor of the outbreaks during the subsequent month.

direct effect on immunity. In order to test for interactive effects, the subjects are divided into two groups, e.g., those demonstrating high social support for the study period and those reporting low support. The correlated t-tests are then run separately for each group comparing high and low months on stress for differences in the outcomes.

Second, a correlated t-test procedure was used to determine if differences in the psychological factors exist in the months prior to a recurrence as compared to the months prior to a recurrence-free period in those subjects with at least one recurrence during the study period. This approach is different from that used above, in which differences in recurrences are evaluated when high and low levels of the psychological factors are compared.[5]

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[5] In addition to the correlated t-test procedures detailed above a repeated measures analysis of variance procedure was also used on these data. The psychological predictor variables were included as covariates. Each covariate at each time point was paired with the dependent variable (e.g., immunity) at that time point. In the covariance model, the dependent variable has a multiple linear regression on the covariate. The strength of the relationship between the covariate and the dependent variable is represented by the regression coefficient B. The coefficient is a weighted average of the regression coefficients of the dependent variable on the covariate estimated separately for each group (if there are grouping factors). If more than one covariate is included in the analysis the regression values computed are similar to those in a simultaneous rather than a hierarchical regression. In other words, the unique variation in the dependent variable for each covariate in relationship to all other covariates is analyzed rather than the unique variation in relationship to only those variables entered into the equation first. No significant relationships were found between psychological factors and outcome using this approach, so these data will not be described further.

Variable Selection and Creation of Composite Scores

Composite stress score. In order to test the hypotheses regarding stress, the multiple stress measures were tested to determine whether they appeared to represent an overall stress dimension. The six individual stress scores (from the Life Experiences Survey, the Daily Hassles Scale, the Anticipated Life Stress Scale, the Residual Stress Scale, the Herpes Stress Scale, and the Goal Progression Scale) were included in a factor analysis to determine if they could be combined into one score or appeared to have more than one underlying dimension. Principal factoring with iteration was chosen using an oblique rotation to allow for correlations among the factors. A two factor solution was produced initially with the first factor containing a much larger percent of the variance than the second (eigen value for factor 1 was 2.18, for factor 2 was .76). As a result, the procedure was rerun requesting a one factor solution. The resulting factor loadings are shown in Table 1. All the stress measures loaded highly on the factor except goal progression. This factor pattern suggests that goal progression is not measuring a construct similar to the other five stress measures. As a result of this factor analysis, the first five measures were combined into an overall stress score and goal progression was analyzed separately. Each of the five stress scores was transformed into a z score (since each used a very different scale) and combined. An overall stress score was obtained for each month and an average computed for the entire study period.

TABLE 1

Factor Loadings for Six Stress Scores

Variable Name[1]	Factor Loading[2]
Life Experiences Scale Score	.64
Hassles Stress Score	.64
Anticipated Life Stress Scale	.74
Residual Stress Score	.77
Herpes Stress Score	.50
Goal Progression Score	-.11

[1] All variables are averages of monthly scores

[2] Based on principal factoring with iteraction

(N=36)

Composite defeat score. Defeat was hypothesized to consist of depression and the presence of feelings of helplessness in relationship to life situations. Three scales were administered to tap this construct: the POMS depression sub-scale, Pearlin's Mastery scale (which contains seven items), and the two helplessness experience scores. These scores and the individual items on the Mastery Scale were entered into a factor analysis to determine if they represented a single dimension and could be reasonably combined. The initial analysis produced a three factor solution but one of the factors had a small eigen value (.77) relative to the other two factors (5.82 and 1.46). As a result,

the procedure was re-run requesting a two factor solution. The factor loadings, as shown on Table 2, indicate that the second factor closely approximates the hypothesized defeat dimension (when a .35 cutoff is used). This factor includes the POMS depression scale, the helplessness experience scores and the items of the Mastery scale which relate to helplessness (items 1,6 and 7). The first factor, on the other hand, appears to measure depression and hopelessness. Since it was hypothesized that a depression-helplessness construct would predict immunological and recurrence outcomes, the values for the variables in the second factor were transformed into z scores and combined to make up the defeat composite score.

Emotion experience scores. The six emotion experience scores (anger, sadness and happiness experience and anger, sadness and happiness re-experience) were originally intended to be used as additional measures of depression and hostility. Specifically, it was assumed that high scores on sadness and low scores on happiness would reflect depressive affect and high scores on anger would suggest hostility. Table 3 indicates that these scores do not in general correlate significantly with the ratings of anxiety, depression and hostility from the POMS. Also the average autocorrelation (Table 4) for the depression, hostility, and anxiety scores over the six measurement periods (the average of the correlations between the score one month and the same score the next month) are quite high (ranging from .55 to.67) while the autocorrelations for the emotion experience scores are much lower (ranging from .18 to .39). The autocorrelations suggest that POMS scores are quite consistent over time in many of the subjects

TABLE 2

Factor Loadings for Defeat Items

Variable Name[1]	Factor Loadings[2]	
	Factor 1	Factor 2
POMS Depression Sub-scale	.23	.71
Mastery Scale Item 1 (little control over things that happen)	.55	.59
Mastery Scale Item 2 (no way to solve problems)	.78	.17
Mastery Scale Item 3 (can do just about anything)	-.82	-.32
Mastery Scale Item 4 (little to do to change important things)	.76	.27
Mastery Scale Item 5 (what happens in future depends on me)	-.64	-.07
Mastery Scale Item 6 (feel helpless dealing with problems)	.47	.69
Mastery Scale Item 7 (feeling pushed around)	.47	.39
Helplessness Experience Score	-.27	.70
Helplessness Re-Experience Score	.13	.35

[1] All variables are averages of monthly scores

[2] Based on principal factoring with interation

(N=36)

while the reported emotion experience scores are not. The low correlations between the POMS and emotion scores suggest that the emotion scores may be measuring an aspect of affective experience different from the POMS scores. Based on these data it was decided to evaluate the relationship between each of these scores and the outcome measures on an exploratory basis rather than combine them as originally intended. These results will then be compared to the relationships between the POMS values and outcome.

TABLE 3

Correlations Between Average Mood and Emotion Experience Scores

	Anxiety	Depression	Hostility
Intensity During Event			
Happiness	.04	-.15	-.06
Anger	.25	.15	.22
Sadness	.34*	.28	.20
Intensity During Recall			
Happiness	-.20	-.29*	-.24
Anger	.20	.33*	.26
Sadness	-.05	.20	.08

* $p<.05$

(n=34)

TABLE 4

Average Autocorrelations of Monthly Mood and Emotion Experience Scores

Mood (n=36)	auto r
Anxiety	.57
Depression	.55
Hostility	.67
Intensity During Event (n=34)	
Happiness	.33
Anger	.30
Sadness	.39
Intensity During Recall (n=34)	
Happiness	.19
Anger	.18
Sadness	.31

Measurement of Herpes Recurrence

The recurrence outcome was measured in two ways. First, the number of outbreaks during the month period following the interview was computed. This number included both verified and unverified recurrences. Second, the number of days from the interview to the first day of the next recurrence was calculated. This second measure was included to determine if a high level of stress during a month period could influence the time to the next recurrence as well as the likelihood of an outbreak.

Preliminary Analyses

It is important to determine whether or not the 19 immunological subjects differ significantly from the 17 subjects who did not have blood drawn. Table 5 displays the demographic and illness history characteristics for the group as a whole and for the immunological sub-group. The immunology and the non-immunology groups do not differ significantly in age, sex, race, years of education, marital status or whether they believe stress is a causative factor in their own recurrences. However, the non-immunological group had genital herpes for significantly longer than did the immunological group.

The relationship between the demographic characteristics and illness history variables and the average values for the outcome measures (helper T cells, suppressor T cells, HSV recurrences and average time to the next recurrence) was then tested using Pearson correlations and analyses of variance (for categorical variables). Race and "Stress as HSV cause" were not tested because there were too few subjects who were not caucacian and who did not see stress as a possible cause of recurrence for meaningful comparisons to be made. The only characteristics significantly related to either the immunological or herpes recurrence outcomes were marital status and number of recurrences in the past six months. Married and separated individuals appear to have fewer suppressor T cells than divorced and single individuals (F=5.933, p=.007). And the number of recurrences in the six month period prior to beginning the study predicts the number of recurrences during the study period (r=.58, p=.000) and the average time to the next recurrence (r=-.53, p=.000).

TABLE 5

Demographic Characteristics of Entire Sample and Immunological Sub-Group

	Entire Sample (N=36)	Immunological Sub-group (n=19)
Age	M = 33.4 SD = 9.5	30.5 6.3
Years of Education	M = 15.9 SD = 2.3	16.1 2.4
Years With Genital HSV*	M = 5.9 SD = 4.9	4.3 3.7
Number Recurrences in Prior 6 Months	M = 4.8 SD = 3.2	4.7 3.0
Sex	Female = 30 Male = 6	18 1
Race	Caucacian = 31 Black = 1 Oriental = 2 Spanish = 2	15 1 1 2
Marital Status	Single = 19 Married = 4 Separated = 3 Divorced = 8 Widowed = 1	11 2 2 4 0
Stress Believed To Be A Cause of Own HSV Recurrences	Yes = 30 No = 2 Unsure = 4	15 2 2

* $p<.05$

Finally, the reliability of the method of coding coping modes from the interview was calculated. Approximately one-third of the coping interviews were coded by the investigator and two-thirds were coded by an independent coder who was trained extensively in the accurate use of the coding manual. Both raters coded a sample of 20 interviews independently as a test of the interrater reliability of the rating scheme. An 88% agreement between ratings was found across all the modes.

The means, standard deviations and ranges for the primary predictor and primary outcome variables are presented in Table 6.

TABLE 6

Primary Predictor and Outcome Variables[1]: Means, Standard Deviations, and Ranges

	Mean	SD	Range
Primary Predictors			
Composite Stress	.04	.63	-1.21 - 1.94
Depression	13.59	8.91	.33 - 39.33
Hostility	12.77	8.50	1.33 - 42.40
Anxiety	9.56	5.51	-2.17 - 21.25
Coping Flexibility	6.34	.90	3.67 - 7.67
Support Satisfaction	23.21	4.79	9.75 - 31.83
Composite Defeat	-.01	.51	-.94 - 1.33
Primary Outcome Variables			
HSV Recurrence	2.56	1.83	0 - 6
Helper T Cells	46.37	4.92	37.67 - 56.33
Suppressor T Cells	25.44	5.17	17.33 - 33.00

[1] all scores are averages over the six months

Major Data Analyses

Psychological Factors and Immunity: Between Subjects Approach

Stress and immunity. Stress was hypothesized to have a direct effect on both helper and suppressor T cells. The average composite stress score was found to be highly correlated with the average proportion of helper T cells (r=-.47,p=.02) and with the average proporrtion of suppressor T cells (r=-.41,p=.04). In both cases, the more stress over the study period the fewer T cells were evident in the peripheral blood. Figure 1 illustrates the size of the difference in T cell numbers depending on level of stress (divided into three equal subgroups). It appears that for helper T cells, there is an 8% difference between the subjects who report high levels of stress and the subjects who report low levels of stress.

The goal progression score, which was not included in the overall measure of stress, was not significantly related to either helper or suppressor T cells but there was a trend suggesting that greater satisfaction with goal progression was associated with more suppressor T cells (r=.32,p=.08).

In order to explore whether or not specific stress measures within the composite stress score accounted for the relationship between this score and immunity, the simple correlations between each of the five stress scores and helper and suppressor T cells were computed. Table 7 indicates that anticipated stress and residual stress had significant correlations with helper T cells (r=-.50, p=.01 and r=-.51, p=.01, re-

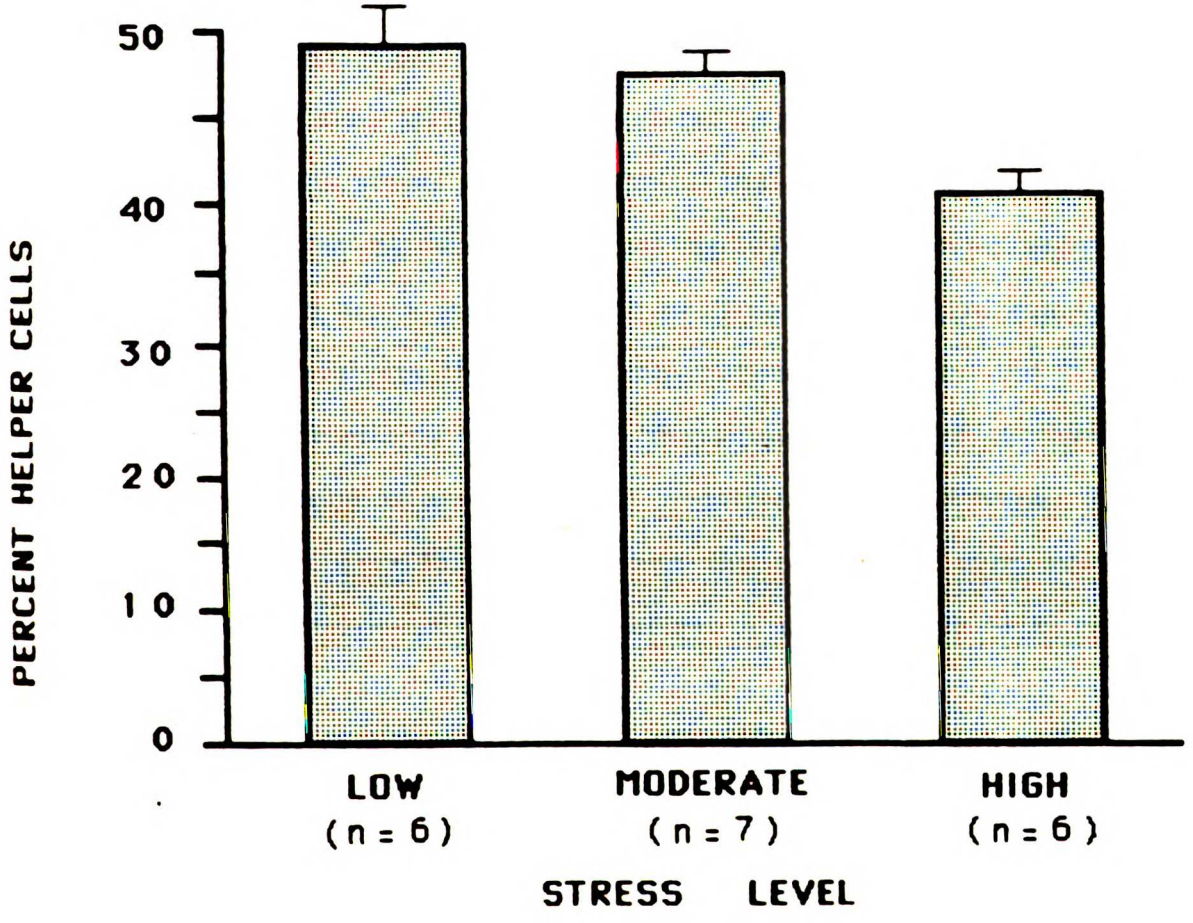


Figure 1: Average Proportion of Helper T Cells at Low, Moderate, and High Stress Levels

spectively) while life event stress and herpes stress had close to significant relationships (r=-.36, p=.07 and r=-.35, p=.07, respectively). These stress scales taken individually did not have significant relationships to the average number of suppressor T cells, however. Hassles Stress, on the other hand, was significantly related to the number of suppressor T cells (r=-.47, p=.02) but not significantly related to the number of helper T cells (r=-.15).

These data indicate that the current life event score (LES) appears to be less strongly related to immunity than the residual and anticipated stress scores. Since the anticipated and residual stressors mentioned by subjects almost exclusively involved negative events and the LES score included both positive and negative events, it was decided to evaluate the relationship between immunity and the LES score derived from only the events the subject reported as "bad" events. The correlation between the LES negative score and helper T cells was significant (r=-.45, p=.03) while the correlation with suppressor T cells was not (r=-.26). Thus, helper T cells appear to vary in relationship to anticipated and residual stressors (predominantly negative events) and in relationship to current negative life changes. Suppressor T cells appear to vary in relationship to chronic ongoing stressful events ("hassles").

Negative mood and immunity. Anxiety, depression and hostility were hypothesized to have direct effects on immunity. The simple correlations between each of these three POMS sub-scale values and immunity are presented in Table 8. All three of the affects have large and significant correlations with suppressor T cells and small and insignificant

TABLE 7

Correlations Between Average Stress Scores and Immunity

	Helper T Cells	Suppressor T Cells
Life Experience Score	-.36	-.30
Hassles Stress Score	-.15	-.47*
Anticipated Life Stress Score	-.50**	-.22
Residual Stress Score	-.51**	-.25
Herpes Stress Score	-.35	-.18
Goal Progression Score	.08	.32

*p < .05
**p < .01

(n=19)

correlations with helper T cells. The direction of the correlations between affect and suppressor T cells are all negative suggesting that the greater the negative mood the fewer suppressor T cells in the peripheral blood. Figures 2, 3, and 4 display the degree of differences in the suppressor T cell proportion depending on level of negative mood (divided into three equal subgroups). There appears to be a 5% change from low to high anxiety, a 7% change from low to high hostility, and a 4% change from low to high depression.

TABLE 8

Correlations Between Average Mood and Immunity

	Helper T Cells	Suppressor T Cells
Anxiety	-.16	-.47*
Depression	-.07	-.49*
Hostility	-.07	-.57**

*p < .05
**p < .01

(n=19)

Negative mood was also hypothesized to have compounding effects over stress on immunity. Each mood was entered into a simultaneous MRC along with stress. Table 9 displays the MRC tables for these analyses. Consistently across the three moods, stress accounts for ap-

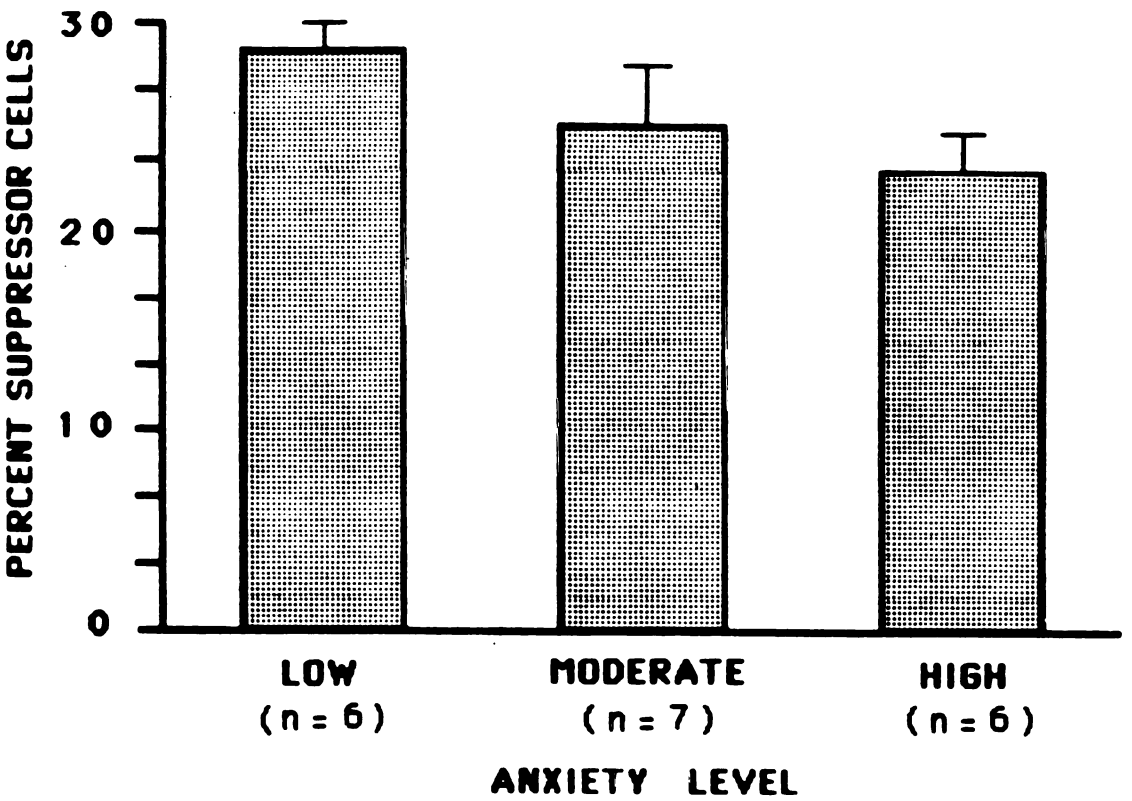


Figure 2: Average Proportion of Suppressor T Cells at Low, Moderate and High Anxiety Levels

