HORMONES, DISTRESS, AND IMMUNE FUNCTIONING IN WOMEN

DISSERTATION

Presentation to the Graduate Council of the University of North Texas in Partial Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

By

Maria Francesca Rubino-Watkins, B.A.

Denton, Texas

August, 1998
The present study set out to investigate the biopsychosocial model of illness using variables previously identified as directly impacting illness or as mediating the relationship between other variables and illness. Oral contraceptive use, stress, and negative affect were investigated as predictors of immunological competence, measured by the level of Immunoglobulin G antibodies to Epstein-Barr Virus Viral Capsid Antigen (EBV-VCA IgG). Thirty-seven healthy female undergraduates were assessed with paper and pencil measures of demographic information, stress, anger expression and management styles, and depressed coping styles. Blood assays revealed current health status, ovarian hormone levels, and EBV-VCA IgG levels. Of the demographic variables, only the reported number of doctor’s visits in the past year was associated with EBV-VCA antibody levels. Though exercise and oral contraceptive use were correlated, neither variable was related to EBV-VCA antibody levels. None of the stress measures from the Daily Hassles Scale was associated with immune functioning. Negative affect, as measured by the STAXI and CAQ, was associated with stress and with immune functioning. Angry reaction, suicidal depression, low energy depression, guilt and resentment, and
boredom and withdrawal were significantly correlated with antibodies to EBV-VCA. Regression analysis revealed angry reaction and boredom and withdrawal as accounting for most of the variance in the model, suggesting that they are independent factors and that both must be known if one is trying to understand the impact of negative affect on illness. Several interaction models were tested for their predictive value of EBV-VCA IgG levels. Unfortunately, these interactions were equally or less effective in predicting EBV scores than the additive model of angry reaction, boredom and withdrawal, and doctor’s visits. For young people in Generation X as well as the unemployed and bereaved who may be experiencing loss of meaning, interventions designed toward goal setting, achievement motivation, and volunteer work may assist these individuals in obtaining or regaining their sense of identity and purpose in life. Such interventions may not only improve their psychological status but also improve their immune functioning and illness susceptibility.
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CHAPTER I

INTRODUCTION

In recent years, biological, psychological, and social factors have been implicated with health status, and attempts to connect these factors in a working paradigm have resulted in such research fields as psychoneuroimmunology (PNI; Ader, 1981). PNI research therefore has the opportunity to integrate the systems of the mind and body conceptually as well as offer empirical evidence supporting a revised approach to health research and health care delivery. Dualism remains the ruling paradigm in clinical practice, and it will take the refinement and subsequent application of current theories toward a more integrative approach to manifest a biopsychosocial model in practice.

Individual difference variables have been excluded by many PNI researchers despite the recognition that they may be implicated in wellbeing. Initially, PNI researchers investigated the conditioning of the immune system (Ader, 1981). Based on the newly created body of knowledge connecting the central nervous system and the immune system, they soon extended their efforts to understanding the stress-illness relationship (Kiecolt-Glaser, Garner, Speicher, Penn, & Glaser, 1984). Baron and Kenny (1986) were some of the first to recognize that including moderating and mediating variables was essential to
maximizing these efforts, especially once it became clear that stress alone does not result in immune system changes. We now have more integrative models to study the factors contributing to illness as has been recommended by others (Critelli & Ee, 1996; Lovallo, 1997; Perkins, Leserman, Gilmore, Petitto, & Evans, 1991). Ideally, an integrative model of illness and disease should include variables such as the individual’s appraisal, genetic predispositions, coping, social support, meaning of stressful experience to the individual, personality, and age (Weiner, 1992). Each of these factors may make an individual more or less susceptible to illness, or may explain how or why a particular variable is related to illness (Baron & Kenny, 1986).

Health and illness are impacted by multiple factors, some directly and others through interaction. Stress, oral contraceptive use, ovarian hormones, and negative affect each have been found to be directly related to immune functioning. However, integrative models testing the relationships between these variables have largely been overlooked. The current study was an attempt to replicate previous findings that each of these variables is associated with immune functioning. Both additive and multiplicative models were used to test predictive value of these variables, guided by the biopsychosocial model of illness.