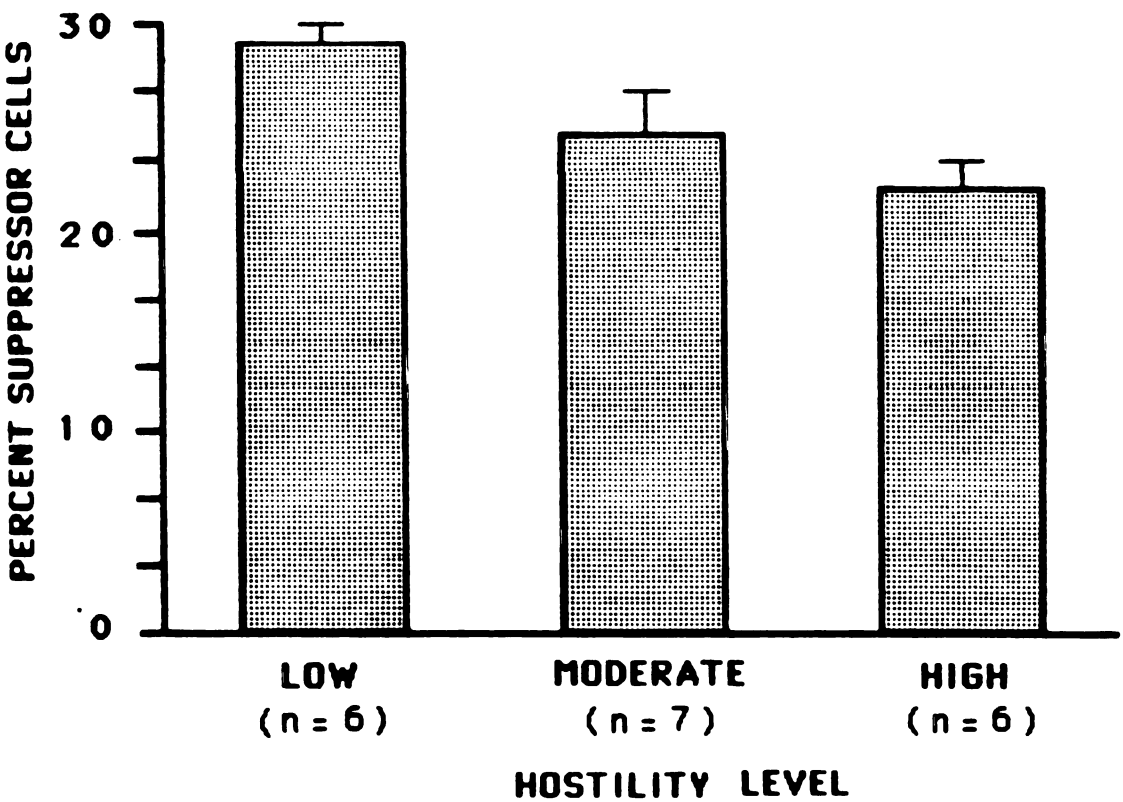


Figure 3: Average Proportion of Suppressor T Cells at Low, Moderate and High Hostility Levels

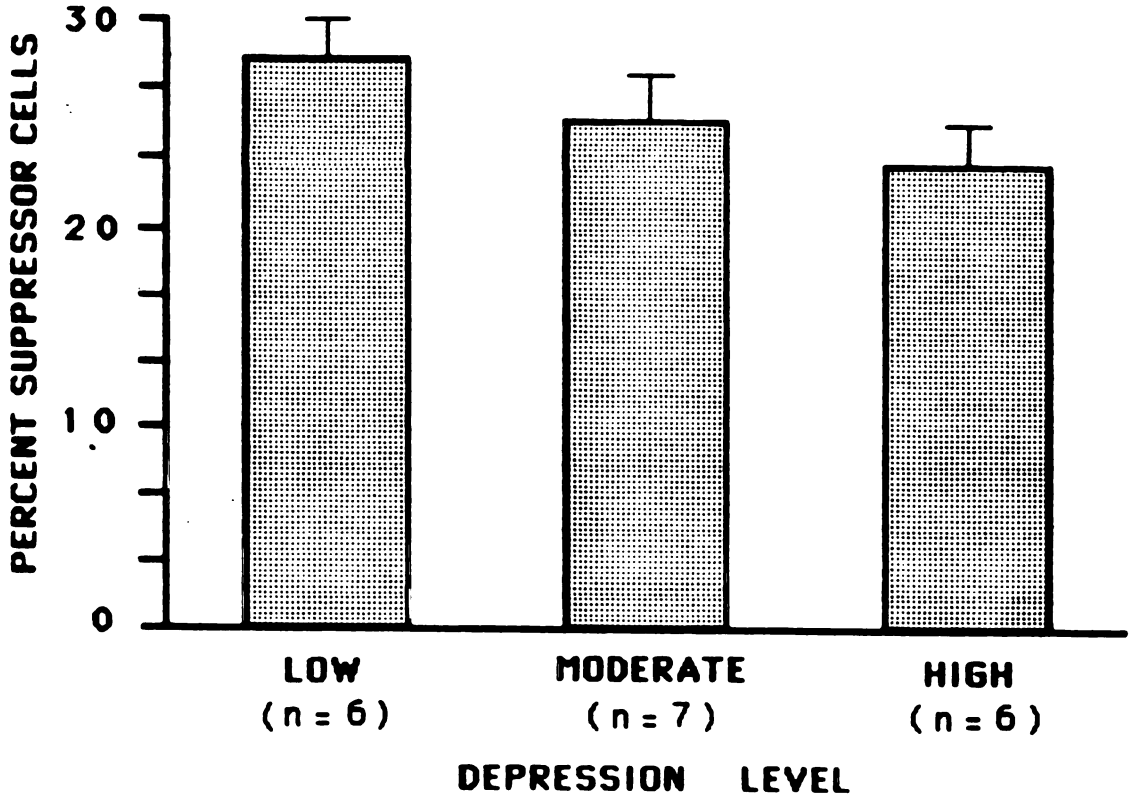


Figure 4: Average Proportion of Suppressor T Cells at Low, Moderate and High Depression Levels

proximately twice the unique variance in helper T cells that mood does (as indicated by the semi-partial correlations). For suppressor T cells, in contrast, stress accounts for very little variance in comparison to mood. Although mood accounts for the majority of the variance in these analyses, none of the moods account for significant independent variance when the effects of stress are removed, although the relationship between hostility and suppressor T cells approaches significance ($p=.07$). Thus mood does not appear to have a compounding effect over stress on immunity. These data suggest that hostility may make a contribution to T cell variability that is more distinct from the effects of stress than the contributions of anxiety and depression.

Stress, mood and immunity. It appears from these data that the T cell subsets are differentially responding to psychosocial factors. Stress appears to be the major predictor of helper T cells and makes little unique contribution to suppressor T cells. Mood is the major predictor of suppressor T cells and makes a small but insignificant contribution to helper T cell variability. These differential patterns of mood and stress correlations are interesting given the high inter-correlations among the stress and mood variables (Table 10).

The hassles stress score is the only stress measure which appears to diverge from the pattern above since it is correlated with suppressor T cells and not helper T cells. This divergence may result from the high intercorrelation between hassles and anxiety which has been suggested in the literature (see Dohrehwend, Dohrenwend, Dodson, & Shrout, 1984). In other words, the hassles score may be highly correlated with suppressor T cells because it is actually measuring anxiety.

TABLE 9

Simultaneous MRCs Predicting Immunity With Average Stress and Mood Scores

	r	sr	t	p
Dependent Variable = Helper T Cells				
Composite Stress Score	-.47	-.56	-2.74	.02
Anxiety	-.16	.33	1.64	.12
Dependent Variable = Suppressor T Cells				
Composite Stress Score	-.41	-.06	-.28	.79
Anxiety	-.47	-.24	-1.14	.27
Dependent Variable = Helper T Cells				
Composite Stress Score	-.47	-.56	-2.68	.02
Depression	-.07	.30	1.44	.17
Dependent Variable = Suppressor T Cells				
Composite Stress Score	-.41	-.12	-.55	.59
Depression	-.49	-.30	-1.41	.18
Dependent Variable = Helper T Cells				
Composite Stress Score	-.47	-.58	-2.83	.01
Hostility	-.07	.34	1.65	.19
Dependent Variable = Suppressor T Cells				
Composite Stress Score	-.41	-.04	- .17	.87
Hostility	-.57	-.40	-1.94	.07

(n=19)

TABLE 10

Intercorrelations Among Average Stress and Mood Scores

	Anxiety	Depression	Hostility
Composite Stress Score	.62***	.37*	.75***
Life Experiences Score	.33*	.13	.48***
Hassles Stress Score	.62***	.49***	.59***
Anticipated Life Stress Score	.45***	.38**	.66***
Residual Stress Score	.41**	.17	.57***
Herpes Stress Score	.44***	.34*	.43***
Goal Progression Score	-.22	-.46***	-.20

* $p < .05$
** $p < .01$
*** $p < .005$

(N=36)

The data indicate that the hassles score is significantly correlated with the anxiety measure (r=.62, p=.000) and this correlation is stronger than the correlation between anxiety and the other stress measures (e.g., LES r=.33, anticipated stress r=.45). Also, when hassles and anxiety are included in a simultaneous MRC predicting suppressor T cells (Table 11) the strength of the semi-partial correlations between each variable and suppressor T cells is greatly diminished and no longer significant, suggesting that they share a great deal of common variance. Thus it is possible that the relationship between the hassles score and suppressor T cells is a function of the relationship between anxiety and suppressor T cells.

TABLE 11

Simultaneous MRC Predicting Suppressor T Cells with Average Hassles Score and Anxiety

	r	sr	t	p
Hassles Score	-.47	-.17	-.765	.46
Anxiety	-.47	-.17	-.769	.45

(n=19)

Since the possibility of a confounded relationship between anxiety and the Hassles score is currently debated in the literature (see Dohrehwend et al., 1984 and Lazarus, DeLongis, Folkman, & Gruen, 1985)

it seemed important to explore this issue more fully by redoing the analyses described above using a simple count of hassles (i.e., the number of Hassle scale items checked as having occurred) rather than the full Hassles score. The Hassles score is weighted by the level of upset and worry that each item causes and it is possible that this weighting contributes to the score's high correlation with anxiety. Also, recent studies with the Hassles Scale have used the frequency of events occurred rather than the score (e.g., DeLongis, 1985).

Consistent with the previously described findings on the Hassles score, the Hassles event frequency does not correlate with helper T cells and has a significant correlation with suppressor T cells (r=-.40, p=.05). When the Hassles event frequency is entered into a simultaneous regression with anxiety predicting suppressor T cells (Table 12), we find that again there is a great deal of shared variance with the hassles' semi-partial correlation reduced to -.12. Thus there appears to be an overlapping relationship between anxiety and the hassles score whether the analysis uses a score based on a frequency count or a score weighted by the level of upset each item generates. used.

Emotion experience scores and immunity. The six emotional experience scores were correlated with immunity as an exploratory test of the relationship between this measure of affective response and immune response. Table 13 indicates that these scores are uncorrelated with helper T cells. However, happiness reported to be experienced during a positive event and happiness felt during the recall of the event are highly and significantly related to suppressor T cells (r=.44, p=.03 r=.47,p=.02 respectively). The higher the happiness ratings the more suppressor T cells present.

TABLE 12

Simultaneous MRC Predicting Suppressor T Cells with Average Hassles Event Frequency and Anxiety

	r	sr	t	p
Hassles Events	-.40	-.12	-.57	.58
Anxiety	-.47	-.28	-1.20	.21

(n=19)

In order to determine the extent to which these ratings are actually measuring the absence of negative mood and are related to suppressor T cells as a result, happiness experience ratings, mood ratings and their interaction were entered into a hierarchical MRC in that order to predict both helper and suppressor T cells[6] (Table 14). These analyses determine if the happiness ratings are significantly related to immunity when mood variation is removed, and whether or not the emotion ratings and mood ratings interact.

The happiness ratings were not found to add significant variance in suppressor T cells over the effects of mood. The happiness ratings also did not add meaningful variation in helper T cells over mood but, unexpectedly, the interaction between mood and the happiness ratings accounted for an extremely large percent of variance in helper T cells (ranging from 28% to 50%). It appears that happiness ratings are only

[6] Only MRCs for "happiness during recall" are displayed in Table 14; "happiness during event" MRCs are very similar.

TABLE 13

Correlations Between Average Emotional Experience Scores and Immunity

	Helper T Cells	Suppressor T Cells
Intensity During Event		
Happiness	-.30	.44*
Anger	-.11	.02
Sadness	-.14	.16
Intensity During Recall		
Happiness	.06	.47*
Anger	-.16	.00
Sadness	-.19	.16

* $p < .05$

(n=18)

TABLE 14

Hierarchical MRCs Predicting Immunity With Average Mood, Happiness During Recall and Mood X Happiness Interaction

	Multiple R	R^2	R^2 change	p
Dependent Variable = Helper T Cells				
Hostility	.06	.004		.81
Happiness Rating	.07	.005	.001	.90
Interaction	.71	.500	.500	.00
Dependent Variable = Suppressor T Cells				
Hostility	.60	.370		.01
Happiness Rating	.63	.400	.030	.38
Interaction	.63	.400	.002	.86
Dependent Variable = Helper T Cells				
Anxiety	.15	.020		.54
Happiness Rating	.16	.020	.001	.91
Interaction	.57	.330	.300	.03
Dependent Variable = Suppressor T Cells				
Anxiety	.50	.250		.04
Happiness Rating	.63	.390	.150	.08
Interaction	.64	.410	.010	.62
Dependent Variable = Helper T Cells				
Depression	.06	.004		.80
Happiness Rating	.07	.005	.001	.88
Interaction	.60	.360	.360	.02
Dependent Variable = Suppressor T Cells				
Depression	.55	.300		.02
Happiness Rating	.61	.380	.070	.20
Interaction	.63	.390	.020	.56

(n=18)

related to helper T cells at particular levels of negative mood.

In order to determine the direction of the interaction, subjects were split into groups, above and below the median on each negative mood. Correlations between the happiness ratings and helper T cells were computed for each group separately and are displayed in Table 15. Again, unexpectedly, the subjects with high negative mood had significant negative correlations between happiness ratings and helper T cells. In other words, the happier they reported themselves to be the lower the number of helper T cells. Subjects who report low negative mood display a significant positive correlation between happiness and helper T cells. The happier they reported themselves to be the more helper T cells are present.

In order to test whether or not this effect holds true for emotional reactions in general and is not specific to happiness ratings, the four other emotion variables were correlated with immunological outcomes for the high and low mood sub-groups. No significant correlations were found between the other emotion ratings and immunity in either the high or low mood groups.

Summarizing the mood, emotion and stress findings, it appears that mood contributes unique variance in suppressor T cells that is distinct from stress. Stress does not contribute to the variation in suppressor T cells uniquely when mood is also considered. Happiness ratings are also significantly related to suppressor T cells. Both stress and mood contribute to the variance in helper T cells but mood is only significantly related to these T cell numbers in interaction with the happiness experience scores.

TABLE 15

Correlations Between Average Happiness Ratings and Helper T Cells for High and Low Negative Mood Groups

	Above Median Hostility	Below Median Hostility
Happiness During Event	-.77	.35
Happiness During Recall	-.59	.63

	Above Median Anxiety	Below Median Anxiety
Happiness During Event	-.87	.61
Happiness During Recall	-.66	.72

	Above Median Depression	Below Median Depression
Happiness During Event	-.66	.64
Happiness During Recall	-.45	.77

(n=18)

Defeat and immunity. Defeat was hypothesized to have a direct relationship to immunity. The simple correlation between the defeat composite score and helper T cells was found to be non-significant (r=-.17). Defeat had a significant relationship to suppressor T cells (r=-.41, p=.04) with fewer suppressor T cells evident as defeat increased.

Defeat was also hypothesized to have a compounding effect on immunity over and above the effects of stress. Table 16 displays the simultaneous MRC tables with defeat and stress. Defeat adds almost no variance to helper T cells when stress is included but stress and defeat account for approximately equal variance in suppressor T cells. However neither defeat nor stress accounts for significant variance when the other is included in the equation. Therefore defeat does not have a significant compounding effect on suppressor T cells over the effects of stress.

Social support satisfaction and immunity. Social support satisfaction was hypothesized to have an interactive effect with stress on immunity. Social support was entered into a hierarchical MRC at the second step after stress, and the interaction between stress and social support (stress x social support) was entered at the third step. It was hypothesized that the interaction term would be significantly related to immunity. Table 17 displays the multiple regression tables for the analysis with helper T cells and the analysis with suppressor T cells. For helper T cells, stress accounts for 23% of the variance and social support adds 4% over and above the effects of stress. The interaction term adds 9% which is non-significant. For suppressor T cells, stress

TABLE 16

Simultaneous MRCs Predicting Immunity With Average Stress and Defeat

	r	sr	t	p
Dependent Variable = Helper T Cells				
Composite Stress		-.47	-.45	-2.04 .06
Defeat	-.17	.08	.37	.72
Dependent Variable = Suppressor T Cells				
Composite Stress		-.41	-.23	-1.03 .32
Defeat	-.41	-.23	-1.04	.32

(n=19)

accounts for 16% of the variance, social support adds 9% and the interaction adds a nonsignificant 2%. Thus, social support does not appear to significantly buffer the effects of stress on either helper or suppressor T cells.

Despite an insignificant interaction term, the percent of variance the interaction adds to stress in helper T cells may be a meaningful amount given that previous research on the buffering effects of social support has rested on much smaller effect sizes. Therefore to understand more fully the nature of the relationships among stress, social support and T cells, the subjects were divided into two groups, those with above the median social support (the high social support group)

TABLE 17

Hierarchical MRCs Predicting Immunity With Average Stress, Social Support and Stress X Social Support Interaction

	Multiple R	R^2	R^2 Change	p
Dependent Variable = Helper T Cells				
Composite Stress Score	.48	.23		.04
Social Support	.51	.26	.04	.39
Interaction	.59	.35	.09	.18
Dependent Variable = Suppressor T Cells				
Composite Stress Score	.40	.16		.09
Social Support	.50	.25	.09	.19
Interaction	.52	.27	.02	.53

(n=19)

and those with below the median social support (the low social support group). Correlations between stress and T cells were computed separately for the high and low social support groups (Table 18). The data indicate a clear interaction; however, the direction of the interaction is the opposite of that found in the social support literature. At low social support, stress appears to have no significant effect on the number of helper and suppressor T cells. However, at high social support there is a strong negative correlation between stress and helper T cells as well as between stress and suppressor T cells. For individuals who were highly satisfied with the support they receive over the course of the study, increased stress corresponded with fewer helper and suppressor T cells. These correlations directly contradict the literature which indicates that when individuals have high levels of social support, stress is <u>not</u> associated with deleterious health effects.

It is interesting to recall that there were differences in suppressor T cell numbers depending on marital status, with married and separated individuals having fewer suppressor T cells over the study period in comparison to divorced and single individuals. These differences do not appear to be a function of current living situation since there were no significant differences in suppressor T cell numbers depending on living situation, e.g., living alone, living with roommate, living with partner, etc. These differences also do not appear to be attributable to differences in the ages of the married/separated group and the divorced/single group since there was not a significant correlation between age and suppressor T cells. Thus, it is not clear why differences in suppressor T cell percantages exist between these groups.

TABLE 18

Correlations Between Average Stress and Immunity for High and Low Social Support Groups

Above Median Social Support	
Helper T Cells	Suppressor T Cells
-.70**	-.67*
Below Median Social Support	
Helper T Cells	Suppressor T Cells
-.25	.26

* $p < .05$
** $p < .01$

(n=19)

Coping flexibility and immunity. Coping flexibility was hypothesized to have an interactive effect with stress on immunity. Coping flexibility was entered into a hierarchical MRC after stress and the interaction between coping flexibility and stress was entered at the third step. It was hypothesized that this third step would be significant. Table 19 displays the multiple regression tables for the helper and the suppressor T cell analyses. Coping flexibility adds 2% of the variance in helper T cells over and above stress and the interaction of coping and stress adds no variance. Coping flexibility adds 6% of the variance in suppressor T cells over and above stress, and the interaction adds a

non-significant 4%. Thus, Coping flexibility does not appear to significantly buffer the effects of stress on either helper or suppressor T cells.

In order to explore the relationship of coping flexibility to other variables measured, simple correlations were computed (Table 20). These data suggest that individuals with greater coping flexibility are in general somewhat more stressed and more anxious. They are not significantly different on other mood or defeat measures nor on their satisfaction with social support.

TABLE 19

Hierarchical MRCs Predicting Immunity With Average Stress, Coping Flexibility, and Stress X Coping Flexibility Interaction

	Multiple R	R^2	R^2 Change	p
Dependent Variable = Helper T Cells				
Composite Stress Score	.48	.23		.04
Coping Flexibility	.49	.24	.02	.59
Interaction	.49	.24	.00	.98
Dependent Variable = Suppressor T Cells				
Composite Stress Score	.40	.16		.09
Coping Flexibility	.48	.23	.06	.27
Interaction	.52	.27	.04	.36

(n=19)

TABLE 20

Correlations Between Average Coping Flexibility and Other Psychosocial Variables

	Coping Flexibility
Stress Composite Score	.27*
Life Experiences Score	.26
Hassles Score	.26
Anticipated Life Stress Score	.31*
Residual Stress Score	.17
Herpes Stress Score	.12
Goal Progression	-.06
Hostility	.12
Anxiety	.31*
Depression	.13
Defeat	.13
Social Support Satisfaction	.04

* $p < .05$

(N=36)

Psychological Factors and Immunity: Within Subjects Approach

Direct effects on immunity. Correlated t-tests were used to test for within subjects effects on the immune measures. Using this procedure, high and low stress months were compare for differences in immunity as were the high and low months for each of the other psychological variables with hypothesized direct effects on immunity. Using the correlat-

ed t-test procedure, results indicated that highest stress, negative mood or defeat months were not more likely to involve different T cell proportions than lowest stress, negative mood or defeat months. However there was a trend suggesting that there may have been more helper and suppressor T cells during months when the subject could most easily re-experience sadness (helper T cells: $t(17)=1.7$, $p=.09$, suppressor T cells: $t(17)=1.74$, $p=.10$).

Compounding effects of hostility, depression, anxiety and defeat over stress were not tested since they had no direct effects.

Interactive effects on immunity. To test for interactive effects of social support with stress, correlated t-tests evaluating differences in immunity at the highest stress month in comparison to the lowest stress month were conducted for the high support group and the low support groups separately. There were no significant relationships in either group. The procedure was repeated for coping flexibility and no significant relationships were found between stress and immunity in either the high coping flexibility or the low flexibility group.

Psychosocial Factors and HSV Recurrence: Between Subjects Approach

Stress and HSV recurrence. Overall stress over the study period did not have a significant correlation with either of the two herpes recurrence measures: the total number of recurrences over the six months or the average time to the next recurrence. Goal progression also did not have a significant correlation with either outcome.

In an exploratory analysis, the five individual stress scores were correlated with the HSV outcomes. Interestingly, residual stress was negatively correlated with the total number of recurrences over the study period (r=-.28,p=.05) and with greater average time to the next recurrence (r=.32, p=.03). The more residual stress, the fewer recurrences and the longer average time to the next recurrence. There was a trend suggesting that increased anticipated stress corresponded with more time to the next recurrence (r=.23, p=.09)

Affect and HSV recurrence. Average hostility, anxiety and depression over the six month period were unrelated to either the total number of recurrences or the average time to recurrence.

The six emotion experience scores were unrelated to the number of recurrences over the study period. However, the experience of happy feelings and sad feelings appear to be related to the average time to the next recurrence. The more happiness felt during a positive event and the more sadness experienced during a sad event, the longer the average time before another recurrence (r=.36,p=.02, r=.34, p=.02 respectively). The sadness felt as the event is recalled had a close to significant relationship to time to recurrence (r=.26,p=.07).

Defeat and HSV recurrence. The composite defeat score was unrelated to either measure of HSV recurrence.

Social support and HSV recurrence. The interactive effects of stress and social support were tested with both HSV outcomes using hierarchical MRC. The interaction step accounted for almost no variance in both outcomes.

Coping flexibility and HSV recurrence. The interactive effect of stress and coping flexibility was tested with both HSV outcomes using hierarchical MRC. The interaction step accounted for a non-significant 2% of the variance in total number of recurrences and no variance in time to recurrence.

Psychological factors and recurrence excluding subjects with non-psychological sources of HSV. Non-psychological factors have been shown clinically to be triggers of HSV, that is, to predispose patients to HSV recurrence. Those suggested include trauma to the skin, menses, fatigue, infection, fever, and sunlight. Menstruation, fatigue, and reported symptoms of infection were assessed in this study, and correlated with recurrence data. Fatigue did not have a significant correlation with the average number of HSV recurrences; the infection score (calculated from the Duke-UNC Health Profile administered to the subjects each month) had a close to significant relationship to numbers of recurrences (r=.27, p=.07). There was not a greater likelihood for recurrences to take place either in the five days prior to the menstrual period, the five days of the menstrual period or the five days following the period in comparison to other time periods (11% occurred prior to the period, 13% occurred during the period, 13% occurred following the period and the remaining 56% occurred at other times in the 28 menstruating women).

It was felt that these nonpsychological factors may play a role in recurrence for some subgroups of subjects and that stress may only be predictive of recurrence rate in subjects whose recurrences are not triggered by either their menstrual cycle, fatigue or other infections. In order to test for this possibility, three analyses were conducted.

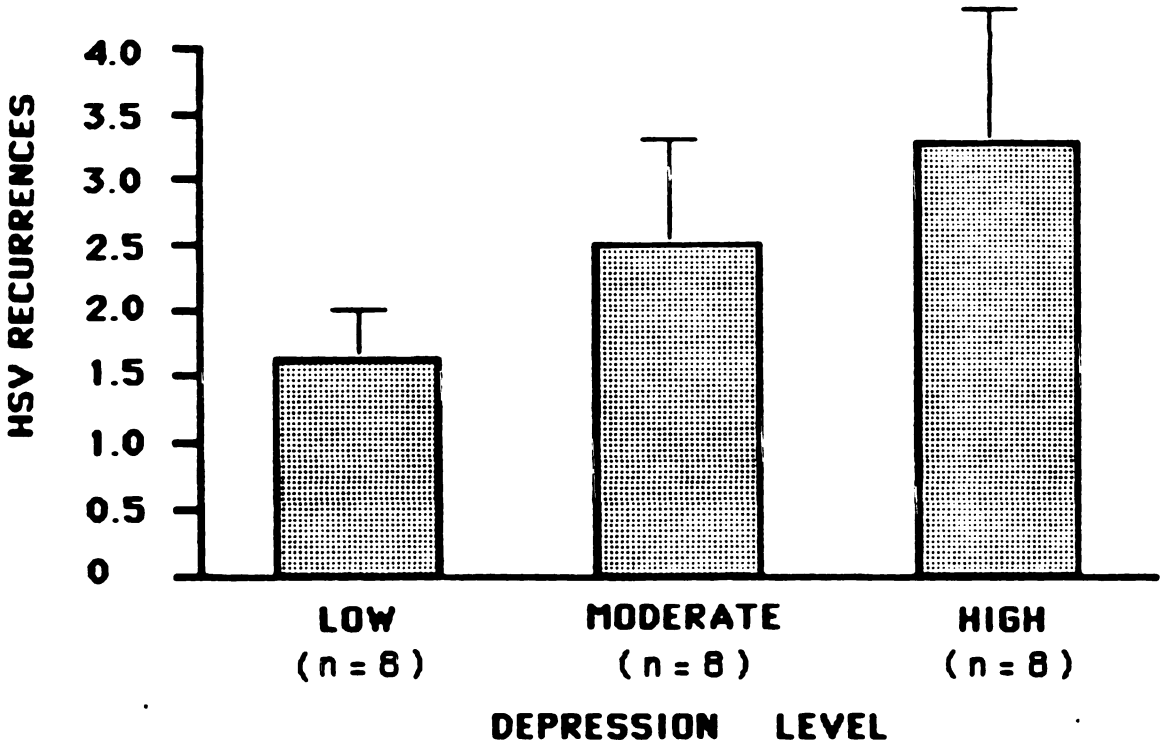
First, the timing of each recurrence in relationship to the beginning of the menstrual cycle was calculated for each menstruating subject. If more than half of a given subject's recurrences occurred during menses or immediately (1-4 days) prior to the menstrual period and that one-half involved more than just one recurrence then that subject was removed from the analysis. Five subjects appeared to have recurrences timed with the menstrual cycle when these rules were applied. However, removing them from the correlations between psychological factors and HSV outcomes did not alter the nature of the relationships found. There were no significant correlations between psychological factors and recurrence outcome in the 31 subjects whose recurrences did not coincide with the menstrual cycle.

Secondly, the infection score was evaluated. This score included the seven health status items consistent with an upper respiratory infection or other viral infection (e.g., fever, difficulty breathing) with each item weighted by the degree of difficulty the subject was having with that symptom. (Subjects rated each symptom as being experienced none, some or alot over the month period; symptoms experienced alot were weighted by 2.) Subjects were divided into three groups: the one-third with the highest infection score, the one-third with the lowest score and the one-third with scores in between. The twelve individuals in the high infection group were removed from the analysis and the correlations between psychological factors and HSV outcome were conducted on the remaining 24 subjects. Again, stress was uncorrelated with HSV recurrence. However, there was a significant correlation between depression and the number of HSV recurrences during the study

period (r=.34, p=.05). In addition, the goal progression score was signficantly correlated with the total number of recurrences (r=-.33, p=.05). Goal progression and depression were highly intercorrelated (r=-.62, p=.001) in this subsample and in the entire sample suggesting that these variables may represent an overlapping construct. Figure 5 illustrates the number of recurrences for subjects differing on level of depression (top, middle, and lower thirds). Subjects in the high depression group had twice as many recurrences as did the subjects in the low depression group. Thus, individuals who were not reporting high levels of symptoms of infection and who were more depressed and/or felt they were making less progress on life goals had more recurrences than individuals who were less depressed or more satisfied with their goal progression. Anxiety, hostility and defeat were uncorrelated with HSV recurrence.

Third, subjects were divided into three groups based on their scores on the POMS fatigue sub-scale: the one-third with the lowest scores, the one-third with the highest scores and the one-third in between. The one-third with the highest fatigue scores were then removed from the analysis. There were no significant correlations between the psychological factors and recurrence for the 24 subjects who did not demonstrate high levels of fatigue.

Thus, the only subgroup that appeared to demonstrate a correlation between psychological factors and recurrence was that group which did not report high levels of symptoms of infection.



* excluding subjects with symptoms of infection

Figure 5: Average Number of Recurrences for Low, Moderate and High Depression Groups

Psychological Factors and HSV Recurrence: Within Subjects Approach

Direct effects on HSV. A correlated t-test was conducted with all the variables expected to have direct effects on recurrence. The maximum stress, anxiety, depression, hostility and defeat months were not more likely to be followed by a recurrence than the minimum stress, anxiety, depression, hostility and defeat months. The maximum months were also not more likely to lead to a recurrence more quickly than the minimum months. However there was a close to significant relationship between the ability to re-experience anger and the number of recurrences, $t(33)=1.95, p=.06$. There appeared to be an increased probability for a recurrence following the month in which the subject reported the highest anger re-experience score in comparison to the month in which the subject reported the lowest anger re-experience score.

Interactive effects on HSV. The subjects were split into two groups, the high support group with above the median scores on overall social support, and the low support group with below median scores. The correlated t-test procedure was then conducted evaluating the relationship between stress and recurrence for each group separately. Stress was unrelated to recurrence in both high and low support groups. A similar procedure was conducted for coping flexibility. Again, stress was unrelated to recurrence in both groups.

A final set of correlated t-tests was performed to determine if levels of any of the psychological factors differed in the months preceding

recurrences in comparison to the months preceding recurrence-free periods for those 29 subjects who had at least one recurrence during the six months in the study. That is, for example, if a subject had two recurrences over the six months, stress levels in the two months preceding the recurrences would be averaged and compared to stress levels averaged over the other four months. This procedure was conducted for all primary psychological variables. The only variable which displayed a significant difference was anxiety. There was significantly less anxiety in the months preceding recurrences than in the months preceding recurrence-free periods, $t(28)=2.33$, $p=.03$.

It was considered that all subjects may not have recurrences following high negative mood periods but that chronically depressed patients may, given results found in the between subjects analyses. In other words, individuals who have recurrences because they are chronically depressed may be more likely to have them following depressive periods whereas others who are not normally depressed may not have recurrences following depressive periods. Therefore, the t-tests for the primary predictors and recurrence were re-run for only subjects above the median on depression. Again, there was significantly less anxiety in the months preceding recurrences than in other months, $t(13)=2.44$, $p=.03$, and a trend suggesting that stress was also lower preceding months with recurrences, $t(13)=2.09$, $p=.06$. There were no significant differences with depression, hostility, or defeat.

Immunity and HSV Recurrence: Between Subjects Approach

A question of importance in this study is whether or not the immunological variables measured in this study play a role in the recurrence of genital herpes. Between and within subjects approach were used to determine the relationships between the immunological and recurrence variables.

Correlations were conducted to determine if the proportion of helper and suppressor T cells correlated with the average number of recurrences reported during the study period and the average time from the blood draw to the next recurrence. No significant correlations were found between helper T cells and the total number of HSV recurrences or the average time to recurrence. There was, however, a significant negative correlation between suppressor T cells and recurrence rate ($\underline{r}$=-.45,$\underline{p}$=.03) and a significant positive correlation between suppressor T cells and time to recurrence ($\underline{r}$=.49,$\underline{p}$=.02). The average number of suppressor T cells, then, is lower in subjects with a greater number of recurrences and in individuals with a shorter average time from the blood draw to the next outbreak.

Immunity and HSV Recurrence: Within Subjects Approach

A within subjects approach is necessary to fully understand whether or not an alteration in one or both of the T cell subsets precipitates a recurrence. The fact that individuals who have more recurrences have fewer suppressor T cells may be an effect of the HSV infection on immunity and not the reason for the increased number of recurrences. Knowledge of the timing of the blood draw in relation to

the recurrence is required to determine if the changes in T cell numbers precede a recurrence or follow it.

Using a method similar to Sheridan and colleagues (1982) who studied T cell subsets and HSV outbreaks, the data from the blood draws that coincided with an outbreak (the two day "prodrome" stage before an outbreak and the first three days of the recurrence) were separated from the others. The proportion of helper and suppressor T cells assayed from these blood draws were averaged. Then the T cell data from the blood draws that coincided with "convalescence" (4 to 14 days from the beginning of the recurrence) were averaged. In addition, two other groups were formed. They included blood draw data that coincided with two pre-recurrence periods (one week pre-prodrome and two weeks pre-prodrome). These two particular groups are of primary interest to this study because they represent two time points when an immune alteration could take place and precipitate a recurrence. Since it is not known how long it takes from a change in immunity to the development of lesions, two possible time frames were selected (one and two weeks pre-prodrome). A fifth group included those values from blood draws that did not take place during, preceding or following a recurrence (the "quiescent" phase).

The average number of each T cell subset for each of the five time periods is displayed in Table 21. T-tests were conducted comparing each period to the quiescent period. There appear to be only slight differences between the helper T cell proportion prior to a recurrence in comparison to the quiescent phase. It does appear that the helper T cell proportion increases on exposure to the virus (during recrudes-

cence). Suppressor T cell values are significantly lower in the 11-18 days prior to a recurrence and during convalescence in comparison to quiescence, $t(39)=3.02$, $p=.01$. Thus, individuals with more recurrences may have a significantly reduced average proportion of suppressor T cells because lower numbers preceed recurrences (by 11-18 days) and immediately follow outbreaks of the disease.

TABLE 21

Proportion of Helper and Suppressor T Cells at Recurrence Stages

	Helper T Cells		Suppressor T Cells	
	%	n of samples	%	n of samples
11 to 18 days prior to recurrence	46.9	8	20.6	8
3-10 days prior to recurrence	44.8	9	25.1	9
During recurrence (2 days prodrome and 0-3 days of recurrence)	49.6	11	24.0	11
Convalescence(4-14 days past first day of recurrence)	43.8	15	20.9	15
Quiescence	47.4	33	27.1	33

a assays from one subject who had cytomegalovirus during study period were deleted since her values were quite low

Depression, Suppressor T cells and Recurrence

One possible pathway emerges which could link a psychological factor to HSV recurrence via changes in T cell numbers. This pathway begins with increased levels of depression which then lead to a decreased proportion of suppressor T cells and finally results in increased numbers of HSV recurrences. Using the between subjects approach, all links in this pathway were found to be significant in the group without other symptoms of infection, i.e., significant correlations were found between depression and suppressor T cells, depression and HSV recurrence, and suppressor T cells and recurrence. Also in terms of timing, suppressor T cells were found to be decreased prior to recurrence which is consistent with this model.

A simultaneous MRC was conducted to test the pathway from depression to suppressor T cells and to recurrence. Depression and suppressor T cells were entered into a simultaneous MRC equation to predict HSV recurrences in the subjects without other symptoms of infection. It was assumed that if suppressor T cells mediate the relationship between depression and recurrence then there should be a good deal of shared variance between the two variables. In fact, the semi-partials indicate that depression assumes all the variance leaving suppressor T cells contributing no variance to recurrence (suppressor T cell $\underline{sr}$=.03, depression $\underline{sr}$=.80). However the sample size for this analysis is 11 (the number of immunological subjects who are not in the high infection group), which may render the correlations unreliable.

Health Habits and Outcome: Between Subjects Approach

The question to be tested here is whether or not the relationship found between psychological factors and outcome is attributable to changes in health-related behaviors resulting from changes in psychological state. The following health habits were evaluated monthly: number of hours slept, amount of alcohol consumed, amount of exercise engaged in and number of cigarettes smoked. However, very few subjects smoked regularly so it was impossible to determine the effects of smoking on the outcome measures. In addition, sexual activity was included here as a possible behavior with potential impact on rate of recurrence.

Averages over the six month period were computed for the following behaviors--number of hours slept daily, liquor consumed during the month (including wine, beer, hard liquor and mixed drinks), average hours of exercise in heavy activity during the week (e.g., running, swimming), average hours of exercise in light activity during the week (e.g., walking, floor exercises), total hours of exercise, and average frequency of sexual activity during the week. Table 22 displays the relationship between these averages and the primary psychosocial variables; Table 23 shows their relationship to the outcome measures. Subjects appear to sleep more when they are anxious (r=.30,p=.04) and to exercise less the more anxious they are (r=-.40, p=.008). There is a trend suggesting that subjects also exercise less the more hostile they feel (r=-.26,p=.06). Increased sleep appears to be associated with fewer helper T cells (r=-.45,p=.02). Increased alcohol consumption is associated with more recurrences for the subjects without other symptoms of

infection (r=.41, p=.02). Also, there is a trend suggesting that increased exercise is associated with increased suppressor T cells (r=.37, p=.06).

The significant and close to significant relationships between health habits and outcome were reviewed. Analyses were then conducted to determine if any of these relationships might explain the correlation between psychological factors and outcome. The three significant health habit-outcome relationships were evaluated: sleep and helper T cells, alcohol and HSV recurrences, and exercise and suppressor T cells. The analyses were conducted to determine whether the relationship between stress and helper T cells was attributable to stress-induced changes in sleep, whether the relationship between depression and recurrences was attributable to increased alcohol consumption while depressed, and whether the relationship between moods and suppressor T cells was a function of changes in exercise. Simultaneous MRCs were conducted to test these three pathways.

It was hypothesized that stress would continue to have a significant relationship to helper T cells when number of hours slept was added to the equation and that the strength of the correlation between stress and helper cells would not be greatly diminished. Results of the MRC (Table 24) indicate that the relationship between stress and helper T cells did not remain significant, although close to significant (sr=-.39, p=.07), but that the strength of the correlation remained similar to its level when sleep hours were not included(r= =-.45). Thus it appears that while there is overlap between stress and hours slept, the two variables also contribute unique variance to helper T cell numbers.

TABLE 22

Correlations Between Average Health Behaviors and Psychological Factors

	Stress	Hostility	Anxiety	Depression
Alcohol Consumption	.13	.08	.17	.19
Hours Slept	.12	.12	.31*	.16
Total Exercise Hours	-.24	-.26	-.40**	-.14
Light Exercise Hours	-.13	-.00	-.18	.08
Heavy Exercise Hours	-.01	-.24	-.13	-.12
Sexual Activity	-.22	-.20	.09	-.11

* $p < .05$
** $p < .01$

(N=36)

TABLE 23

Correlations Between Average Health Behaviors and Immunity and Recurrence

	Helper T Cells (n=19)	Suppressor T Cells (n=19)	HSV Recurrence[1] (n=24)
Alcohol Consumption	.15	-.11	.41*
Hours Slept	-.45*	.08	.06
Total Exercise Hours	.27	.37	-.31
Light Exercise Hours	.22	-.08	-.02
Heavy Exercise Hours	-.07	.16	-.24
Sexual Activity	-.09	.02	.26

[1] For individuals who are not in high infection group

* $p < .05$

The second set of equations includes negative moods and exercise predicting suppressor T cells. In all three mood equations, mood maintains moderate sized correlations with suppressor T cells when exercise is in the equation. However, only hostility maintained a significant correlation (sr=.46, p=.04), while depression maintained a close to significant correlation (sr=-.40, p=.08).

The third equation included depression and alcohol consumption predicting herpes recurrences with the subjects who had high levels of

TABLE 24

Simultaneous MRCs Predicting Outcome With Average Health Behaviors and Psychological Factors

	r	sr	t	p
Dependent Variable = Helper T Cells (n=19)				
Hours Slept	-.45	-.36	-1.77	.10
Composite Stress Score	-.47	-.39	-1.93	.07
Dependent Variable = Suppressor T Cells (n=19)				
1. Exercise Hours	.37	.18	.88	.39
Hostility	-.57	-.46	-2.30	.04
2. Exercise Hours	.37	.16	.74	.47
Anxiety	-.47	-.33	-1.50	.15
3. Exercise Hours	.37	.23	1.09	.29
Depression	-.49	.40	-1.88	.08
Dependent Variable = HSV Recurrence (n=24)[1]				
Alcohol Consumption	.41	.40	2.2	.04
Depression	.34	.33	1.8	.09

[1] for individuals who are not in high infection group

other infection symptoms removed. Depression maintains only a close to significant correlation with recurrence when alcohol consumption is in the equation, although again, the strength of the correlation between depression and recurrence is not very much diminished (sr=.33 r=.41).

In all the above cases, the fact that some of the psychological factors are no longer significantly related to outcome when health habits are included in the equation appears to be a function of lost degrees of freedom when two variables rather than one are included in the equation. It does not appear that the variables are sharing variance since the size of the correlations do not diminish appreciably.

In sum, it appears that some of the health behaviors examined do correspond with psychological states and some predict the immunological and HSV outcomes. However, it does not appear that psychological factors act exclusively through health behavior changes in affecting immunity and recurrence.

Health Habits and Outcome: Within Subjects Approach

A within subjects approach was then attempted to test the relationship of the health habits to the outcomes. The month when each health behavior was at its maximum was compared to the month when the behavior was at its minimum in terms of proportion of helper and suppressor T cells. None of the health-related behaviors was significantly related to either T cell subset or to HSV recurrence outcomes.

DISCUSSION

Overview

The results of this study suggest that high levels of stressful experience and negative affect over a six month period coincide with low levels of two types of immunological cells (helper and suppressor T cells) in patients with chronic genital herpes. Stress and affect do not have similar relationships to the two cell types however. Negative affects, as measured by the Profile of Mood States subscales of anxiety, depression and hostility, as well as feelings of defeat are negatively related to suppressor T cells. The more the subject reports the presence of each negative mood over the study period the fewer suppressor T cells are evident. Stress does not appear to contribute to variability in suppressor T cells over the influence of these affects.

The relationship of stress and mood to helper T cells is quite different. Stress has a negative relationship to helper T cells. The more stressful experience reported over the study period the fewer helper T cells are evident. Mood, however, does not have a simple relationship to helper T cells. Mood appears to interact with the ability to reexperience positive feelings in its relationship to helper T cells. Individuals who display a discontinuity in their reported mood and positive emotion--either by reporting negative mood and easily experienced happiness or by reporting positive mood and difficulty experiencing happiness--have fewer helper T cells than individuals who display more consistency in reported mood and positive emotion.

In sum, mood has a strong and direct relationship to suppressor T cells while stress does not. Both stress and mood have a relationship to helper T cells but the relationship between mood and these T cells is dependent on the subjects' reporting of the experience of happiness.