**Oral Contraceptives**

Initially, hormone dosages in oral contraceptives (OCs) were higher than needed for effectiveness, and numerous negative side effects and health risks
led many women to discontinue use. Direct relationships among oral contraceptive use and hormone levels (estrogen and progestin) (Johnson & Everitt, 1980), reactivity to stress (Marinari, Leshner, & Doyle, 1976), negative mood (Roy-Byrne, Rubinow, Gold, & Post, 1984), immune functioning (Martin, 1985) and health were established (Hatcher, Trussell, Stewart, Kowal, Guest, Cates, & Policar, 1990). Current dosages are low, however, and 59% of 15-44 year old women in the U.S. use oral contraceptives (Peterson, 1995). Fewer studies have been published investigating the negative side effects and health risks of low-dose formulations. As such, the effect of OCs on human systems other than the reproductive system remains unclear.

**Normal vs. Regulated Menstrual Cycle**

For normal cycling women, phases differ strongly with regard to concentrations of serum estrogen and progesterone, with maximum estrogen (E2) concentrations but low progesterone (P4) concentrations during the preovulatory phase (Hatcher et al, 1990). During the midluteal phase, P4 is highest while E2 levels are moderately enhanced. Both hormone concentrations are at a minimum during the menses.

The normal menstrual cycle is replete with feedback loops (e.g., when estrogen levels peak, release of other hormones is triggered, those hormones peak, and estrogen levels, consequently fall) (Hatcher, et al, 1990). Although this tendency persists to some degree when synthetic hormones are added, the rises and falls are not as dramatic (Johnson & Everitt, 1980). Rather, with oral
contraceptive use the hormones are much more stable; progestin maintains a generally consistent level throughout the cycle and estrogen levels may or may not remain constant (Hatcher, et al, 1990).

**Estrogen and Progestin in Contraception**

Oral contraceptive components of estrogen and progestin produce plasma concentrations of the same hormones which exert powerful negative feedback effects on Follicle Stimulating Hormone and Luteinizing Hormone secretion. They mimic to some extent events normally seen during the luteal phase of the cycle (Johnson & Everitt, 1980).

In each woman taking OCs, the total estrogenic effect will be the result of estrogen from an oral contraceptive and endogenous estrogen from the ovaries and adipose tissue (Hatcher, et al. 1990). Progestins are the main component which keep a woman from becoming pregnant; whereas, estrogen is added primarily for health benefits (Hatcher, et al, 1990).

**OC Use and Immune Function**

Both estrogen and progesterone have immunosuppressive effects. Pharmacological concentrations of estrogens reduce the size, weight, and cell counts of the thymus gland, retard stem cell proliferation in bone marrow, and decrease Natural Killer (NK) cell activity (Martin, 1985). Also, estrogen is associated with inhibition of suppressor T-cell activity and increased autoantibody production (Ahmed, Dauphinee, Montoya & Talal, 1989).
Synthetic progesterone also has been demonstrated to suppress the immune system; it acts locally to decrease granuloma formation and prolongs the lives of skin grafts. It is associated with increased susceptibility to infections during pregnancy and inhibits T cell activation and transformation of lymphocytes to blast cells. Progesterone may also affect macrophage functions and reduce leukocyte numbers within the uterus (Johnson & Everitt, 1980).

OC Use and Health Implications

There is an abundance of data suggesting health implications of OC use, including both risks and benefits. Many of the health risks associated with OCs stem from the blood-clotting action of estrogen. OC use is associated with stroke and heart disease (Kelly, Gorelick & Mirza, 1992), and users are at four times the risk of dying from stroke compared to nonusers (The Royal College of General Practitioners, 1981). Users have higher incidences of myocardial infarction (Katerndahl, Realini & Cohen, 1992), but are at no greater risk for morbidity or mortality (Derman, 1990). Women over age 35 who smoke are at much greater risk for thromboembolism and hypertension. There is higher prevalence of Systemic Lupus Erythematosus (SLE) and erythema nodosum for OC users (Beaumont, Gioud, Kahn & Beaumont, 1989; Scarpa, Scognamiglio, Casaburo, Oriente, Blondi & Oriente, 1989) and there is evidence that oral contraceptives containing estrogen provoke exacerbations of SLE in women (Schuurs & Verhuel, 1989) and mice (Ahmed & Talal, 1989). There is also increased risk of developing pyridoxine (Vitamin B6) deficiency and anemia (Martin, 1985).
Physicians are instructed to refrain from prescribing OCs for women with estrogen-dependent neoplasia, a history of liver cancer or impaired liver function, migraine headaches, diabetes mellitus, planned major surgery, sickle cell disease, active gallbladder disease, Gilbert's disease, renal disease, cervical cancer, and hypertension (Hatcher, et al., 1990). Conflicting reports regarding the effect of OCs on susceptibility to rheumatoid arthritis suggest reduced incidence in women using the pill, on the one hand, and no reduction in incidence among pill users on the other (Denman, 1991).

The benefits of taking combined OCs include the fact that the estrogen component balances out the progestin's negative effect of reducing HDL cholesterol and possibly increasing LDL cholesterol (Adams, Clarkson, Rudel, Koritnik & Nash, 1987; Blackburn & Luepker, 1987). Furthermore, OC use prevents and treats endometriosis (Hatcher, et al., 1990) and prevents osteoporosis (Kleerekoper, 1991). Through inhibition of ovulation, estrogen also lowers the risk of ovarian cancer by about 50% (The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development, 1987); and of functional ovarian cysts by 90% (Hatcher, et al., 1990). There is general agreement that estrogen neither raises nor lowers the risk of breast cancer (Mishell, 1989), and authorities claim that the pill can be less dangerous than closely spaced pregnancies (Hatcher, et al., 1990; Martin, 1985).
Direct effects of oral contraceptives, estradiol, and progesterone on health and immune functioning consistently have been demonstrated, however, their effect on other systems of the body have been less consistent. Findings suggest a general reduction in arousal for OC users (Marinari, Lesher, & Doyle, 1976; Graham & Sherwin, 1987; Warner & Bancroft, 1988), but findings regarding effects on depressed and anxious mood remain unclear (see Long & Kathol, 1993 and Patten & Love, 1993 for reviews). Recently, the possibility of oral contraceptives having a mediating role in the relationship between cognitive and emotional coping factors was suggested (Rubino, Doster, Kelly, Goven, & Moorefield, 1995). Also, the mediating role of anger management has been suggested in the relationship between oral contraceptives and immune functioning (Franks, 1993). The interrelationships remain unclear and complex.

Although oral contraceptives have beneficial effects on some users' physical and mental health, they are overwhelmingly associated with immunosuppression and health risks. The pill is one of the most well investigated drugs on the market. However, the dawning of the new era of “low-dose” combination pills and their association with fewer health risks and negative side effects has been associated with less literature being published in health-related journals. In consideration of the large numbers of women using this method of contraception and the extensive list of health risks and immunological effects of synthetic estrogen and progesterone, a greater understanding of these relationships is needed. That the relationship between oral contraceptive use
and immune functioning may involve stress, either as a mediator or as a primary factor suggests a need for research in this area.