In contrast to what might be expected from the stress and disease literature, neither social support nor coping flexibility had positive direct effects or positive moderating effects on T cell subset proportions. In fact, stress appeared to have the most deleterious effects on T cells when the subjects reported a high social support level.

None of the primary psychological factors measured in this study was associated with HSV recurrences when all of the subjects were evaluated. In addition to potential psychological triggers of recurrence, various non-psychological potential triggers were evaluated, e.g., the menstrual cycle, fatigue, and infection. Fatigue did not correlate with recurrence rate. Menstruating women in the sample, overall, did not show a pattern of recurrences timed with particular points in the menstrual cycle, although a small sub-group of women did demonstrate a consistent pattern of recurrences at particular points in the cycle. However, increased levels of symptoms of infection did show a close to significant relationship to recurrence rate.

HSV recurrence rate may be predicted by psychological factors only in subjects who do not have recurrences triggered by other factors such as infections. Therefore, analyses were also conducted eliminating subjects who displayed a high number of symptoms of other types of infection. These analyses showed that depression and satisfaction with goal progression were significantly related to recurrences. That is, in

subjects who were not experiencing symptoms of another infectious process, increased levels of depression and decreased satisfaction with goal progression corresponded to an increased rate of HSV recurrences over the study period.

The possibility of a psychobiological pathway linking a psychological factor to HSV recurrence via changes in the proportion of the T cell subsets was examined. One of the T cell subsets measured in this study--suppressor T cells--did appear to fluctuate timed with subjects' cycle of recurrences. Individuals who experienced more recurrences had fewer suppressor T cells than individuals who experienced a smaller number of recurrences over the period of the study. And the decreased numbers of suppressor T cells appeared to occur one to two weeks prior to a recurrence as well as during the convalescent phase. Therefore a psychological factor that is associated with decreased suppressor T cell numbers could have an etiologic relationship to recurrences of HSV. Depression was associated with a decrease in suppressor T cells; depression was also related to HSV recurrence in patients who did not display a large number of infection symtoms. Thus, increased levels of depression may result in decreased levels of suppressor T cells which may then increase the individual's risk of developing a recurrence.

Health-related behaviors were tested to determine whether psychological factors acted through health behaviors to influence immunity and HSV recurrence rate. Behaviors including sleep and exercise were associated with stress and mood levels. These behaviors as well as alcohol consumption were also associated with immunity and HSV. However

the strength of the relationships between psychological factors and outcome was not diminished when these health behaviors were controlled for. Thus it appears that both health habits and psychological factors contribute to changes in T cell values and to herpes recurrences but that the effect of psychological factors on these outcomes does not occur exclusively through health-related behavior changes.

The ability of the psychosocial and non-psychosocial factors to predict when recurrences would take place (i.e., within subjects) was also tested. The only factor which was significantly associated with fluctuations in HSV recurrence over time was anxiety. Contrary to expectation, there were lower levels of anxiety in the months preceding an HSV recurrence than in the months preceding recurrence-free periods.

Table 25 provides an overview of all the results of this study. The discussion will first focus on overall issues raised by the results and will then focus on the confirmation and non-confirmation of individual hypotheses. Methodological and theoretical issues raised by the study will then be addressed.

TABLE 25

Summary of Relationships Between Psychosocial Predictors and Outcome

	HSV Recurrence	Helper T Cells	Suppressor T Cells
Primary Predictors			
Composite Stress		D	D
Goal Progression	D[1]		
Hostility		I	D
Depression	D[1]	I	D
Anxiety	WS	I	D
Defeat			D
Social Support Satisfaction		I[2]	I[2]
Coping Flexibility			
Exploratory Predictors			
Anger Experience	WS[3]		
Sadness Experience	D		
Happiness Experience	D	I	D

D = Direct Between Subjects Effects

I = Interactive Between Subjects Effects

WS = Within Subjects Effects

[1] for individuals not in high infection group
[2] significant using median split, nonsignificant using MRC
[3] p=.06

Discussion of Results

Between Subject Versus Within Subject Results

This study found a strong relationship between the average amount of stress and negative mood over a six month period and the average proportion of helper and suppressor T cells evident. However, no relationship was found between month-to-month fluctuations in stress and mood over the six month period and month-to-month fluctuations in immunity. Considering these results together, it would appear that individuals who are chronically stressed are more immunologically depressed (in terms of helper and suppressor T cells) than are individuals who are less stressed, but that more acute changes in stress level may not coincide with transitory changes in immunity. Previous research has evaluated either acute stressors such as medical student examinations or the accumulation of previously experienced stressful life experiences (e.g., the number of major life changes over the past six months was correlated with one assessment of immune function). In earlier studies, acute stressors have been associated with immune changes while accumulated stresses have not been shown to be predictive of immune deficits. The current study is the first test of whether current stress level measured over an extended period of time is correlated with current immune state measured over the same period of time. In other words, what was tested in the between subjects analyses is whether chronic exposure to stressful circumstances could result in <u>concurrent</u> changes in immune parameters.

Also, these data suggest that stable psychological phenomenon such as traits may be more predictive of immunity than more transient changes in state since average mood levels predicted average immune values but monthly fluctuations in mood did not predict monthly fluctuations in immunity. For example, the average mood measures may assess stable dispositions such as trait anxiety which may have a greater effect on immunity than short-lived states of anxiety.

There are a number of alternative ways to interpret the presence of between subjects effects in this study and the absence of within subjects effects. First, it may be that helper and suppressor T cell numbers do not respond to month to month changes in psychological state and stress level or that these changes take place in only a small percentage of the population. Instead, a chronically stressful situation over a period of time may be required before these T cell sub-sets will change sufficiently to be detected. The proportion of helper and suppressor T cells is fairly stable over time with the majority of normal individuals varying only 3-4 percentage points around their own mean (Taylor, Marshall and Fahey, 1985). Other measures of immunity with greater within subject variability may be more likely to respond to acute stress changes. It is possible that the few studies that have found within subjects effects in more stable immune parameters, such as these T cell subsets, have found them because the effects were confounded with other variables that do cause transitory shifts in immunity such as major sleep deprivation or dietary deficiencies.

The second interpretation of the data is based on the particular period of time selected for study in this project. Previous psychoimmu-

nological research has taken either an exclusively between subjects approach (e.g., the bereaved are more immunological depressed than controls) or a within subjects approach that has focused on a particular period of time when a stressor is "pre-determined" to take place. For example, a series of studies by Kiecolt-Glaser and colleagues(e.g., Kiecolt-Glaser et al., 1984) used a within subjects approach focusing on the stressor of the medical exam and comparing this time period with two presumably less stressful periods. In contrast, the current study evaluates the relationship between stress and immunity in a "random segment" of the subject's normal life. No particular stressful event will neccessarily occur during the six month period. Subjects may be experiencing a relatively calm and peaceful period of life, or a turbulent and difficult period in life or this six month period may fall somewhere in between. More importantly, the subject's stress level may be consistent over the course of the six month period or it may be quite inconsistent. In other words, subjects may be responding to a chronically stressful period or a "chronically" non-stressful period or they may have extremely stressful months as well as non-stressful months.

The autocorrelations of stress and mood suggest that the majority of the subjects in this study were consistent in their level of stress and mood over the six months. If they were stressed or felt anxious one month they were very likely to feel similarly the next month. Also, the stresses that individuals chose to discuss during the monthly interview were most often stresses of long duration, such as financial problems or long-standing problems with a partner, rather than acute stresses. There were a number of major life changes that did occur

during the study period (five subjects experienced the death of a close family member during the study period--father, brother or sister; three had abortions; others changed jobs or moved, suffered major personal failures--e.g., failing the psychology licensing exam for the fifth time--or separated from their partners). While this number is large, in several cases the stressful experience took place at the beginning of the study so that the subjects were responding to it throughout the study period. In other cases, a major stressful event took place in more than one of the six months so that there were no clear differences in stressfulness from month to month. Thus, in many subjects there was very little opportunity to evaluate changes in stress level from month to month. As a result, it may not have been possible to detect stress-related within subjects effects on immunity despite strong differences between highly stressed individuals and less stressed individuals. Studies which focus on a particular stressful event, such as an exam, and compare its effects on immunity to the effects of a more benign period, will not have such problems.

An inspection of the month to month fluctuations in the stress and mood values indicates that a small group of subjects did demonstrate marked fluctuations in stress and/or mood from month to month with some months above the sample median in stress and other months below. If this group were larger and could be studied separately, it is possible that changes in immunity tied to changes in psychological state might be detectable.

There are two other possible interpretations of the results that relate to the instruments used. First, the instruments chosen to monitor

month to month fluctuations in psychosocial response may not have adequate sensitivity to detect more minor changes in psychological state. For example, the POMS, which was used to measure mood, may be adequate to capture more stable mood states or affective styles but may not capture minor fluctuations in mood. The fact that the POMS has high test-retest reliability over a one month period suggests that either individuals tested did not fluctuate in mood from one month to another or that the instrument was not successful in detecting actual changes.

Second, the reliance on self-report measures of psychological processes may have made detection of changes in state more difficult. Individuals may in fact vary in mood and stress level quite a bit over a six month period. They may, however, have consistent patterns of reporting their psychological state which mask "real" state changes. For example, subjects who tend to deny to themselves and others that they feel negative feelings may consistently report that they are feeling fine when, in fact, their mood level is changing. The autocorrelations tend to support this interpretation. All of the self-report measures of psychosocial variables display high autocorrelations. Coping flexibility as well as the individual coping modes, which are based on an inferential process from interview data, have small autocorrelations. The emotion experience ratings which ask about current emotional state have low autocorrelations. Possibly the inclusion of non-self report measures of state or other more sensitive instruments (of emotion, for example) would have allowed any masked within subjects relationships to become apparent.

Finally, the time periods used in this study may have obscured within subjects effects. When subjects are asked to describe their mood and stress level over a month period they may have to engage in an averaging process since, during a month period, they may have had very good days and very bad days. This averaging process may have washed out actual differences in state and resulted in each month appearing to be quite similar to the next. If a shorter time frame had been used instead, for example a one week period, then averaging may not have been required and changes in state may not have been obscured. The same time period problem is relevant for the immune measures. A measure of immunity once a month may not be representative of the immune status of that individual for the entire month. More frequent measurements of immunity would have been more representative of fluctuations in immune state and might have been more likely to be tied to simultaneous changes in psychological state.

In sum then, the presence of between subjects effects of stress and mood on helper and suppressor T cells and the lack of within subjects effects may be attributable to the fact that these cells respond to more chronic stress or to long-term affective characteristics and not to acute stressors or transitory shifts in affect. Alternatively, the results may be a function of the "random segment of life" approach used in this study and the likelihood that using such an approach could result in the selection of periods which contain little variability in stress level for the majority of subjects. Or, the instruments used may have been insensitive to subtle changes in state or have been highly influenced by characteristic reporting styles. Finally, the assessment periods may

have been too long and resulted in subjects averaging their stress levels, obscuring actual changes in state.

Overall Effects of Predictors on Immunity

As will be discussed in greater detail below, all negative psychological states were correlated with decreases in either helper or suppressor T cells, or both. Helper T cells serve a variety of functions which amplify the immune response and play a major role in activating other aspects of immunity to kill virally infected cells. Thus it appears consistent that stress would be correlated with decreases in helper T cells which would then put the individual at greater risk of contracting a viral infection. However suppressor T cells serve an opposite function, which is to down-regulate the immune response and protect the individual from an over-active immune reaction. Thus, it might be expected that suppressor T cells would increase under stress and therefore inappropriately "turn off" the immune response when it is needed. Instead, suppressor T cells decreased when individuals reported more negative mood, stress and defeat. Also, it might be expected that an increase in suppressor T cells would precede a recurrence since a increase in this sub-population of cells might create an environment in which virus particles could replicate since activation of certain effectors would be suppressed. However, suppressor T cell percentages decreased prior to recurrent disease.

These apparent anomalous findings can be understood from a number of perspectives. First, other recent research on stress and T cell sub-sets have also found suppressor T cells to diminish under stress,

although often the change does not reach significance (Kiecolt-Glaser, et al., 1984; Schaeffer, Baum,Davidson, & Reynolds, 1985). So the findings of this study are consistent with findings using different stress paradigms. Also, it is important to recognize that the suppressor T cell assay measures not only a subpopulation with suppressor activity but also a population of cells with cytotoxic activity--cytotoxic T cells. Cytotoxic T cells are cells that are capable of killing virally infected cells. A decrease in their numbers could place the individiual at increased health risk. It is impossible to determine whether the decrease in the proportion of suppressor/cytotoxic T cells represents a predominant decrease in suppressor T cells or a predominant decrease in cytotoxic T cells. Newer techniques allow for the differentiation of suppressor T cells from cytotoxic T cells so that this distinction can be made in future studies.

Another possible explanation for the suppressor T cells findings is the location from which the cells were drawn. The assay measures the numbers of T cell sub-sets in the peripheral blood. It is not known whether an assessment of T cell numbers in the serum is representative of T cell numbers at the genital level where these sub-sets would be required to mount an effective immune response against HSV viral particles. For example, it is possible that the numbers that appear at the periphery are the inverse of the numbers at the local level because cells are recruited to the site of viral replication, thus depleting numbers at the periphery. However, it is not currently possible to measure these sub-sets and other aspects of immunity from local secretions and therefore all data on immunity and HSV infection is based on peripheral blood samples.

In addition, it is important to recognize that a decrease in the proportion of suppressor T cells does not imply that the suppressor cell function is necessarily depressed. While the data suggest that the percentages of both helper T cells and suppressor T cells diminish in relationship to negative moods and stress, we do not know whether the functional ability of these cells is altered by changes in psychological state. Changes in numbers do not necessarily correspond to an alteration in the immune response since the functioning of the cells may remain unaltered and the decreased numbers may still be sufficient to fight infection. Thus it would be useful for future work in this area to include both quantitative and functional assays.

In sum, the decreased percentages of suppressor T cells during increased levels of negative mood and prior to recurrent HSV infection are difficult to interpret. Further research would be useful which distinguishes the various sub-types of this population of cells in relationship to both psychological factors and HSV recurrence.

Stress and Immunity

Previous research has shown that individuals exposed to major stresses such as bereavement or the more minor stress of medical student examinations display changes in immunity (Bartrop et al., 1969; Kiecolt-Glaser et al., 1984). Life events as measured over a two week period have also been shown to predict immune changes (Locke et al., 1979). The current study evaluated not only life changes over a six month period but also the chronic "hassles" of daily living, the anticipation of life change, the residual effect of previous life changes, lack

of satisfaction with progression on life goals and stresses particular to individuals who have herpes. Anticipated stress and residual stress appeared to have a stronger relationship to immunity than did more current life change or current herpes-related stress, but this occurred only when both positive and negative current events were evaluated. When only negative current events were considered, then the effects of residual, current and anticipated events showed similar relationships to immunity. These effects were quite different from the effects of the chronic ongoing stresses of daily living, however.

The stress results suggest that individuals respond immunologically to current stressful events, but also to current upset and worry over previous events and the anticipation of future events. The detection of the effects of stressors that did not take place during the study period results from defining stress broadly to include current effects of past and future stressors. Studies that focus exclusively on the effects of a particular event (e.g., an exam) will overlook other sources of distress.

It is also possible that the stress findings are heavily influenced by reporting style. That is, subjects may respond to all the stress event questionnaires in a similar fashion. Those who are upset and worried about current events may also report being upset and worried about past and future events. The factor analysis results suggest that subjects did respond to these questionnaires similarly. The underlying dimension being tapped may be the subjects' tendencies to become upset or to report being upset, and not the presence or absence of events. It is interesting to note, however, that when frequency checks of

stressful events (or hassles) were used in the analyses rather than stress scores weighted by the subject's reaction to the event, the results were very similar. Thus, this "worrying" response style may influence not only the ratings of level of upset in reaction to events but also the number of events the subject reports occurred during a specified time period. Thus, an alternative interpretation of the results may be that a relationship exists between a "worrying" response style and immune measures rather than between particular kinds of life events and immunity.

Hassles versus life events. This study was also able to compare a life event inventory with the hassles scale, the subject of a number of previous research projects (Kanner et al., 1981). All previous research on this topic has evaluated the relative effects of these types of stress scores on self-reported health status. Interestingly, this study confirms the relationships between these measures and self-reported symptoms of infection using the Duke-UNC Health Profile. There is a stronger correlation between Hassles and infection symptoms than between life events and these symptoms. These differences are present even when a frequency check of Hassles Scale items is used instead of the Hassles score.

The effects of these two categories of stressors shows quite a different pattern with respect to immunity. Hassles do not appear to be related to the number of helper T cells while the overall LES has a close to significant relationship with this T cell subset and the negative LES has a significant relationship. The Hassles Score is correlated with suppressor cells; however, the relationship between hassles and sup-

pressor T cells disappears when the variance due to anxiety is removed. The relationship of the LES to helper T cells does not diminish when the effects of anxiety are removed. These data suggest that the strength of the correlation between hassles and suppressor T cells may be a result of the overlap between the hassles scale score and anxiety.

The overlap between hassles and anxiety could occur as a result of three possible situations. First, the Hassles Scale and the POMS anxiety subscale may be measuring the same thing (r=.62). In other words, the items on the Hassles Scale use words that appear to pull for symptoms of anxiety, such as "concern over," "worry about," etc. (see Dohrenwend et al., 1984). Second, anxiety could be a very frequent accompaniment of exposure to minor ongoing stressors. Therefore a measure of exposure to these stressors and a measure of anxiety would be highly correlated and would display overlapping relationships to other variables. The two variables would covary, then, not because they are measuring the same thing, but because exposure to hassles and feelings of anxiety so often coexist. Third, scales differ in the vagueness and subjectivity of their items. It may be that the more vague the items, the more that the psychological traits and states of the individual influence responses to the items. Projective testing is based on this notion that the perception of stimuli that are unstructured and nonspecific will be influenced by the traits and state of the individual. In other words, anxious individuals or individuals who are experiencing a state of anxiety when they fill out the hassles scale may fill it out to contain more hassles than individuals who are less anxious when they fill out the forms. Responses to the scale are then influenced not only

by the experiences that have occurred over the assessment period and the subjects' appraisal of those experiences but by the psychological state of the individuals at the time they fill out the scale.

This projective process might be more of a problem with the Hassles Scale than some other stress scales because the stressors listed are those that are ubiquitous and the question the respondent must face is whether or not the situation has been a problem, not whether or not the situation has occurred. The more the respondent must make a judgment and attempt to recall previous feelings, the greater the risk that this recall will be influenced by the current state of mind. For example, the answer to the question "Did you move this past month?" may be less a function of the state of the individual than is "Did you have financial problems last month?" or "Did you have concerns about the future?"

The three explanations for overlapping relationships between anxiety and the Hassles Scale score have different implications. While it can be argued that anxiety and hassles cannot be disentangled when a relational stress model is used (see Lazarus et al., 1985), it is a separate and important methodological question to determine if psychological traits and states of the individual influence the tendency to recall the presence of chronic stressors during a specified period. This second possibility would have important implications for valid research on hassles and psychological and health outcomes. These data suggest that for some reason anxiety and the Hassles Scale score are highly interrelated and that further investigation of scale properties might be useful.

Goal progression. Satisfaction with progression on life goals was hypothesized to measure a dimension of stress and contribute to variability in immunity and recurrence. The factor analysis results indicated that the goal progression score did not measure a construct similar to the other types of stress scales used. Also, this score did not have a significant relationship to helper T cells and had only a close to significant relationship to suppressor T cells. However, goal progression was significantly related to HSV recurrences over the study period when individuals with symptoms of other infection were removed from the analysis. The other stress measures did not have a relationship to recurrence.

What does the goal progression scale measure? The subjects select five high priority life goals and then each month they rate their satisfaction with their progress on each goal. For example, most of the subjects included "giving and receiving love" as one of their highest priority life goals. Individuals who were not in relationships or who wished for more fulfilling relationships often felt dissatisfied with their progress on this goal. Other goals revolved around issues such as having children, living a challenging life, having a satisfying career, etc. In most cases, then, lack of goal satisfaction implied the absence of a particularly desired situation. It has been suggested that the absence of important life changes may represent an important aspect of stress (Cohen, 1981) but this construct has been measured only rarely in stress-disease research.

Mood and Immunity

Only one study in the literature has evaluated the relationship between mood state and immunity in a normal population (Van Dyke, 1985). In this study, bereaved individuals who were depressed showed decreased levels of natural killer cell activity when compared to bereaved subjects who were not as depressed; however, the differences did not reach significance. Other studies have found a relationship between depression and immunity but only when patients with major depressive disorders were studied (see Stein et al., 1985). In other words, patients with major depressive disorders showed decreases in various immune parameters in comparison to individuals without a major depressive disorder.

The results of the current project indicate that in a non-disturbed sample, mood over a six month period is related to the number of helper and suppressor T cells in the peripheral blood. These results make an important contribution to the psychoneuroimmunology literature because they indicate that not only stressful experience but also one's affective state are related to immune status.

What is being measured by the POMS subscales? Although the test constructors describe their scales as representing various moods, affect researchers might not agree. The various categories of affect (e.g., emotion, mood, emotion-related traits, emotion-related pathology) have not always been carefully distinguished. Using a scheme for defining these categories developed by Ekman (1984), the average POMS score could represent the mood of the individual over the study period or it could indicate an emotion-related trait or an emotion-related pathology.