**Stress**

Stress is generally defined as a state of altered homeostasis resulting from an external or an internal challenge (e.g., referred to as a stressor) (Chrousos, Loriaux, & Gold, 1988). Distress results only when the demands of the stressor are perceived to exceed one's own ability to cope (Lazarus & Folkman, 1984). Stressors can be classified into three types of events including cataclysmic events, negative life events, and daily hassles. The experience of cataclysmic events often results in cognitive and emotional disturbances (Uddo, Allain, & Sutker, 1996) and may be syndromatic, as in the case of Vietnam War veterans under frequent study and diagnosed with post traumatic stress disorder (Kulka, Schlenger, Fairbank, Hough, Jordan, Marmar, & Weiss, 1990). However, the relationship between traumatic events and physical health problems is not routinely studied, despite the fact that many different PTSD populations (e.g., rape victims, war veterans) frequently report somatic complaints (Uddo, Allain, & Sutker, 1996). Both negative life events (Holmes & Holmes, 1970) and daily hassles (Chamberlain & Zika, 1990; Kuiper, Olinger, & Air, 1988; Kuiper, Olinger, & Martin, 1988; Weinberger, Hiner, & Tierney, 1987) are associated with health. Major life events are related to larger immune changes compared to hassles, but both have been related to well-being (Herbert & Cohen, 1993). Some suggest that the intensity of hassles predicts health better than the frequency with which
they occur (Ruffin, 1993; Wu & Lam, 1993). Both of these kinds of events have been measured by self-report methods, and researchers generally agree that both kinds of stress overlap with negative affectivity (Critelli & Ee, 1996). This overlap prevents the drawing of conclusions regarding the stress-illness relationship. While it appears that the stress-illness relationship is consistent, the purported relationships between stress and illness may actually reflect linkages between negative affectivity and illness (Critelli & Ee, 1996). Removal of negative affect and health-related items from measures of stress has been suggested as a method for clearing up this confound (Dohrenwend & Dohrenwend, 1981) and so far, revised measures have been used with some success (Longhorn, 1992). Also, inclusion of separate stress and negative affect measures has been recommended in order to help clarify relative contributions of each to immune functioning and illness (O'Leary, 1990).

**Stress-Illness Model**

The current model used in stress-illness research guided one of the most often cited meta-analytic studies in the field, authored by Herbert and Cohen (1993). The model states that stress leads to distress (e.g., negative affective states such as anxiety and depression) which then results in immune system alterations. Also, appraisal of the event has been found to be a necessary component of the relationship between stress and illness (Lazarus and Folkman, 1984). As such, the causal flow for this model progresses from the event to appraisal to negative affect, culminating in immune system changes or illness.
(see Cohen, Evans, Stokols, & Krantz, 1986; Krantz, Glass, Contrada, & Miller, 1981). Additionally, in their conceptualization of the stress-illness relationship, Cohen and Williamson (1991) suggest that stress may influence susceptibility to infectious agents either by a. Altering biologic susceptibility and predisposing persons exposed to a pathogen to infection, b. Initiating or triggering a process that allows a pathogen that is already in the body (e.g., a latent virus) to reproduce, and c. Contributing to maintenance of an ongoing pathogenic process. In most cases, stressful experience does not linearly or by itself produce disease (Weiner, 1992).

The concepts of hardiness (Kobasa, 1979), resilience (Younkin & Betz, 1996), and toughness (Dienstbier, 1989) are a few examples of the positive association which exists between stress and immune outcome when influenced by personality traits and other individual differences. Physiological toughness is defined by low sympathetic nervous system (SNS) arousal base rates but high stress-induced arousal which interacts with psychological coping and corresponds with positive performance, emotional stability, and immune system enhancement (Dienstbier, 1989). Other individual difference variables such as biological reactivity have also been found to mediate the stress-illness relationship (Boyce, Chesney, Alkon, Tschann, Adams, Chesterman, Cohen, Kaiser, Folkman, & Wara, 1995). Research allowing for the contributions of individual differences has introduced complexity into the stress-illness model, but also has spurred more creative and inclusive study. Until characteristics such as
toughness were documented sympathetic nervous system arousal associated with stress was thought universally to be negative.

**Stress and Coping**

Coping styles appear to mediate the relationship between stress and illness. Active coping is defined as a defense reaction in animal studies (Schneiderman & McCabe, 1985 cited in Toates, 1995). It is behavior exhibited by the animal in order to learn the contingencies in the environment. When no contingencies are present, the animal develops what Seligman called "learned helplessness (1975). Active coping provides an ameliorating effect on bodily measures of stress (Goesling, Buchholz, & Carreira, 1974 cited in Toates, 1995); whereas, learned helplessness results in symptoms very similar to depression, such as poor appetite and weight loss, psychomotor alteration, loss of energy or fatigue, loss of interest in usual activities, sleep changes, and indecisiveness (Weiss & Simson cited in Toates, 1995). In addition, depressed individuals often experience feelings of worthlessness, and recurrent thoughts of death and suicide. Learned helplessness has been linked to poor cancer outcome (Greer, Pettingale, Morris, & Haybittle, 1985; Temoshok, 1985) and increased susceptibility to illness and death (Engel, 1968; Schmale, 1958).

**Stress, Emotion, and Physiological Effects**

Both stress and emotions are known to be associated with substantial physiological changes, including activation of the sympathetic adrenal-medullary (SAM) system, the hypothalamic-pituitary-adrenocortical (HPAC) system, and
other endocrine systems (O'Leary, 1990). Although each system is triggered by
specific kinds of stressors and emotions, often both are engaged simultaneously.

First, during the SAM response, the adrenal medulla secretes
catecholamines (ie., norepinephrine and epinephrine) also known as stress
hormones. The effect is identical to that of direct sympathetic innervation
including, but not limited to, symptoms of increased blood pressure, increased
heart rate, increased blood flow to the skin, and increased release of
endogenous opioids. This system is engaged most strongly in connection with
fear and anger as well as other acute emotional states such as excitement.
Interestingly, endogenous opioids are also associated with changes in mood,

The HPAC response is involved more during more chronic responses to
stress, depression, and social deprivation. In this sequence of events,
corticotropin releasing factor is released into the portal system serving the
hypothalamus and pituitary gland. The pituitary releases adrenocorticotropic
hormone (ACTH) into the circulation while simultaneously endorphin precursors
are released. ACTH travels through the circulation to the adrenal cortex where it
stimulates the release of cortisol and corticosterone. The effects of these
hormones in response to stress include increased glucose production, increased
urea production, suppression of immune mechanisms, exacerbation of herpes
simplex, associated feelings of depression, hopelessness, helplessness, and a
loss of control. The HPAC has been called the "passive coping" system since it appears to be activated when active coping is not possible (Everly, 1989).

**Stress and Immune Functioning**

As mentioned above, a negative relationship between stress and immune functioning has been found consistently. A meta-analysis of the findings on stress and immunity in humans found decreases in proliferative response to mitogens and NK cell activity, increase in numbers and percentages of circulating white blood cells, lower immunoglobulin levels, and higher antibody titers to Epstein-Barr Virus (EBV) and Herpes Simplex Virus (HSV) in response to stress (Herbert & Cohen, 1993). Other meta-analytic results agreed that higher antibody titers against EBV are consistently related to stress, but found inconsistent evidence and non-significant findings regarding percentage of NK cells, and salivary IgA (sIgA) concentration (Van Rood, Bogaards, Goulmy & Houwelingen, 1993). In regards to actual health outcome, stress has been related to susceptibility to the common cold (Cohen, Tyrrell, & Smith, 1991).

Stress affects many systems in the body, including the immune and endocrine systems. The central nervous system is responsible for the appraisal of events as stressful, and for the display and engagement of coping responses. Both active and passive coping may be employed and both styles may involve emotional management aspects, which in turn may impact health according to the stress-illness model.
Negative Affect