For example, an individual with a high depression score could be 'feeling blue' throughout the study period (a mood) in response to a stressful situation; or the subject could be a melancholic individual who characterologically experiences depressive affect (considered a dysthymic disorder by Diagnostic and Statistical Manual III criteria); or finally the high score could indicate a pathological state such as a major depressive episode in which particular emotions are flooded and the individual has difficulty carrying out the tasks of daily living. Unfortunately, the average of the monthly POMS scores does not allow these distinctions to be made since we do not know the history of the subject prior to beginning the study (in order to to distinguish mood from trait) nor the extent of symptomatology so that a pathological state could be diagnosed. However, these distinctions may be quite important in terms of their possible impact on immunity. For example, chronic trait-like melancholia may have a different influence on immunity in comparison to an acute depressive reaction (given the animal research on the differential influence of chronic versus acute stress). Future research is needed making careful distinctions among affect categories. (The remaining discussion of the POMS data will refer to the subscale values as representing negative moods for convenience despite the fact that this distinction cannot be made.)

Results indicate that stress and mood have quite different relationships to different T cell subsets. In terms of direct effects, stressful life experience is more highly predictive of helper T cells while negative mood is more predictive of suppressor T cells. Previous research has also not shown that variability in one T cell subset is related to one

type of psychological factor while variability in another subset is related to another psychological factor, because, in general, either stress or mood is evaluated, and not both.

The relationship between negative moods and helper T cells was quite different from their relationship to suppressor T cells. Mood appeared to be directly and negatively correlated with suppressor T cells. The relationship between mood and helper T cells was much more complex, however. Mood appeared to interact with the experience of happiness score and the re-experience of happiness score. Subjects who displayed a higher negative mood score over the six months and who reported strong happiness experience scores had fewer helper T cells than subjects who had high negative mood and weaker happiness experience scores. The amount of variance that the interaction between mood and the happiness scores accounted for is much more than is commonly found in stress-disease research. For hostility, it accounted for twice as much variance as did stress or mood alone on either T cell subset (50%).

There are a number of possible interpretations of the interaction between mood and happiness ratings. First, it is quite possibly spurious because it is based on a small sample of subjects (n=19). With a small sample, only a few subjects' tendencies can have a major influence on the direction of the relationship. However the strength of the relationship between these variables and helper T cells warrants further exploration. Second, it may be that this particular combination of factors represents a particular affect management strategy or reporting style with a strong relationship to immunity. A subgroup of these indi-

viduals reported that they were very nervous, depressed, angry or upset over the course of the study but they also reported that they felt very happy during a happy event and very happy as they talked about the event. The mood ratings were derived from questionnaires filled out by the subject when he or she was alone. On the other hand, the happiness ratings were requested verbally at the end of the interview after the subjects had described two stressful situations, their negative reactions to them, and how they tried to handle each. It may be that some subjects become uncomfortable admitting to others and/or to themselves that they were having difficulty handling situations and may feel a need to communicate in some way that they are not doing quite as badly as it might appear. These individuals may be able to admit to negative moods on a questionnaire but they may need to downplay these feelings in an interview situation especially after revealing a series of negative experiences they have recently confronted. Thus, they may need to "put on a happy face" in such social situations for their own and the others' benefit. On the other hand this combination may represent an unconcious form of denial of certain emotional responses. However there is no way to determine from this apparent mismatch between states that the subjects are actually denying anything.

It is possible that the individuals who display high levels of negative mood and high happiness re-experience scores are individuals who can feel quite upset over a long period of time but who can also feel quite happy. In other words, the fact that they report feeling intense negative emotional states does not preclude their feeling positive emotional states. It may be then that it is intensity of felt experience

(both positive and negative) that is related to outcome. However, this proposition is somewhat less likely given that the interaction effect does not occur when anger or sadness ratings are combined with mood ratings. The validity and importance of this particular combination of responses must await confirmation in future research.

Three different negative moods were measured during the study period--hostility, anxiety, and depression. However, the three moods had quite similar relationships to helper and suppressor T cells. All three moods had a significant negative correlation with suppressor T cells and no direct relationship to helper T cells. In other words, there were no instances in which one mood had a significant relationship to an aspect of immunity and another did not. The strength of the relationship between each mood and the immune measures was also very similar although hostility appeared to have the strongest relationship to immunity and the effects of hostility appeared to be the most distinct from stress. These findings suggest that negative affective states do not have differential effects on the cell subsets. Alternatively, the scales may not be adequately differentiating distinct mood states so that individuals who feel anxious may also report feeling hostile when in fact there are differences in these states. Or, reporting biases may have over-ridden actual differences in mood state as discussed previously. It cannot be determined from these results whether these three affective states actually covary when a six month period is evaluated and have similar relationships to the immune measures or whether measurement problems produced the similarities in results.

Emotion and Immunity

Emotion was measured in this study because it was assumed that emotion and/or long-term affective states could function as the final link in the chain from stressful life experience, through appraisal of that experience and the moderating effects of personal and social resources, to physiological change. If affect does serve as the final link then emotional responses and/or moods and other affective states should have a stronger relationship to outcome than the other psychological factors measured such as stress, social support, and coping. The emotion experience ratings themselves were originally included in order to represent additional ways to assess long-term affective states such as mood. However, the ratings seemed to function quite differently than the mood ratings so they were analyzed separately.

The emotion experience ratings had a complex relationship to immunity. The two happiness ratings were positively correlated with suppressor T cells. For the subjects as a whole, the stronger the happiness score the more suppressor T cells. High scores on these two variables in individuals with high negative mood have a negative impact on suppressor T cells. The sad experience scores were not related to average number of T cell subsets. Variations in sadness re-experience scores, however, displayed a trend towards predicting changes in helper and suppressor T cells. The more sadness re-experienced the more of each T cell subset. The anger experience scores were unrelated to average T cell subsets. Thus happiness and sadness experience scores have a positive relationship to immunity except when the subject reports chronic negative mood over the study period.

The emotion experience ratings had relationships to both immunity and HSV recurrence using both a between subjects and a within subjects analysis. The relationships are complex and difficult to interpret, however. A few conclusions can be drawn. First, the different emotion ratings did not have identical relationships to immunity (or recurrence) in contrast to the more similar findings across the three moods. Thus, individuals do appear to distinguish between positive and negative emotion ratings and to respond differentially to the two negative emotions measured--sadness and anger. The generally low autocorrelations also suggest that reporting biases do not overwhelm fluctuations in these ratings. That is, individual affect intensity ratings fluctuated from month to month. And, for some of the ratings, these fluctuations were timed with fluctuations in the immunity and HSV outcomes.

What do these ratings measure? The affect experience questions ask subjects to rate how much they felt a particular emotion as they experienced the event that generated the emotion and how much they feel the feeling while they discuss the event. In a sense, these ratings measure the individual's access to their past and present emotional reactions. As discussed previously, it seems possible that the way individuals are feeling during the interview will influence their recall of the intensity of their particular emotional responses. For example, depressed subjects may rate themselves as feeling a low level of happiness during a happy event because their depression overshadows their recall of a previously happy event. However, the data clearly indicate that emotional responses are not exclusively a function of mood ratings since the intercorrelations are not high and the variables relate quite differently to other factors.

As discussed by Ekman (1984), the depression and other long term affective states may define the threshold for emotional responses and set the stage for particular emotional reactions during a particular time period but do not completely determine the specific emotions that will result. For example, individuals with some forms of depression may show blunting of emotional response across all emotions but individuals will experience more or less of each particular emotion (within this blunted range) in response to the contingencies of the situation and other factors. However, it is important to recall that the values used in the between subjects analyses were the <u>average</u> emotion experience ratings over the six month period. (The <u>individual</u> emotional experience scores were used in the within subjects analyses.) Thus the averages do not represent individual emotional reactions but probably represent emotional response "tendencies." In other words, individuals who respond to anger-provoking situations with high levels of anger will have high average anger scores while more complacent individuals may have lower scores. Thus, these scores may represent response styles or tendencies.

It is unlikely that a particular emotional response is capable of causing a change in relatively stable immune parameters such as T cell subset proportions since emotional changes occur frequently and stable immune parameters do not fluctuate with such frequency. On the other hand, emotional response tendencies during a specific time period may be indicative of chronic affective states with consequent changes in immunity.

Are these chronic affective states or tendencies to respond with particular emotions synonymous with affect as measured by the POMS? The POMS requests subjects to describe their general emotional response over a month period--possibly their "free-floating" affective state--whereas the emotion experience ratings request a rating of emotion intensity in response to a particularly charged situation. In other words, the POMS requests overall feelings and the experience ratings request responses elicited by specific situations. Thus the average POMS value is the average overall reported feeling of the subject over the study period while the average emotion rating is their average reported response to highly provocative situations.

In other areas of research, it has been demonstrated that baseline unprovoked levels of state are not as predictive of biological phenomena as are responses made when provoked. For example, the observed level of hostility in cardiac patients as measured by non-verbal and vocal behavior is not as predictive of future cardiac events as is the level of hostility displayed during "provocation" in the interview, i.e., when the interviewer asks the patients to describe a situation that made them feel upset or when the interviewer speaks too slowly during the interview (and aggravates the fast-paced patient) (Rosenman & Chesney, 1980). The data from the current study suggest that self-reported basal levels of affect and self-reported "provoked" levels may have different and in some cases interactive effects on immunity and HSV recurrence. These different patterns might be better understood if an actual provocation were used and observable manifestations of affect tallied (as in Type A research).

Defeat and Immunity

There is a great deal of interest in the relationship between helplessness and related phenomena and the etiology and progression of cancers as well as the immunological processes that protect individuals from the development and spread of tumors. Experimental studies have shown that animals exposed to stressors will become more immunologically depressed if they have no control over their exposure to the stressor (Laudenslager & Ryan, 1983). No previous data have evaluated the effects of helplessness on immunity in humans, however.

This research study has shown a relationship between chronic feelings of helplessness and depression (the combination was labeled defeat) and suppressor T cells. Individuals who consistently report themselves to feel helpless and depressed over the six month period have fewer suppressor T cells than individuals who feel less depressed and helpless. Multiple regression analyses indicated that the relationship between the defeat measure and suppressor T cells was not merely a function of stress level. In other words, the measure maintains a moderate correlation with the T cell subset even when stress level is included in the regression equation. Thus it appears that this particular combination of feelings of helplessness and depressive affect may be important in its own right in relationship to immunity.

The defeat measure combines a number of different kinds of responses including the depression sub-scale from the POMS, the intensity with which subjects report feelings of helplessness during a situation that made them feel helpless and the intensity of those feelings during recall of the situation, reporting that they have little control

over things that happen to them, reporting feeling helpless in dealing with problems, and feeling pushed around in life (the latter three items from the Mastery Scale). Five of the six items focus on some form of helplessness; however the overall scale correlates highly with the POMS depression subscale (r=.84) and functions in relationship to the immunological outcomes in a way similar to the depression sub-scale. Thus, it appears from these data and the factor analysis results that subjects who report feeling depressed also report feeling helpless. Depression is often defined in terms of feelings of helplessness (Gatchel & Baum,1983); these data support this definition. Future work is necessary, however, to more fully define the nature of the phenomena measured by the combination of items in the defeat score.

Social Support and Immunity

The literature on social support and disease has found social support to have either direct and positive effects on health outcome or interactive effects such that social support buffers against the effects of stress. This study failed to confirm either direct positive effects or buffering effects. Instead, social support was found to have a <u>negative</u> relationship to immunity in individuals who were highly stressed. In other words, stress was correlated with fewer helper and suppressor T cells only in subjects with high social support satisfaction and not in subjects with low support satisfaction.

There are a number of interpretations of these data. First, social support satisfaction may not always have positive health implications, as has been suggested by Wortman & Conway (1985). Or it may have ef-

fects in reducing the report of physical symptoms but have no effects on immunological parameters. Social support has not been evaluated in relationship to aspects of immunity, and only rarely in relationship to verifiable immunologically-related diseases, so there are little data with which to compare the results of this study.

Alternatively, social support satisfaction may have different effects depending on the nature of the stressful situation. Much of the previous research on social support has looked at support in the context of current life changes. The composite stress score used in this study included not only current life changes, but chronic ongoing hassles, anticipated events and residual effects of previous life changes. It may be that social support is not as helpful in buffering the effects of some of these types of stressors. For example, distress from previous events (residual stress) may not be as amenable to the helpful effects of advice and information, etc. as current stressful events since the stressor took place some time ago and may just require time for the effects to diminish. In fact, discussing prior stressful events with others may serve to remind individuals of them and increase upset rather than decrease it, since often there is little that can be done to change the event other than attempt to put it out of one's mind. Similarly, many subjects included, on the Anticipated Life Stress Scale, events that they hoped would not occur, that they had very little control over, and that were unlikely to occur but that they worried about anyway, e.g., the company they worked for going bankrupt. Focusing too heavily on low probability events that one cannot control may result in increased levels of upset; certain forms of support and discussion

about these events might contribute to this type of unnecessary attention. Thus, it may be that social support is useful for situations where discussion can have an impact on the situation, can help the individual focus on important aspects of the situation, or help to change the individual's feelings about the situation. However support and discussion may have negative effects if the most effective strategy for dealing with a situation is to put it out of one's mind, temporarily or over the long-term.

The results of this study may be a function of the social support measure used, on the other hand. The scale measures satisfaction with five categories of support (emotional, information, help and assistance, self-esteem, and sense of belongingness) across five referent groups (partner, close friends, co-workers, supervisors, and relatives). The subjects are required to rate their level of satisfaction with the support received of each type by each group on a seven point scale. One of the problems with the scale is that subjects must average their level of satisfaction in relationship to any referent category that includes more than one individual. So for example, if the subject has three close friends, and the subject is very satisfied with the support received from one and very dissatisfied with the support received from the other two, the resulting value will be the subject's average of his or her satisfaction with the three individuals. Thus, it is possible that this averaging procedure washes out the high and low feelings of satisfaction the subject experiences. It is also possible that one dimension of support is more important in buffering stressful effects than others and averaging across all five dimensions obscures the effects of one support

type. Because this scale has only been used in a few studies, it is unclear whether the results are a function of the nature of this particular instrument or whether the same results would have occurred with other instruments. Other support instruments suffer from similar problems and other problems as well (see Thoits, 1983) but it cannot be determined whether other scales might have generated different results. Also, it may have been that the measurement of other forms or dimensions of social support, for example, the number of contacts with supportive others or the reported availability of support may have had a different type of relationship to the outcome measures.

It is also possible that other measurement issues influenced the data generated. This study relied on a composite of self-report measures of stress and on a self-report measure of social support. The measures of stress did not assess the exposure to stressful events; they assessed how upset and worried the subject was about reported past, present and future events. In other words, they do not verify the presence of stressors but rather provide a record of the effects of the events the subject reports to have experienced or expects to experience. For example, the Hassles scale asks subjects to rate how upset or worried they have been about situations such as financial problems. The LES asks subjects to check off major events that have occurred and rate the effect the event has had on their lives.

Given the social support buffering hypothesis, we would expect that when exposed to stressors, individuals with a positive social support network would not become as upset by the stressors and therefore would not show the negative physiological consequences that would be

seen in individuals without support. In other words, the stressors would not cause such emotional and physiological arousal because of the way in which social support helped the individual to cope with or appraise the stressful situation. If that is true, then in this study individuals with high social support scores should actually have low overall stress scores, since the stress score reflects response to stressors. The correlation between the social support score and the composite stress score indicates that there is in a fact a moderate negative correlation between social support satisfaction and the composite stress score (r=-.24, p=.08). Thus, it may be more accurate to conceptualize the composite stress score as a response to stress and not the variable with which social support interacts.

Thoits (1983) has made the point that to adequately conceptualize social support and its relationship to stress and psychological and health outcomes, the buffering variable should not be emotional social support, e.g., satisfaction with support received. Instead the buffering variable should be some form of social interaction, involvement or social role variable (such as role identity or role performance) which can be measured independently of the individual's response to the interaction. Emotional support would then be considered a descriptive phrase that guides the search for the social origins of psychological and physical well-being and links social life to emotional experience. In this way, the confound between the perception of emotional support and the outcome or emotional reaction to this support can be eliminated. Research could then determine whether specific types of interactions between the subject and specific individuals in the subject's network could buffer

the effects of stressful life experience on emotional well-being and consequent physiological state.

Thoits' type of reconceptualization might be useful in a study of this type. If the social support variable were defined in terms of observable or quantifiable interaction qualities then the effects of these qualities in relation to the stress score could be assessed. For example, the interaction of the subject and his or her partner could be analyzed using procedures developed by John Gottman (1979) for analyzing the verbal and non-verbal behavior in marital interaction. It could then be determined if certain interaction qualities protect individuals from emotional and physiological arousal when the subject is exposed to stressful life situations. It would seem that this type of approach would be a more clear test of the interaction of two variables in predicting a third since the interacting variables (e.g., social support and stress) would not be two measures of the same thing, which creates both conceptual and statistical problems.

Coping Flexibility and Immunity

Recently coping researchers have begun to suggest that it may be unreasonable to expect that there are one or two ideal coping strategies that are related to adaptive outcomes, but that what may be most important is the ability to draw on numerous coping methods for handling stressful situations (Cohen et al.; 1982). The coping flexibility measure used in this study was an attempt to assess such a repertoire of coping strategies that might buffer the effects of stress. However, this study did not find an interactive effect of stress and coping flexi-

bility on immunity. Coping flexibility also did not have a direct effect on immunity.

Who are the individuals who were found to use the greatest number of coping modes in dealing with the stressful situations discussed at each monthly interview? It appears that these individuals report more overall stress or upset and worry over life situations and are more anxious than individuals who use fewer coping modes to respond to stressful situations. These correlations may suggest that more coping strategies are required when individuals are exposed to more stressful or anxiety-provoking situations. On the other hand, it may be that highly anxious individuals when exposed to stressful situations exhaust their repertoire of methods to handle the situations, attempting all methods that come to mind, because they cannot find a few effective strategies.

Possibly the lack of findings is attributable to the way coping was assessed. Coping flexibility was assessed (that is, the number of strategies used) rather than the relationship between specific modes and outcome. It may be that the number of strategies used is not related to physiological outcomes because it combines so many different types of strategies, with potentially contradictory effects. Instead, it may be more useful to focus on broad categories of coping strategies as has been done in previous research (e.g., Cohen et al., 1986) or to group the strategies into categories and then look at flexibility within these broad categories.

The coping flexibility measure was actually an indicator of the number of strategies used in dealing with stressors, rather than the repertoire available. It may be that having a number of coping strategies at

one's disposal as a resource upon which to draw is positive. However, the adaptive strategy may be to wisely choose the appropriate strategies for each situation. Effective responders to stressful situations, then, may be those with a large number of coping strategies to draw upon and a small number used at each stressful encounter. Those who use a large number of strategies at each encounter may have many to draw upon but may not make appropriate choices given the nature of the situation. To measure this possible configuration, the researcher might look at the number of different modes used over multiple assessment periods in relationship to the number used at any one encounter.

Also, it is important to closely scrutinize the types of strategies used in response to particular types of situations. There may be types of situations that require a much more circumscribed repertoire of strategies and other situations that would be more adaptively responded to with a great diversity of strategies. Therefore, the researcher could look at coping flexibility only in relationship to situations that might require a variety of approaches and not in relationship to those that require only certain approaches.

Psychosocial Factors and Herpes Recurrence

Stress and recurrence. Many patients report that they have herpes outbreaks when they are under stress. Eighty percent of the subjects in this study believe that stress has something to do with their outbreaks. However, stress measured in numerous ways did not predict the number of recurrences during the study period, nor were high stress periods more likely to be followed by recurrences than low stress periods.

There are a number of possible explanations for the lack of stress effects on recurrence rate. First, there may in actuality be no relationship between stressful life experience and recurrence. Subjects' assumption of this relationship may result from their need to feel that they understand what causes their recurrences and may allow them to feel that they can exert some control over their recurrence rate in the future. To date no prospective studies have found a relationship between stressful life experience and recurrence. The studies that have reported such a relationship involve the retrospective report of the patient once they have had a recurrence and thus suffer from the problems of retrospective bias.

Alternatively, the relationship between stress and HSV recurrence may be quite subtle and depend on an adequate assessment of the timing of the stressors in relationship to the recurrence. For example, despite no significant relationship between stress and recurrence, subjects in the study did report that they had stress-induced recurrences during the study period. In one case, a subject was asked to make a presentation to a school that demanded quite a bit of time and effort and that she reported was quite stressful since she was not confident that she could do the job properly. She had a recurrence two days after the day in which her effort and feelings of anticipatory stress peaked. The study protocol did not pick up the relationship between stress and recurrence in this subject. First, in terms of between subjects effects, she was not a highly stressed individual over the course of the study. Thus her data would not have supported the relationship between stress level over the course of the study and recurrences be-

cause she was a low stress individual with a moderate number of outbreaks.

Second, her stress level did not appear to be high for the month when the preparation for the class occurred because she actually performed quite well in the presentation and so her overall estimation of her stress level for the month was not high. As mentioned previously, the monthly stress assessment required the subjects to average their stress level for the month period, obscuring high stress periods during an otherwise low stress month. Thus, we would not have seen a high stress month preceding a month with a recurrence. Most importantly, her recurrence did not take place in the month following the month she prepared for the class. It took place in the same month, only two days following preparation for the event. Thus, even if she had done poorly on the presentation and her overall stress level had been high for the month, a stress effect on subsequent recurrences would not have been detected.

It is clear that it would have been difficult to detect the relationship between this subject's stressful experience and her subsequent recurrence. First, the relationship could not have been assessed retrospectively, by, for example, asking her during the stress interview to estimate her stress level for each day surrounding the experience and calculating the number of days to the recurrence. Again, this retrospective account would be biased by the fact that she had already had the recurrence and may have reasons for wanting to believe that her recurrence was activated by stress. A simple tallying of the date of the event in relationship to the date of recurrence would not have suf-

ficed since she did not have a recurrence following the presentation but following preparation for the presentation. Therefore, it would have been necessary to have stress level assessments during the experience quite frequently, and probably daily, since the recurrence took place so quickly after her anticipatory stress period and she felt satisfied with her performance quickly after that.