Negative Affect and Health

Extensive research has been performed regarding the nature of emotions and their impact on physical well-being. Both positive and negative emotion affect immune functioning, however, some findings are contradictory. Self-reported humor moderates the immunosuppressive effects of stress (Martin, & Dobbin, 1988), but laboratory-induced positive emotion is directly immunosuppressive (Knapp, Levy, Giorgi, Black, Fox, & Heeren, 1992). Similarly, negative emotion is associated with immunosuppression (Labott, Ahleman, Wolever, & Martin, 1990; Knapp, Levy, Giorgi, Black, Fox, & Heeren, 1992). Negative affect was associated with symptomatology, illness, and poorer health behaviors (Colligan; 1985, Dahlstrom, Welsh & Dahlstrom, 1972). Individuals who experienced higher levels of negative affect reported feeling fatigued at seven times the rate of people without emotional problems (Chen, 1986), and after reviewing numerous studies, Friedman and Booth-Kewley (1987) postulated a "disease-prone personality" which involves depression, anger/hostility, anxiety, and possibly other aspects of emotional experience and management. Although negative affect has been identified as immunosuppressive and a health risk (Friedman & Booth-Kewley, 1987), the characteristics of negative affect which contribute to immune functioning and disease processes have yet to be confirmed. Therefore, instruments assessing multidimensional aspects of negative emotion are likely to be most useful.
Depression and Anger

Depression and anger have been hypothesized as being related; however, the issue remains controversial. While anger has been shown to be a predictor of depression (Clay, Anderson, & Dixon, 1993; Kopper & Epperson, 1996), others have noted that anger and depression often occur simultaneously rather than depression resulting from anger (Beck, 1976; Weissman & Paykel, 1974). The etiology and connection between these emotional experiences are unclear.

Theories of Depression

Several theories have been proposed for the etiology and maintenance of depression. Conceptualizations have included depression as the result of a deficit in social reinforcement (see Thase, 1995 for review), the result of interpersonal stress (Klerman, Weissman, Rounsaville, & Chevron, 1984), the result of an inability to understand events and anticipate the future (Kelly, 1955), and as the result of biologic or genetic predisposition (see Schatzberg, 1995 for review). Klein, Wonderlich, & Shea (1993) consider depression to be separate and distinct from personality, thus eliminating debate over state- and trait-aspects of depression. However, others maintain that both states and traits are involved (Watson & Tellegen, 1985). Whatever the etiology, depression has been conceptualized most thoroughly by Cattell (1970) who devised a scale assessing multidimensional aspects of what he thought depression to be—a stable pattern of emotional coping.
Depression and Immunity

Generally, depression has been associated with immunosuppression and increased risk of infection (Heisel, Locke, Kraus, & Williams, 1986). Patients hospitalized with major depressive disorder have been shown to have lower levels of slgA (Stone, Cox, Valdimarsdottir, Jandorf & Neale, 1987); lower NK cell values (Heisel, Locke, Kraus & Williams, 1986); slowed delayed hypersensitivity response (Darko, Wilson, Gillin & Baird, 1991); upregulated expression of Interleukin-2 receptors (Maes, Bosmans, Suy, Vandervorst, DeJonckheere, & Raus, 1990); impaired lymphocyte response to mitogens, lower absolute numbers of B and T cells, and higher cortisol levels (Krueger, Levy, Cathcart, Fox & Black, 1984; Schleifer, Keller, Myerson, Raskin, Davis & Stein, 1984; see Darko, Gillin, Bulloch, Golshan, Tasevska, & Hamburger, 1988; Schleifer, Keller, Bond, Cohen, & Stein, 1989 for contradictory findings). Possible effects of hospitalization and comorbid psychiatric illness on immune functioning do not seem to account for the altered immunity observed in depressed patients; however, the severity of depressive symptoms may be a factor in determining the magnitude of immune changes. Schleifer, Keller, Siris, Davis, and Stein (1985) found that ambulatory patients with major depressive disorder were similar to healthy controls; they had no decrease in mitogen responses.

Similarly to clinical depression, recent conjugal bereavement negatively impacts immune functioning. Depression is frequently a concomitant of bereavement and may be the mediating mechanism by which bereavement
alters immunity (Parkes, 1984). Bereaving widows have reduced NK cell activity and elevated cortisol levels (Irwin, Daniels, Bloom, Smith, & Weiner, 1988; Irwin, Smith, & Gillin, 1987); reduced mitogen response (Schleifer, Camerino, Thornton, & Stein, 1983); and significantly lower T cell activity (Bartrop, Lazarus, Luckhurst, Kiloh, & Penny, 1977).