In sum, while no stress effects were detected in this study, the timing of the measurements of stress and the measurements of recurrence precluded the detection of possible relationships due to month long averaging of stress level which may have averaged out high stress and low stress periods as well as obscuring more immediate responses to stress. Thus, future research is needed with more frequent assessment periods in order to determine whether or not stressful life experience is, in fact, predictive of recurrence.

Depression and recurrence. While stress level over the course of the study was not related to recurrence for the entire sample, depression level was correlated with recurrence in analyses which eliminated patients with symptoms of infection. However, within subjects analyses showed that depressive episodes were not more likely to be followed by a recurrence than less depressive episodes. Depressive episodes did not predict recurrence even when only those subjects who reported high levels of depressive symptoms over the study period were included in the analysis. In other words, individuals who are more depressed over the study period have more recurrences than less depressed individuals but their recurrences are not more likely to follow the months when they feel the most depressed.

Because within subject depression effects were not found, it is important to recognize that the between subjects correlation may have occurred between depression and recurrence because individuals with more recurrences are more depressed in response to their recurrent episodes. In other words, depression may be correlated with recurrence rate over the study period because subjects with more recurrences are more depressed than subjects with less recurrences. An inspection of the high depression group and the situations that they report to cause their depression during the stress interviews suggests that in most cases reported depression is not a result of herpes-related situations but other categories of events, e.g., problems on the job, arguments with partner, etc. Also, the depression results are consistent with the data from prospective studies on herpes of the lip which have found that unhappy mood predicts recurrence rate (Luborsky et al., 1976).

It is also possible that both are true; having multiple outbreaks may cause individuals to become depressed and that increased levels of depression over a time period may create a physiological environment conducive to more recurrences. The suppressor T cell data actually tend to support this notion. Depression is correlated with decreased numbers of suppressor T cells and decreased numbers of suppressor T cells occur prior to recurrent episodes as well as immediately following them. Thus, depression could activate a recurrence via changes in T cell subset numbers (or a correlated immunological phenomena) which then result in further episodes of depression which cause suppressor cell decreases (or maintain low levels) which then make further recurrences likely and so on. While this is a plausible hypothesis, further

evidence is required to confirm that in fact depression can act on HSV recurrence rates and that the correlation is not exclusively the effect of HSV on depression.

Emotion and recurrence. Emotion re-experience scores were related to HSV recurrence. Individuals who could most easily re-experience happy and sad feelings had longer recurrence free periods after the assessment period than did others. These results are interesting when combined with the depression results given that some forms of depression involve a blunting of affect. Thus, depressed individuals may not easily re-experience their feelings and either the depressive mood or the inability to re-experience happy and sad feelings may have a negative impact on disease state.

Non-psychological Factors and Recurrence

Psychological factors were compared to non-psychological factors in the prediction of HSV recurrence. Three factors were chosen because anecdotal and some research evidence suggest that they play a role in the activation of either oral or genital recurrences. These factors were fatigue, the menstrual cycle, and infection. Fatigue and the menstrual cycle did not appear to predict recurrence whereas the infection score had a close to significant relationship to recurrence. Although these factors did not appear to play a major role in predicting recurrence rate across the subject sample, it was considered that sub-groups of subjects may be responding to these factors and that recurrences might only be predicted by psychological factors in subjects who did not manifest high levels of these factors. Therefore analyses were performed

on the sample with the subjects with high levels of fatigue removed, and then with subjects with high levels of infection symptoms removed, and then with subjects whose recurrences appeared to be tied to their menstrual cycle removed. The only relationship between psychological factors and recurrence in any of these groups occurred, as previously described, in the group without high levels of symptoms of infection.

With a larger sample, and an increased number of time points, it would be very interesting to group subjects based on their within subjects correlation between these factors and recurrence. Thus, subjects who have a high correlation between fatigue and recurrence could be isolated, for example. It could then be determined if some individuals have their recurrences predominantly determined by a single factor or a particular interaction of factors.

Health-related behaviors were another group of non-psychological factors studied in order to determine if psychological factors acted on HSV recurrence exclusively via changes in these behaviors. While specific behaviors did appear to correspond to psychological factors (i.e., exercise, hours of sleep) and also to predict both T cell sub-set numbers and recurrences (i.e., alcohol consumption, exercise, and hours of sleep) the strength of the correlations between psychological factors and these outcomes was maintained when the variance attributable to the unique effects of the psychological factors was evaluated.

Future research might more fully evaluate this problem by studying other health factors such as diet, or by using non-self-report measures of health behaviors such as nutritional assays or measures of physical stamina. Again, sub-groups may respond to the lack of sleep or alcohol consumption and not the sample as a whole.

What do these findings tell us about the validity of the nerve versus skin trigger theory? To reiterate, viral particles may be shed to the periphery throughout the "latent' state requiring a local defect for an increase in viral replication and lesion formation. Alternatively, virus may only be shed from the ganglion in response to a trigger to the nerve. Do the factors predicting recurrence appear to be acting at the nerve or local level? Depression, infection and suppressor T cells could all act at the local level to create an environment conducive to viral replication. Both depression and infection could alter the immunological milieu and the host response to the virus. The decrease in suppressor-cytotoxic T cells prior to recurrence could be a manifestation of this subtle change. Depression could also activate a parasympathetic pathway acting on the sacral ganglion directly. However, it is unclear how infection or a T cell subset change could act on the neuron. Thus, these data tend to support a skin trigger or skin and nerve trigger theory more than they do a nerve trigger theory alone. However, it is also possible that other unmeasured factors are acting in conjunction with measured factors to support a combined skin and neural trigger theory. This possibility could be explored in future research.

Review of Methodological Issues

A number of methodological issues arise in the design of research on a random "segment of life" which attempts to study the covariation between two systems--the psychological and the biological. These issues will be discussed below.

Number of Assessment Periods

This study utilized six monthly assessment periods. Another approach might have been to study only one assessment period at which time psychosocial measures could have been administered, blood drawn for immunological assay, and the length of time to the next recurrence tabulated. Data from this study suggest that the latter approach would have produced unreliable and possibly spurious results. For example, when the correlations between psychological factors and immunity at each month are reviewed, it becomes clear that they are very variable. For example, when one looks at the relationship between hostility and suppressor T cells for each month separately, the correlations range from -.15 to -.59. A one time correlation is clearly an unreliable measure of the relationship between psychological and biological factors; however, the majority of the data in psychoneuroimmunology is based on a one-time assessment (with the research by Kiecolt-Glaser et al. a notable exception). Averaging over six administrations increases the reliability and generality of the correlations by decreasing the likelihood of spurious findings due to extraneous factors (Epstein, 1983). Increasing the frequency of assessment to greater than six would further reduce error and would also allow the data to be analyzed using a time series approach. This data analytic approach may be most appropriate for determining the covariation between two systems; however, it requires more than six data points for its use.

Length of Assessment Periods

What is the most appropriate length of time for each assessment to cover? This is a difficult question which should be based on three issues. First, how variable are the psychological phenomena under study? If mood is of primary concern, for example, then it should be considered whether a measure of mood that covers a month period is representative of the entire month or only representative of a much shorter time period. As discussed previously, it appears that a month period is too long for both stress and mood assessment. Subjects reported to the experimenter that they averaged their stressful periods with their nonstressful periods. The stress interviews revealed examples of very stressful events occuring during months that appeared to be relatively unstressful because of this averaging process. And immediate relationships reported between an event and recurrence could not be detected. Thus, it is likely that a shorter assessment period, possibly one week, would have been more appropriate given the nature of the variables under study.

Second, the variability of the biological phenomena evaluated must be considered. T cell sub-set percentages for example are fairly stable over time so a longer assessment period may be adequate but other assays, for example, natural killer cell activity, are highly variable and may require much more frequent assessments.

Third, the timing of changes in psychological and biological factors in relationship to the health measure studied must be considered. How long does it take from a major change in stress or immunity to a recurrence of HSV, for example? Unfortunately, little is known about the

changes in immunity prior to recurrences since subjects have not been followed over time and assessed periodically on immune status. The data from this study suggest that T cell percentages can vary from week to week. Also, there is anecdotal and animal evidence that presumed HSV triggers such as sunlight and skin trauma can result in a recurrence quite quickly, in as little as one day. It is important to gather together as much data and anecdotal and preliminary findings as possible so that an adequate time frame is used in the study and relationships between triggers and outcome are not obscured.

Assessment of Outcome

This study did not rely on self-report measures of health status exclusively. The outcome variables were immunological statusand documented recurrences. Thus, this study does not suffer from the problem of confounded relationships between independent and dependent variables as do many of the studies in the stress-disease literature. The inconsistencies in results of this study when compared to other stress-disease studies may follow from the lack of confounding and the reduced likelihood of "false-positive" relationships.

On the other hand, the HSV recurrence data are not based solely on documented recurrences. Approximately 60 percent of recurrences were not documented because of difficulty scheduling appointments with doctors, etc. Therefore it is possible that the HSV outcome is itself confounded with psychological factors. For example, depressed patients may be more likely to misconstrue their irritated skin as herpes lesions than non-depressed patients. However, a number of aspects of the

study make this possibility less likely. First, it is much more likely that error will occur in the recall of a variety of health symptoms such as headaches, stomach aches, sore throats, etc. than in the recall of HSV recurrences. Recurrences are readily visually detectable on the skin and do not require judgments about feelings, such as headaches do. Also, the subject need only pay attention to one type of physical phenomena rather than multiple, and subjects are vigilant to these symptoms since they require major changes in behavior such as sexual abstinence in order to avoid transmitting the virus to others. However, genital herpes is an emotionally charged disease and it may be that subjects fail to detect lesions for psychological reasons, such as denial that they must be sexually abstinent or inform a new partner that they have HSV. Therefore, future research should include more incentives for subjects to have recurrences documented so that the possibility of confounding can be reduced. Confounding can never be totally eliminated however unless patients are monitored constantly.

Assessment of Independent Variables

This study relied almost exclusively on self-report measures of psychosocial factors. Stress, mood, social support and defeat were measured with questionnaires. Emotion and coping were measured from an interview. As discussed above, this type of assessment may have caused problems, i.e., reporting biases may have obscured the real relationship between these psychosocial factors and outcome. Two methods could be used to reduce these problems. If only self-report assessments are possible, then a measure of social desirability and/or

other reporting styles could be added to the assessment repertoire. Subjects could then be grouped on the basis of their reporting style and relationships calculated between psychological factors and outcome separately for the two groups. For example, the Weinberger, Schwartz, and Davidson (1979) technique for measuring repression-sensitization could be administered. This scale purports to differentiate subjects who report themselves to be low on anxiety and are truly low anxious from those who also report low anxiety but are actually "repressing" their anxious feelings.

A second alternative would be to include non-self report measures of psychological status. For example, measures of facial expression of emotional state or vocal indicators of emotion could be added to self-report assessments. These techniques are not subject to manipulation by reporting styles and may provide a more valid measure of emotional state, especially in conjunction with self-report. Alternatively, a projective test (such as the Thematic Aperception Test) could be administered. If strict coding guidelines are followed, this test measures in a reliable fashion a number of factors, such as helplessness or social anxiety. And projective tests appear to suffer less from reporting biases than do non-projective tests. However, there are many problems with projective testing which must be balanced against its advantages when a battery is selected.

Theoretical Implications

These results support a variation of the classic stress-disease model. In the classic model, stressful experiences, which are not moderated by coping processes and personal and social resources, result in dysphoric affect and physiological change (Lazarus & Folkman, 1984). Personal resources that have been evaluated include "hardiness," (Kobasa, 1979), mastery," (Pearlin & Schooler, 1978), and others. The data from this study suggest that it is possible that the presence of stressful life experiences are not required for the generation of negative affective and physiological change. Rather, the lack of correspondence between the overall goals and aspirations of the individual on the one hand and specifics of the individuals' life situation on the other, may result in negative emotional states and health outcomes. In this model, then, it is the absence of desirable situations rather than exclusively the presence of undesirable situations that can result in negative outcomes. The high correlation between goal progression and depression suggests that one possible outcome of this absence is depression. Thus prolonged dissatisfaction with one's overall life situation may result in depression with possible health consequences.

It may be important to conceptualize the psychosocial factors with potential health implications along two dimensions. First are the exigencies of the current life situation including for example, major life changes, chronic ongoing situations of daily living, anticipation of future difficulties as well as the nature of the individuals' social relationships and the coping strategies they are using to handle stressful situations. The second dimension would include more stable characteristics

of the individual and the environment. Current theory includes such personal resources as hardiness and coping repertoire within this stable dimension. This dimension would include characteristics which determine, in part, the vulnerability of the individual to the effects of current situations. The individual's goals and aspirations could be included in this dimension and considered in conjunction with the extent to which these goals have been realized. The affective response would then follow from the combination of the current life situation and the more stable characteristics of the person and his or her environment. Emotional distress might result not only from the occurrence of stressful life situations inadequately moderated by coping processes and stable characteristics such as hardiness, but also from the absence of desirable situations or, phrased another way, the lack of fit between the individual's goals and his or her current life situation. In the second case, stressful life situations are not required for a negative emotional response.

Clearly goal progression and stressful experience are interacting concepts. Individuals who feel that they are not fulfilling their goals may perceive life circumstances as more stressful than individuals who are satisfied with their goal attainment. And individuals exposed to multiple stresses will probably be less satisfied with their goal attainment. Also, the absence of particularly desired situations probably suggests the presence of particularly undesired situations, e.g., feeling that one's career is not advancing may suggest the presence of an undesirable work situation or unchallenging work. Nevertheless, these data suggest that goal progression or the absence of desirable life

changes may be an important variable for inclusion into theoretical and research paradigms of stress and disease. Previous research has focused almost exclusively on the presence of stressful experience and has neglected to measure the unmet needs of individuals and their physiological and health consequences.

In addition these data suggest that a more complex model of affective responses to life circumstances would help to more fully formulate the relationship between psychological and physiological processes. These data suggest that long-term affective states such as moods may have different effects on immunity than tendencies to respond to provocative situations with particular emotional reactions. Therefore, it may be useful to include both forms of affective response as well as methods for managing emotion when attempting to understand the relationships among affect, immunity and health outcome.

The stress-disease model could actually be reframed in terms of the affective response. First, the relationship of affective states to various physiological changes could be determined. Four types of affective variables could be evaluated: emotional responses to situations, more long-term "free floating" affective states such as mood states, characteristic tendencies to respond emotionally to provocative situations, and characteristic tendencies to experience one mood more often than another. Then, methods of coping with affective states could be evaluated with specific reference to emotion management strategies or those strategies that modify emotional responses. For example, recent capabilities to differentiate "felt" from "unfelt" smiles using facial asymmetry data (Ekman & Friesen, 1983) could add considerable information

about characteristic methods for managing emotion and its expression. Social support could be conceived in terms of the way in which it supports particular emotion management strategies as Thoits (1985) has proposed or the way in which it directly influences emotional state. For example, social interaction could be observed as it produces changes in emotional states as has been done in the work of Gottman (1979). Other personal resources such as hardiness could be viewed as potential moderators of affective state and of affect management strategies. Stressful experiences could then be defined in terms of their provocation of affective state and would include both the presence of undesirable events and the absence of desirable events. The advantage of this type of framework is that it would focus on the affective response as the final link in the chain to physiological changes and health risk as well as those psychosocial factors which influence affective response.

Future Research

Future research on the relationship between psychosocial factors, immunity and genital herpes simplex recurrence could extend the results of the current study in the following ways. First, it is important to followup on the data which suggest a relationship between depression and goal progression and recurrence rate. It could then be determined if depression in interaction with other factors triggers recurrences or if recurrences cause depression or if both are true. It would be important to determine if only a sub-group of individuals respond to depressive episodes with recurrences and to describe this sub-group more fully. Also, it would be important to determine the factors which interact

with depression in triggering recurrences. For example, depression and lack of goal satisfaction may provide the background vulnerability against which certain recurrence triggers might be more likely to result in a recurrence. In other words, depression might result in a local immunological defect. If at the same time virus shedding takes place or is triggered by another factor such as trauma to the skin, then a recurrence may take place. On the other hand, depression may cause a local immunological defect which will have no impact on lesion formation if virus is not shed to the periphery.

In addition, the role of stress in activating recurrences must be more fully explored. Since month long evaluation periods in this study precluded determining whether acute changes in stress resulted in immediate recurrences, it is important to evaluate these relationships more fully. It would be useful to include a full battery of stress inventories as was used here but to administer them more frequently so that rapid changes in stress could be evaluated.

The role of affect, both mood state and tendencies to respond to situations with specific emotions, should be evaluated more fully. Interesting results were obtained using an exploratory method of defining emotion; these results could be followed up on using a more intensive exploration of affect and more standardized and valid methods of measuring affect including behavioral measures which are not influenced by reporting biases. In this way the interaction effect found between negative mood and the happiness ratings could be better understood.

The role of other immunological factors in the etiology of HSV recurrences warrants exploration. It would be useful to evaluate func-

tional assays (i.e., those that look at the functioning of various immunological cells) and particularly those which display some within subject variability since these may be good candidates for being influenced by the changing emotional state of the individual. Also, assays which might shed light on the role of suppressor-cytotoxic T cells in the possible activation of recurrence would be useful.

Future research in this area could benefit from the following methodological suggestions: frequent assessments of both psychosocial and immunological factors over an extended period of time, reliance as much as possible on non-self-report data in conjunction with self-report, measurement of reporting style and sub-grouping of subjects in terms of differences in reporting style, and the combination of both assessment of the current life situation and more stable characteristics of the individual which may interact with the properties of the current life situation. Recasting the theoretical framework upon which the study is based in terms of the affective responses which may produce the immunological and consequent recurrence changes would streamline variable selection and focus in on the variables most relevant to the physiological processes under study.

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Appendix A

LIFE EXPERIENCES SURVEY

Instructions: Listed below are a number of events which may bring about changes in the lives of those who experience them. Rate each event that occurred in your life during the past 6 months as GOOD or BAD (circle which one applies). Show how much the event affected your life by circling the appropriate number from "1" to "7", with "1" indicating no effect at all on your life and "7" indicating an extreme effect on your life.

If you have not experienced a particular event in the past 6 months, leave it blank.

Please look through the entire list before you begin so that you will have an idea of the type of events you will be asked to rate.

Event	Type of Event	Effect of Event on Your Life (not at all → extremely)						
1. Marriage	good bad	1	2	3	4	5	6	7
2. Detention in jail or comparable institution	good bad	1	2	3	4	5	6	7
3. Death of spouse	good bad	1	2	3	4	5	6	7
4. Major change in sleeping habits (much more or much less sleep)	good bad	1	2	3	4	5	6	7
5. Death of close family member								
a. mother	good bad	1	2	3	4	5	6	7
b. father	good bad	1	2	3	4	5	6	7
c. brother	good bad	1	2	3	4	5	6	7
d. sister	good bad	1	2	3	4	5	6	7
e. grandmother	good bad	1	2	3	4	5	6	7
f. grandfather	good bad	1	2	3	4	5	6	7
g. other _____	good bad	1	2	3	4	5	6	7
6. Major change in eating habits (much more or much less food intake)	good bad	1	2	3	4	5	6	7
7. Foreclosure on mortgage or loan	good bad	1	2	3	4	5	6	7
8. Death of close friend	good bad	1	2	3	4	5	6	7
9. Outstanding personal achievement	good bad	1	2	3	4	5	6	7

Event	Type of Event	Effect of Event on Your Life (not at all … extremely)						
10. Minor law violations (traffic tickets, disturbing the peace, etc.)	good bad	1	2	3	4	5	6	7
11. Male: Wife's/Girlfriend's pregnancy	good bad	1	2	3	4	5	6	7
12. Female: Pregnancy	good bad	1	2	3	4	5	6	7
13. Change in work situation (different work responsibility, major change in working conditions, working hours, etc.)	good bad	1	2	3	4	5	6	7
14. New job	good bad	1	2	3	4	5	6	7
15. Serious illness or injury of close family member:								
a. mother	good bad	1	2	3	4	5	6	7
b. father	good bad	1	2	3	4	5	6	7
c. brother	good bad	1	2	3	4	5	6	7
d. sister	good bad	1	2	3	4	5	6	7
e. grandmother	good bad	1	2	3	4	5	6	7
f. grandfather	good bad	1	2	3	4	5	6	7
g. other _____	good bad	1	2	3	4	5	6	7
16. Sexual difficulties	good bad	1	2	3	4	5	6	7
17. Trouble with employer (in danger of losing job, being suspended, demoted, etc.)	good bad	1	2	3	4	5	6	7
18. Trouble with in-laws	good bad	1	2	3	4	5	6	7
19. Major change in financial status (a lot better off or a lot worse off)	good bad	1	2	3	4	5	6	7
20. Major change in closeness of family members (increase or decrease in closeness)	good bad	1	2	3	4	5	6	7
21. Gaining a new family member (through birth, adoption, family member moving in, etc.)	good bad	1	2	3	4	5	6	7
22. Change of residence	good bad	1	2	3	4	5	6	7

	Event	Type of Event	Effect of Event on Your Life (not at all … extremely)						
23.	Marital separation from mate (due to conflict)	good bad	1	2	3	4	5	6	7
24.	Major change in church activities (increased or decreased attendance)	good bad	1	2	3	4	5	6	7
25.	Marital reconciliation with mate	good bad	1	2	3	4	5	6	7
26.	Major change in number of arguments with spouse (a lot more or a lot less)	good bad	1	2	3	4	5	6	7
27.	Married male: Change in wife's work outside the home (beginning work, ceasing work, changing to a new job, etc.)	good bad	1	2	3	4	5	6	7
28.	Married female: Change in husband's work (loss of job, beginning new job, retirement, etc.)	good bad	1	2	3	4	5	6	7
29.	Major change in usual type and/or amount of recreation	good bad	1	2	3	4	5	6	7
30.	Borrowing more than $10,000 (buying home, business, etc.)	good bad	1	2	3	4	5	6	7
31.	Borrowing less than $10,000 (buying car, TV, getting school loan, etc.)	good bad	1	2	3	4	5	6	7
32.	Fired from job	good bad	1	2	3	4	5	6	7
33.	Male: Wife/Girlfriend having abortion	good bad	1	2	3	4	5	6	7
34.	Female: Having abortion	good bad	1	2	3	4	5	6	7
35.	Major personal illness or injury	good bad	1	2	3	4	5	6	7
36.	Major change in social activities (e.g., parties, movies, visiting)	good bad	1	2	3	4	5	6	7
37.	Major change in living conditions of family (building new home; remodeling; deterioration of home, neighborhood, etc.)	good bad	1	2	3	4	5	6	7
38.	Divorce	good bad	1	2	3	4	5	6	7
39.	Serious injury or illness of close friend	good bad	1	2	3	4	5	6	7

	Event	Type of Event		Effect of Event on Your Life						
				not at all						extremely
40.	Retirement from work	good	bad	1	2	3	4	5	6	7
41.	Son or daughter leaving home (due to marriage, college, etc.)	good	bad	1	2	3	4	5	6	7
42.	Ending of formal schooling	good	bad	1	2	3	4	5	6	7
43.	Separation from spouse (due to work, travel, etc.)	good	bad	1	2	3	4	5	6	7
44.	Engagement	good	bad	1	2	3	4	5	6	7
45.	Breaking up with boyfriend/girlfriend	good	bad	1	2	3	4	5	6	7
46.	Leaving home for the first time	good	bad	1	2	3	4	5	6	7
47.	Reconciliation with boyfriend/ girlfriend	good	bad	1	2	3	4	5	6	7
48.	Beginning a new schooling experience at a higher academic level (college, graduate school, professional school, etc.)	good	bad	1	2	3	4	5	6	7
49.	Changing to a new school at same academic level (undergraduate, graduate, etc.)	good	bad	1	2	3	4	5	6	7
50.	Academic probation	good	bad	1	2	3	4	5	6	7
51.	Being dismissed from dormitory or other residence	good	bad	1	2	3	4	5	6	7
52.	Failing an important exam	good	bad	1	2	3	4	5	6	7
53.	Changing a major	good	bad	1	2	3	4	5	6	7
54.	Failing a course	good	bad	1	2	3	4	5	6	7
55.	Dropping a course	good	bad	1	2	3	4	5	6	7
56.	Joining a fraternity/sorority	good	bad	1	2	3	4	5	6	7
57.	Financial problems concerning school (in danger of not having sufficient money to continue)	good	bad	1	2	3	4	5	6	7

Other recent experiences (in the last 6 months) which have had an impact on your life. Please list and rate:

	Event	Type of Event		Effect of Event on Your Life						
				not at all						extremely
58.		good	bad	1	2	3	4	5	6	7
59.		good	bad	1	2	3	4	5	6	7
60.		good	bad	1	2	3	4	5	6	7

Now, please look over the events that have occurred in the past 6 months and circle those events that have occurred within the last month.

Appendix B

DAILY HASSLES SCALE

Directions: Hassles are irritants that can range from minor annoyances to fairly major pressures, problems, or difficulties. They can occur few or many times.

Listed below are a number of ways in which a person can feel hassled. First, circle the hassles that have happened to you in the past month. Then look at the numbers on the right of the items you circled. Indicate by circling 1 through 7 how much a problem each of the circled hassles has been for you in the past month. If a hassle did not occur in the last month, do NOT circle it.

HASSLES:

		not at all						extremely
(1)	Misplacing or losing things	1	2	3	4	5	6	7
(2)	Troublesome neighbors	1	2	3	4	5	6	7
(3)	Social obligations	1	2	3	4	5	6	7
(4)	Inconsiderate smokers	1	2	3	4	5	6	7
(5)	Troubling thoughts about your future	1	2	3	4	5	6	7
(6)	Thoughts about death	1	2	3	4	5	6	7
(7)	Health of a family member	1	2	3	4	5	6	7
(8)	Not enough money for clothing	1	2	3	4	5	6	7
(9)	Not enough money for housing	1	2	3	4	5	6	7
(10)	Concerns about owing money	1	2	3	4	5	6	7
(11)	Concerns about getting credit	1	2	3	4	5	6	7
(12)	Concerns about money for emergencies	1	2	3	4	5	6	7
(13)	Someone owes you money	1	2	3	4	5	6	7
(14)	Financial responsibility for someone who doesn't live with you	1	2	3	4	5	6	7
(15)	Cutting down on electricity, water, etc	1	2	3	4	5	6	7
(16)	Smoking too much	1	2	3	4	5	6	7
(17)	Use of alcohol	1	2	3	4	5	6	7
(18)	Personal use of drugs	1	2	3	4	5	6	7
(19)	Too many responsibilities	1	2	3	4	5	6	7
(20)	Decisions about having children	1	2	3	4	5	6	7

The Hassles Scale
Page Two

		not at all						extremely
(21)	Non-family members living in your house.....	1	2	3	4	5	6	7
(22)	Care for pet.....	1	2	3	4	5	6	7
(23)	Planning meals.....	1	2	3	4	5	6	7
(24)	Concerned about the meaning of life.....	1	2	3	4	5	6	7
(25)	Trouble relaxing.....	1	2	3	4	5	6	7
(26)	Trouble making decisions.....	1	2	3	4	5	6	7
(27)	Problems getting along with fellow workers.....	1	2	3	4	5	6	7
(28)	Customers or clients give you a hard time.....	1	2	3	4	5	6	7
(29)	Home maintenance (inside).....	1	2	3	4	5	6	7
(30)	Concerns about job security.....	1	2	3	4	5	6	7
(31)	Concerns about retirement.....	1	2	3	4	5	6	7
(32)	Laid-off or out of work.....	1	2	3	4	5	6	7
(33)	Don't like current work duties.....	1	2	3	4	5	6	7
(34)	Don't like fellow workers.....	1	2	3	4	5	6	7
(35)	Not enough money for basic necessities.....	1	2	3	4	5	6	7
(36)	Not enough money for food.....	1	2	3	4	5	6	7
(37)	Too many interruptions.....	1	2	3	4	5	6	7
(38)	Unexpected company.....	1	2	3	4	5	6	7
(39)	Too much time on your hands.....	1	2	3	4	5	6	7
(40)	Having to wait.....	1	2	3	4	5	6	7
(41)	Concerns about accidents.....	1	2	3	4	5	6	7
(42)	Being lonely.....	1	2	3	4	5	6	7
(43)	Not enough money for health care.....	1	2	3	4	5	6	7
(44)	Fear of confrontation.....	1	2	3	4	5	6	7
(45)	Financial security.....	1	2	3	4	5	6	7
(46)	Silly practical mistakes.....	1	2	3	4	5	6	7
(47)	Inability to express yourself.....	1	2	3	4	5	6	7
(48)	Physical illness.....	1	2	3	4	5	6	7

		not at all						extremely
(49)	Side effects of medication	1	2	3	4	5	6	7
(50)	Concerns about medical treatment	1	2	3	4	5	6	7
(51)	Physical appearance	1	2	3	4	5	6	7
(52)	Fear of rejection	1	2	3	4	5	6	7
(53)	Difficulties with getting pregnant	1	2	3	4	5	6	7
(54)	Sexual problems resulting from physical problems	1	2	3	4	5	6	7
(55)	Sexual problems other than those resulting from physical problems	1	2	3	4	5	6	7
(56)	Concerns about health in general	1	2	3	4	5	6	7
(57)	Not seeing enough people	1	2	3	4	5	6	7
(58)	Friends or relatives too far away	1	2	3	4	5	6	7
(59)	Preparing meals	1	2	3	4	5	6	7
(60)	Wasting time	1	2	3	4	5	6	7
(61)	Auto maintenance	1	2	3	4	5	6	7
(62)	Filling out forms	1	2	3	4	5	6	7
(63)	Neighborhood deterioration	1	2	3	4	5	6	7
(64)	Financing children's education	1	2	3	4	5	6	7
(65)	Problems with employees	1	2	3	4	5	6	7
(66)	Problems at work due to being a man or woman	1	2	3	4	5	6	7
(67)	Declining physical abilities	1	2	3	4	5	6	7
(68)	Being exploited	1	2	3	4	5	6	7
(69)	Concerns about bodily functions	1	2	3	4	5	6	7
(70)	Rising prices of common goods	1	2	3	4	5	6	7
(71)	Not getting enough rest	1	2	3	4	5	6	7
(72)	Not getting enough sleep	1	2	3	4	5	6	7
(73)	Problems with aging parents	1	2	3	4	5	6	7
(74)	Problems with your children	1	2	3	4	5	6	7
(75)	Problems with persons younger than yourself	1	2	3	4	5	6	7
(76)	Problems with your lover	1	2	3	4	5	6	7

		not at all						extremely
(77)	Difficulties seeing or hearing	1	2	3	4	5	6	7
(78)	Overloaded with family responsibilities	1	2	3	4	5	6	7
(79)	Too many things to do	1	2	3	4	5	6	7
(80)	Unchallenging work	1	2	3	4	5	6	7
(81)	Concerns about meeting high standards	1	2	3	4	5	6	7
(82)	Financial dealings with friends or acquaintances	1	2	3	4	5	6	7
(83)	Job dissatisfactions	1	2	3	4	5	6	7
(84)	Worries about decisions to change jobs	1	2	3	4	5	6	7
(85)	Trouble with reading, writing, or spelling abilities	1	2	3	4	5	6	7
(86)	Too many meetings	1	2	3	4	5	6	7
(87)	Problems with divorce or separation	1	2	3	4	5	6	7
(88)	Trouble with arithmetic skills	1	2	3	4	5	6	7
(89)	Gossip	1	2	3	4	5	6	7
(90)	Legal problems	1	2	3	4	5	6	7
(91)	Concerns about weight	1	2	3	4	5	6	7
(92)	Not enough time to do the things you need to do	1	2	3	4	5	6	7
(93)	Television	1	2	3	4	5	6	7
(94)	Not enough personal energy	1	2	3	4	5	6	7
(95)	Concerns about inner conflicts	1	2	3	4	5	6	7
(96)	Feel conflicted over what to do	1	2	3	4	5	6	7
(97)	Regrets over past decisions	1	2	3	4	5	6	7
(98)	Menstrual (period) problems	1	2	3	4	5	6	7
(99)	The weather	1	2	3	4	5	6	7
(100)	Nightmares	1	2	3	4	5	6	7
(101)	Concerns about getting ahead	1	2	3	4	5	6	7
(102)	Hassles from boss or supervisor	1	2	3	4	5	6	7
(103)	Difficulties with friends	1	2	3	4	5	6	7
(104)	Not enough time for family	1	2	3	4	5	6	7

		not at all						extremely
(105)	Transportation problems	1	2	3	4	5	6	7
(106)	Not enough money for transportation	1	2	3	4	5	6	7
(107)	Not enough money for entertainment and recreation.	1	2	3	4	5	6	7
(108)	Shopping	1	2	3	4	5	6	7
(109)	Prejudice and discrimination from others	1	2	3	4	5	6	7
(110)	Property, investments, or taxes	1	2	3	4	5	6	7
(111)	Not enough time for entertainment and recreation..	1	2	3	4	5	6	7
(112)	Yardwork or outside home maintenance	1	2	3	4	5	6	7
(113)	Concerns about news events	1	2	3	4	5	6	7
(114)	Noise	1	2	3	4	5	6	7
(115)	Crime	1	2	3	4	5	6	7
(116)	Traffic	1	2	3	4	5	6	7
(117)	Pollution	1	2	3	4	5	6	7

Have we missed any of your hassles? If so, write them in below:

(118)	_____	1	2	3	4	5	6	7
(119)	_____	1	2	3	4	5	6	7
(120)	_____	1	2	3	4	5	6	7

Appendix C

RESIDUAL STRESS SCALE

Previous Life Experiences

Listed below are the life experiences you indicated have occurred in your life over the past 6 months.

1.

2.

3.

4.

5.

6.

7.

Residual Effects of Life Experiences

Sometimes experiences that occurred some time ago still continue to affect a person, either causing changes in their life situation or changes emotionally. For example, if you changed jobs 6 months ago you might still be adjusting to the new job situation. Or if you ended a relationship 6 months ago you might still be thinking about the other person alot. Do you think that any of the past experiences listed above are still affecting you?

Please look over the life experiences described above and list those (if any) that have been affecting you in some way over the past month. Then rate on a scale from 1 to 7 how upset or worried you have been over the past month as a result of the current effects of this experience.

(continued on next page)

experience	level of upset or worry						
	not at all						extremely
1.	1	2	3	4	5	6	7
2.	1	2	3	4	5	6	7
3.	1	2	3	4	5	6	7
4.	1	2	3	4	5	6	7
5.	1	2	3	4	5	6	7

Appendix D

ANTICIPATED LIFE STRESS SCALE

Sometimes people become upset or worried about events that have not yet occurred but are expected to occur in the future. Are there any situations that you anticipate may be occurring in your life in the next 6 months or fear may occur in the next 6 months? If so, over the past month, have you been upset or worried about this possible upcoming experience? Please list the experiences that you anticipate might occur in the next 6 months and then rate how upset or worried you have been over the past month about each event.

Possible Upcoming Life Experience	Level of Upset or Worry						
	not at all						extremely
1.	1	2	3	4	5	6	7
2.	1	2	3	4	5	6	7
3.	1	2	3	4	5	6	7
4.	1	2	3	4	5	6	7
5.	1	2	3	4	5	6	7

Appendix E

HERPES STRESS SCALE

Rate on the 7 point scale below how upset or worried you felt in the previous month in relation to each situation described below. A "1" would indicate that the situation did not cause you to feel upset or worried at all. A "7" would indicate that the situation caused you to feel as upset or worried as you have ever felt.

1 2 3 4 5 6 7
not at all extremely

We would like to focus on situations that are related to having herpes. These situations may be stressful to some people and not at all stressful to others.

First, does the fact that you have herpes influence your sexual activity or your feelings about sexual relationships in any way?

Yes No

If so, how upset or worried did you feel this month about sexual concerns related to herpes (even if you have not been sexually active)?

1 2 3 4 5 6 7
not at all extremely

Second, has the fact that you have herpes influenced your sense of attractiveness or the way you think about your body?

Yes No

If so, how upset or worried have you felt this month while thinking about your body or your attractiveness?

1 2 3 4 5 6 7
not at all extremely

Third, do you have any fear or anxieties about possible future health consequences resulting from having herpes?

Yes No

If so, how upset or worried did you feel this month about these possible health consequences?

1 2 3 4 5 6 7
not at all extremely

Fourth, how upset or worried or fearful are you of giving herpes to someone?

1 2 3 4 5 6 7 does not
not at all extremely apply

Fifth, do you experience any pressure from your partner about your having herpes?

Yes No does not apply

If so, how upset or worried are you about this pressure?

1 2 3 4 5 6 7
not at all extremely

Sixth, how upset or worried or fearful are you of the possibility of having a recurrence?

1 2 3 4 5 6 7
not at all extremely

Appendix F

GOAL PROGRESSION SCALE

Instructions given verbally: the Values and Commitments Inventory consists of a list of values or goals. Please read over the list. Choose the five goals that are most important or essential to you at this point in your life.

An ESSENTIAL item is one which is extremely necessary to you, personally, if you are to have a good life.

An IMPORTANT item is one which is important, but not absolutely necessary to a good life.

A DESIRABLE item is one which is agreeable, but not especially important to a good life.

NOT MY CONCERN describes an item which means nothing to you, one way or the other.

A REJECTED item is one which you do not desire or want for yourself.

ESSENTIAL/IMPORTANT

Maintain close relationships with relatives..... _____

Try things, be enterprising..... _____

Have worthy beliefs, values..... _____

Live within my means..... _____

Be aware, understanding..... _____

Be a leader..... _____

Be successful in getting concrete rewards..... _____

Satisfy any appetite or impulse..... _____

Career advancement..... _____

Have sexual satisfaction..... _____

ESSENTIAL/IMPORTANT

Cultivate close friendships..... _____

Be helpful, charitable..... _____

Compete successfully..... _____

Increase knowledge..... _____

Have power, control..... _____

Be generous to others..... _____

Dedicate myself to causes..... _____

Achieve acknowledgement, praise..... _____

Have means, possessions..... _____

Please people, be liked, popular..... _____

Give and receive love..... _____

Enjoy play, sports, and travel..... _____

Be married..... _____

Do creative work..... _____

Put others before myself..... _____

Be well organized..... _____

Have children..... _____

Be attractive..... _____

Be tolerant..... _____

Have much leisure time..... _____

Contribute my share..... _____

Have no duties, complete freedom..... _____

Leave my mark on the world..... _____

Stand for fairness and justice..... _____

Be adaptive, easy-going..... _____

Be cautious, conservative..... _____

Honor my parents..... _____

Explore new possibilities, be adventurous..... _____

ESSENTIAL/IMPORTANT

Have comfort, luxury..... _____

Accomplish things in life..... _____

Accept authorities (school, church, political)..... _____

Master difficulties, overcome dangers, problems..... _____

Lead a religious life..... _____

Work to convert people to the right way of thinking. _____

Have things my way..... _____

Uphold law and order..... _____

Try to improve things..... _____

Help my country surpass others..... _____

Accept denials and frustrations..... _____

Have an easy life without problems..... _____

Strive toward total fulfillment..... _____

Have complete security..... _____

Be sensitive to others' needs..... _____

Be aggressive..... _____

Avoid getting my feelings hurt..... _____

Submit to others' wishes..... _____

Develop myself as a person..... _____

Give free expression to my feelings..... _____

Resign myself to misfortunes..... _____

Avoid mistakes..... _____

Beat out competitors..... _____

Be honest with myself and others..... _____

Make a name for myself, be famous..... _____

Determine my goals clearly..... _____

Always hope for the best..... _____

Strive for meaning in my life..... _____

ESSENTIAL/IMPORTANT

Have a leisurely retirement..... _____

Be a maverick..... _____

Be taken care of..... _____

Life Goal Priority List

These are the life goals that you rated as most important/essential to you at the initial interview.

1.

2.

3.

4.

5.

Progression on Life Goals

For each goal, please rate your sense of satisfaction with your progress in accomplishing this goal over the LAST MONTH. Use the scale below to make your rating for each goal.

1	2	3	4	5	6	7
not at all satisfied						extremely satisfied

goal	rating (circle one number for each goal)						
Goal Number 1	1	2	3	4	5	6	7
Goal Number 2	1	2	3	4	5	6	7
Goal Number 3	1	2	3	4	5	6	7
Goal Number 4	1	2	3	4	5	6	7
Goal Number 5	1	2	3	4	5	6	7

Appendix G

COPING INTERVIEW

Instructions to Interviewer:

Ask the subject to choose 2 situations that happened over the past month that caused them to feel stressed or upset and about which they are willing to talk. These situations can be events that took place during the month or ongoing problems that began before this month but continued into the month.

1. Ask the subject to specify the aspects of the situation that resulted in their feelings of upset. For example, if they choose to discuss their job, ask them to tell you what exactly was stressful on the job over the past month. Once the situation has been described, ask the subject the following questions:

2. How did you react to the situation?

3. Specifically, what feelings did you have in reaction to the situation?

4. Was there anything that you did to try and deal with the situation? (If yes), what did you do (ask for details)?

PROMPTS

5. Did you think about the situation in any particular way in order to handle the situation?
5a. Did you ever try just not to think about it? (If yes), how did you do that?

6. Sometimes people do different things to get a situation out of their minds, for example by getting involved in some kind of activity that makes them forget about it. Did you find yourself doing that? (If yes), what kinds of activities did you get involved in?

7. Did you talk to anyone about your situation? (If yes), who?

What was your purpose in talking to the person, for example did you want to get more information about the situation?

Did you want to get advice?

(If yes), did they give you advice? (If yes), did you find the advice useful? (If yes), did you follow it?

Or did you have the conversation to express your feelings or just talk about it?

8. Sometimes people make themselves feel better by eating, drinking, smoking, taking medication, sleeping more and so on. Did you find yourself doing any of these? (If yes), which ones?

9. Did you develop a plan for how to deal with this situation in the future? (If yes), what was it?

10. Is there anything else you did to influence the situation or how you felt about it? (If yes), what?

Appendix H

COPING MODES CODEBOOK

Format

Each subject was asked to describe two stressful situations that had occurred over the past month. The subjects were asked to describe the situation, how they felt in the situation, and how they handled or did not handle the situation including how they thought about the situation. As the subject began to describe the situation the interviewer took extensive notes on the "Coping Interview Form" under the "description" section. As the subject began to describe their reaction to the situation the interviewer took notes under "Reaction to situation" and "Specific emotions felt". If the subject did not spontaneously provide a reaction in terms of feelings or emotions, the interviewer prompted the subject by asking for specific feelings in reaction to the situation. Then the interviewer asked the subject how they handled the situation. The interviewer recorded the subjects responses in the appropriate category on the coding form.

General Instructions for Coding

1. Read through the entire description and reaction to the situation for a picture of the nature of the problem. This is an important step because a response is only considered a coping response and coded if it relates directly to the problem or to alleviating the feelings attached to the problem. Sometimes subjects just begin to talk as they describe their coping strategies and bring in other situations and other coping strategies they have used in the past or that they are using in relationship to other problems. These are not coded.

2. Read through each sentence that falls after the reaction section. First decide if it is related to the problem described. If so, then decide if it is merely an observation about the problem or a method of coping with it. In other words, is it an attempt, either behavioral or intrapsychic to help manage the problem, the others in it, the feelings that arose from the problem, or the thoughts that result from the problem? Or is it merely more description of the nature of the problem, who was involved, what happened to the subject, how the situation made the subject feel, etc? This distinction will become clearer when the specific coping responses are reviewed.

3. If the sentence is related to the problem and it does appear to be a coping response then decide which mode fits it best by reading over the attached coping mode descriptions and choosing the one most consistent with the sentence. This is the most important judgement. It is

not useful to try to infer what the subject is thinking, e.g., I know that if she said this she must have meant that. Stick close to the linguistics of the sentence. The coding rules will offer examples and linguistic rules that will help make these distinctions.

4. On the code sheet mark the subject's id and interview number and then list the coping responses, in order from the first to the last, next to the appropriate number. This particular coding strategy does not consider the strength of the use of a particular coping mode. In other words, the coder does not distinguish between modes used alot versus modes used a little. Or between modes that seem primary over those that seem secondary. The purpose is to determine whether or not the mode was used during the course of dealing with the stressful situation.

Coding Categories for Modes of Coping

The original coding scheme had 24 modes of coping. They have been condensed to the following 11 codes based on the reliability of making differential judgements and other factors. An expanded manual with all 24 codes and further discussion of coding strategies is available upon request.

PROBLEM-FOCUSED DIRECT ACTION = behavioral or verbal ACTION aimed at solving the stressful problem.
a. behavior must be relevant to the problem described under description of the problem. If it is relevant to another problem then it is not coded at all.
b. a description of an overall behavioral tactic such as "taking one step at a time" if it seems to refer to behavior rather than thoughts fits here.
c. stopping a physiological response in the service of attempting to solve a problem would fit here (e.g., problem is getting ready to give a talk and strategy is to not let body react so that subject will be effective).
NOT CODED. Thoughts or feelings are not behaviors and do not fit in this category.
EXAMPLES-discussing marital problems with spouse, giving advice to another in the problem situation, looking for a job, reorganizing files, dont let body react (when a reaction would be counterproductive, as when a person has too much anxiety before a talk).

EMOTION-FOCUSED DIRECT ACTION = behavioral or verbal ACTION aimed at dealing with or alleviating the emotion attached to the problem. Behavior done to change the person's own mood, relieve depression, make self happier, feel a sense of control.
a. The easiest mistake to make here is to include thoughts or feelings that make one feel better. This catagory is for BEHAVIOR only.
b. all "yes" to question 8 fit here unless the subject reports LESS sleeping which is a reaction to stress rather than a coping strategy. MORE sleep in order to remove self from the feeling would fit here.
c. doing things the subject enjoys doing to make them feel better (e.g., shopping, things they enjoy). Code as Suppressing Thoughts,

those behaviors that the subject enjoys doing but they do specifically to distract themselves.
NOT CODED. Thoughts which are emotion-focused do not fit in this category. Releases of emotion are difficult to code. First, it must be determined if the release is a coping strategy or purely a reaction to the situation. Look for indications that the person is "blowing up" to release tension, to make themselves feel better, to get out the feelings, etc. If it does fall into one of these categories and therefore does seem like a coping strategy then look at whether the blow up is behavioral or internal. If it is a behavioral strategy, e.g., "yelled a spouse to get it out of my system" then code here. If is internal, e.g., "let myself feel incredible rage" then code as Enhance Emotion below. If the release is purely reactive and not a coping strategy then don't code at all.
EXAMPLES-humor, dancing, relaxing, yoga; smoking, eating, or drinking more, exercising, sleeping when it is done to dull the emotion or avoid it, sulking (this is the expression of affect to dampen the experience of affect). See especially question 8.

Differences between emotion-focused and problem-focused direct action.
Watch for behaviors like yoga or exercise that might appear to be emotion-focused but are actually done to solve the problem, for example if the problem is back pain.
If there is not enough information to code a behavior as either then code it as Other.

INHIBITION OF ACTION = restraining oneself from the physical action that one has contemplated doing. Must include INTENT TO ACT and then inhibition of behavior. If intent is not evident then it does not fit in this category. So "stopped doing something" fits here because intent is implied by the fact that they stopped doing the behavior. However, "did not hit him" does not fit here because it is not clear that the subject intended to hit "him." Subject is merely saying that he did not.
NOT CODED. Inhibition of thoughts or feelings does not fit here.
EXAMPLES-felt like hitting him but held myself back, thought about telling him off but didn't.

SUPPRESSION OF THOUGHTS = a behavior or an intrapsychic process done to keep something out of the subject's mind.
a. activities engaged in by the subject for the purposes of distracting the subject from the problem or the feelings attached to the problem. All "yes" to question 6 fit here.
b. intrapsychic attempts to try not to think about something, to put it out of mind. All "yes" to question 5a.
EXAMPLES - went to movies to distract self, read a book (listed under the question 6 category), just tried to forget about it.

Differences between emotion-focused direct action and suppressing thoughts.
Behavioral distraction is actually a sub-type of emotion-focused direct action. So, look at a behavior that is used to regulate an emotion and first decide if it is specifically reported to be used to distract the subject. If so, code as suppressing thought. If not, then it will fit under emotion-focused direct action.

SUPPRESSION OR INHIBITION OF FEELINGS = attempting to keep oneself from feeling a particular way. Or suppressing the feeling when it begins to be felt. Any intrapsychic attempt to not let something bother the subject.
NOT CODED. An easy mistake to make here is to include BEHAVIOR that deals with emotion. Such behavior would go under emotion-focused direct action. This category is restricted to THOUGHTS which suppress or inhibit feelings. Do not include suppressing the expression (which would be inhibition of behavior). In this category include only an intrapsychic attempt to dampen an emotion. Smoking is a behavior which changes a mood so it is called emotion-focused direct action while "keeping myself from getting too upset" is an intrapsychic attempt to inhibit emotion.
Another possible mistake is confusing the suppression of thoughts with the suppression of feelings. If a thought is suppressed then code as Suppression of Thought.
EXAMPLES-started to feel angry but pushed it away, tried to suppress my nervousness, trying not to get upset, did not let it bother me.

TURNING TO OTHERS FOR SOCIAL SUPPORT = contact with others over the phone or in person to express feelings, get reassurance, encouragement, support, understanding, validation of feelings, etc.
a. All "yes" to question 7-express feelings.
NOT CODED. If subject just tells a friend about the situation but does not acknowledge that they told the friend how they felt, or that they wanted support etc. then the behavior is not coded.
EXAMPLES-got it off my chest, reached out to others. I talked to her and she validated my feelings.

INFORMATION SEEKING = contact with people or objects (e.g., books) to get information or advice relevant to the stressful problem. Often this contact will be with a professional person , e.g., a lawyer, doctor, accountant.
a. all "yes" to question 7-get information or advice.
b. if a subject makes a call for information and does not get through or the information is not available, still code because the subject did seek information.
c. consultation that does not involve a person, e.g., a horoscope, a crystal, magazines, books, or a library fits here.
EXAMPLES-found out about jobs from counselor, asked a question, got second opinion from a doctor, went to the library to look up about that job, looked to see what my horoscope said.

DECISION MAKING = exploring the etiology of the problem or possible ways to solve the problem, constructing a plan for the the future, or specifically thinking through steps to accomplish a task.
a. Trying to figure out and explore how the subject feels about a situation or person. Questioning the etiology of the problem - "why do I feel this way" or "what is the pattern that keeps recurring". Include exploration of feelings about the problem or exploration of the etiology of the problem or patterns in types of problems typically faced by the subject.

EXAMPLES-I spent some time thinking about why I always get so upset when he does that. I realized that I get myself in this situation alot - why is that?

b. Weighing the pros and cons of a decision, thinking through a course of action, considering alternatives or paying attention to ambivalent feelings or vacillations between 2 or more possible ways to handle a situation.

EXAMPLES-I think about going to visit him in Europe and then I think that he'd probably think I was nuts and then I think that I should just do it and be brave. Thinking about how to solve a problem. I went over the various alternatives to see which seemed best.

c. Any plans or thoughts about what the person will do in the future relevant to the problem situation, including behavioral or intrapsychic plans (e.g., plans to distract oneself). Includes anything listed under the plans section of the interview form unless the subject says they MAY or MIGHT do a particular thing. These would not be coded at all. If something in the plan section uses present tense and clearly looks like something they have already done or are currently doing then don't code here. Conditional plans (if x occurs then I will do y) are coded as plans.

NOT CODED. A major resolution to make a major shift in life does not fit here because the resolution is a current strategy for dealing with the situation (e.g., "I've decided that I will never let myself get into this kind of situation, I am seeing things from a new perspective.) That would be coded as Reappraisal.

EXAMPLES-I'm going to stop worrying about it, I'll start looking for a job. I'm going to break up with him if he does it again.

d. Thinking out actions before doing them, rehearsal. Thinking through the steps necessary to accomplish a task. Taking self through an upcoming event. The focus here is on rehearsing the situation in the mind before it happens.

EXAMPLES-I figured out ahead of time what I would say if she asked about herpes. I thought through what I needed to do to come off well in the interview.

REAPPRAISAL = Looking at the stressful situation in a new way, getting a new perspective on it, redefining the situation, wishing the situation would change, lowering one's expectations for the situation, or encouraging oneself that one can handle the situation.

a. construing situation as a challenge

b. realizing it's only temporary, or that it takes a long time

c. justifying or rationalizing away a situation or behavior (he deserved it.)

d. looking at or reevaluating the positive aspects of the situation

e. looking at or reevaluating the positive aspects of own behavior in situation

f. putting responsibility for situation on someone else

g. realizing that nothing else can be done about the situation. If the subject mentions this AND says they they are now just accepting the situation or are being passive in the situation then code as Passiveness/ Acceptance.

h. realizing something about the other person in the situation's motives or reasons for doing what they did. This is close to intense analysis

of the situation under Decision-Making but with Decision-Making there is a more extensive "looking at" the other person and why they might do what they did. Here the response can be as simple as "I realized it's not his fault".
i. wishing that situation would change. Hoping for a better situation in the future.
j. telling self that you can do it, that you've done it before, that others can do it so you can too. Reminding self about capabilities, strength, independence in order to encourage self to deal with situation. Giving oneself a pep talk.
k. changing the goal of the situation to something lower than previously expected. Lowered what would be necessary to make the subject feel OK about the situation.
NOT CODED. If the person is looking at the situation but they are not changing or attempting to change their perspective on it then it is coded as intense analysis of feelings about situation under Decision-Making.
EXAMPLES-I'm better off to have surgery cause then I'll know if I have cancer. I realized that it would give me a chance to test my abilities. I figured he deserved it anyway (in context of subject doing something negative to someone else). I figured it can't go on forever. I tried to see it from a positive light. Thinking positive. Realized that I could do it even though I was scared, I've done this before so I can do it now, I'm a strong person so I know I can take it. Figured I'd be happy with any job even if it's not in my line of work.

PASSIVITY/ACCEPTANCE/GIVING UP = Deciding not to do anything about the problem and just live with it (passivity). Accepting that what will happen will happen. Giving up on trying to cope with the problem. The person must mention this specifically as a strategy; if they don't then this category must not be used.
a. Deciding not to do anything. This is different than realizing that nothing can be done. It is still possible that the subject will do something even if they realize nothing can be done. To be coded in this category the subject must say that they are NOT GOING TO DO ANYTHING. If they just say that nothing can be done then code as Reappraisal.
b. Realizing that what will happen will happen, letting fate takes it course. This process is accepting that "what will be will be." This may appear to be adaptive while giving up may seem maladaptive. Nevertheless both strategies are coded here.
c. Giving up because the subject feels he or she can't deal with it.
NOT CODED. If the subject only mentions that things will get better then don't code as acceptance. Only code if the subject also adds that they are accepting it or letting it happen. In other words, a subject can feel things will get better but not be passive at all.
Also, just saying there is nothing that can be done is not sufficient. The subject must also mention that they are accepting future, or giving up or letting things happen.
Also, mentioning that they didn't do anything about the situation is not coded here. That is not a coping response, it is the absence of a coping response; while deciding to give up or be passive etc. is an intrapsychic coping response.

example-You just have to live with it, must accept it psychologically. Nothing can be done in the office so I just have to live with the smoke.

RUMINATING/ENHANCING EMOTION = worrying about the event and reworking it over and over mentally, hashing it out in the mind. The release or experience of emotion in order to cope with the situation.
a. worrying and reworking event over in mind
b. letting the feelings happen or "working through the feelings" would fit here. Catharsis or letting the feelings out fits here. Also include intensification of feelings by thinking thoughts that make the feeling more intense.
c. keep in mind that this category will combine strategies that seem adaptive (e.g, working through the feelings) with ones that may not seem to be (thinking negative thoughts to make myself angrier at him). This is true for many categories.
NOT CODED. Do not code if the subject just reports worrying about the situation. Use it only if they are actually going over it and it seems to be an attempt to come to some conclusions about the situation. A blow-up which seems to be primarily a reaction to the stressful situation would not fit here.
EXAMPLES-I keep thinking that I could have done it differently. Let feelings happen, talk self through the feeling, thinking revenge thoughts (to make oneself get angrier)

Appendix I

SOCIAL INTERACTION SCALE: SATISFACTION SUBSCALE

Instructions given verbally: In this questionnaire we are interested in how satisfied you are with the support that is available to you from people in your life. There are five kinds of support we are interested in (point out the five types on the form) and five groups of people we are interested in (point out the five groups on the form). I would like you to rate how satisfied you are with the support of each kind that is available to you from each of these groups of people. Use this 7 point scale from 1 which is not at all satisfied to 7 which is extremely satisfied. So, for example, if you are moderately satisfied with the help and assistance that is available to you from your close friends then you would put a 4 in this box (point to the appropriate box). Also, there are a few other kinds of questions to fill out on the form.

1 2 3 4 5 6 7
not at all extremely

Satisfaction: How satisfied are you with support that is available to you from each group?

	Help and assistance (giving of services)	caring (feeling of closeness)	feeling of being valued (respected, worthwhile)	a feeling of partnership (part of group)	information (giving advi and suggesti
spouse/partner					
close relatives					
close friends					
coworkers/fellow students					
supervisors/ professors					

Appendix J

PEARLIN'S MASTERY SCALE

How strongly do you agree or disagree that over the past month:

1. I seem to have little control over the things that have been happening to me.

1 - - - - 2 - - - - 3 - - - - 4 - - - - 5 - - - - 6 - - - -7
strongly disagree | mildly disagree | mildly agree | strongly agree

2. There is really no way I can solve some of the problems I have been having.

1 - - - - 2 - - - - 3 - - - - 4 - - - - 5 - - - - 6 - - - -7
strongly disagree | mildly disagree | mildly agree | strongly agree

3. I have been feeling like I can do just about anything I really set my mind t

1 - - - - 2 - - - - 3 - - - - 4 - - - - 5 - - - - 6 - - - -7
strongly disagree | mildly disagree | mildly agree | strongly agree

4. I have been feeling like there is little I can do to change many of the impo things in my life.

1 - - - - 2 - - - - 3 - - - - 4 - - - - 5 - - - - 6 - - - -7
strongly disagree | mildly disagree | mildly agree | strongly agree

5. I believe that what happens to me in the future mostly depends on me.

1 - - - - 2 - - - - 3 - - - - 4 - - - - 5 - - - - 6 - - - -7
strongly disagree | mildly disagree | mildly agree | strongly agree

6. I have often felt helpless in dealing with the problems of my life.

1 - - - - 2 - - - - 3 - - - - 4 - - - - 5 - - - - 6 - - - -7
strongly disagree | mildly disagree | mildly agree | strongly agree

7. I have been feeling that I'm being pushed around in life.

1 - - - - 2 - - - - 3 - - - - 4 - - - - 5 - - - - 6 - - - -7
strongly disagree	mildly disagree	mildly agree	strongly agree

Appendix K

THE DUKE-UNIVERSITY OF NORTH CAROLINA HEALTH PROFILE: SYMPTOM STATUS SCALE

Here are a number of questions about your health. Please read each question carefully and give your best answer. You should answer questions in your own way. There are no right or wrong answers.

During the past month:

How much trouble have you had with:

	None	Some	Alot
1. Eyesight	____	____	____
2. Hearing	____	____	____
3 Talking	____	____	____
4. Smelling odors	____	____	____
5. Tasting food	____	____	____
6. Appetite	____	____	____
7. Chewing	____	____	____
8. Swallowing	____	____	____
9. Moving your bowels	____	____	____
10. Passing water/urinating	____	____	____
11. Breathing	____	____	____
12. Sleeping	____	____	____
13. Walking	____	____	____

During the past month:

How much trouble have you had with:

14. Headache	____	____	____
15. Hurting or aching in any part of your body	____	____	____
16. Itching in any part of your body	____	____	____
17. Indigestion	____	____	____
18. Fever	____	____	____
19. Getting tired easily	____	____	____
20. Fainting	____	____	____
21. Poor memory	____	____	____
22. Weakness in any part of your body	____	____	____
23. Feeling depressed/sad	____	____	____

24. Nervousness ____ ____ ____

During the past month:

How much trouble have you had with:

25. Weight loss ____ ____ ____
26. Weight gain ____ ____ ____
27. Unusual bleeding ____ ____ ____
28. Sexual performance ____ ____ ____

Appendix L

HEALTH HABIT INTERVIEW

1. (for women) What was the date of the first day of your last menstrual period?

Now I will be asking you some questions about your health habits over the past month.

2. On the average, approximately how many hours of sleep did you get each night over the past month?

3. On the average over the past month, how often in a typical week did you drink wine or beer?

How many glasses of wine or beer would you drink each day on those days?

How often in a typical week this last month did you drink hard liqour?

How many glasses of hard liquor would you drink each day on those days?

4. Did you get regular exercise this month? yes no

(if yes), how many days in a typical week did you exercise?

How long did each exercise routine last typically?

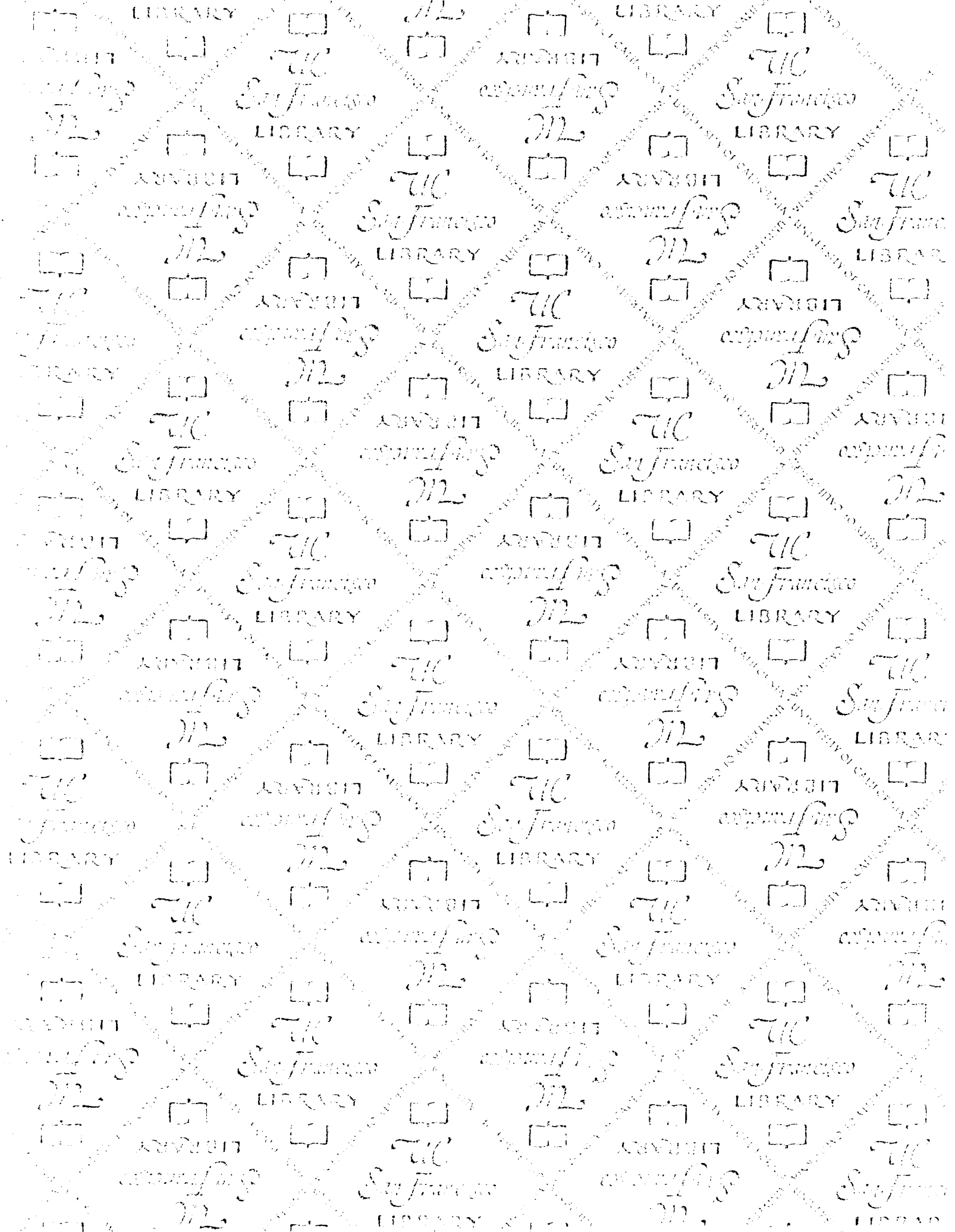
What type of exercise did you do?

5. Do you smoke cigarettes, cigars or a pipe? (If yes), over the last month, did you smoke cigarettes, cigars or a pipe? (If yes), how many cigarettes (or) did you smoke a day on the average?

6. I would now like to ask you a few questions about your sexual activity. Have you been sexually active with another person over the past month?

7. If so, what has your level of sexual activity been over the past month?

1	2	3	4	5
daily or more	4-6 times a week	2-3 times a week	once a week	every 2 weeks or less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