The possibility of an association between psychiatric syndromes and EBV has been investigated and findings are inconsistent. Some suggest that depression is significantly related to EBV antibody levels (DeLisi, Nurnberger, Goldin, Simmons-Alling, & Gershon, 1986); whereas, others contend that there is no consistent relationship (Amsterdam, Henle, Winokur, Wolkowitz, Pickar & Paul, 1986). EBV may cause a recurrent illness with some aspects of symptomatology similar to that of affective disorders (Jones, Ray, & Minnich, 1985); however, EBV does not appear to be a necessary condition for the development of depression or other mood disorders (Cooke, Langlet, & McLaughlin, 1988). EBV reactivation, like other immune alterations, may occur only in more severely depressed patients (Cooke, Warsh, Hasey, McLaughlin, & Jorna, 1991).

Depression and Health

Depression has been proposed as an important source of vulnerability leading to morbidity and mortality (Avery, & Winokur, 1976; Green, 1966; Murphy, Monson, Olivier, Sobol, & Leighton, 1987). Depressed patients suffer more severe infections, such as acute coryza and influenza, than mentally
healthy control subjects (Heisel, Locke, Kraus & Williams, 1986), and have altered susceptibility to certain illnesses, including infectious diseases (Jemmott & Locke, 1984; Kemeny, Cohen, Zegans & Conant, 1989), autoimmune disorders (Solomon, 1981), and allergies (Stein, Miller, & Trestman, 1981). The association between depression and cancer is less clear with some reports of a positive relationship (Fox, 1981; Grossarth-Matick, Bastianans, Kanazir, Vetter, & Schmidt, 1985; Persky, Kempthorne-Rawson, & Shekell, 1987; Schmale & Iker, 1966) and other reports of inconsistent or negative findings (Anisman & Zacharko, 1983; Fox, 1978; Zonderman, 1995). Herpes simplex virus (HSV) and human immunodeficiency virus (HIV) also are associated with depressed mood. Unhappy mood, in general (Katcher, Honori, Brightman, Luborsky, & Ship, 1973) has been observed to precede herpes recurrences. Individuals with depressed mood have been found to have higher HSV recurrence rates and those with more severe depression have twice as many recurrences as less depressed subjects (Kemeny, Cohen, & Zegans, 1989). Regarding HIV-related immune parameters, Kemeny and colleagues (1991) have found that depressed mood in nonbereaved HIV+ men is associated with lower percentages of CD4 (helper cells), higher percent of CD8 (suppressor cells), and a lower proliferative response to the mitogen PHA (phytohemagglutinin), all measures which may impact progression of HIV (Kemeny, Fahey, Schneider, Weiner, Taylor, & Visscher, 1988 cited in Kemeny, 1991).
State-Trait Anger Theory

Spielberger and associates (1985) have developed a theory of anger which encompasses the experience and expression of this emotion. The central thesis is a distinction between the experience of anger as an emotional state (state anger) and individual differences in anger as a personality trait (trait anger). When state anger is experienced with high frequency over time, then the person is classified as experiencing trait anger. Persons high in trait anger have a greater tendency to perceive a wider range of situations as anger provoking (e.g., annoying, irritating, frustrating) than individuals low in trait anger, tend to respond to these situations with higher levels of state anger, and tend to experience more intense elevations in state anger whenever annoying or frustrating conditions are encountered. Support for Spielberger's state-trait theory of anger was provided by Deffenbacher and colleagues (Deffenbacher, Oetting, Thwaites, Lynch, Baker, Stark, Thacker, & Eiswerth-Cox, 1996).

Spielberger et al's theory of state- and trait-anger has been widely accepted and the State Trait Anger Expression Inventory (STAXI; Spielberger, 1991) is one of the most commonly used scales in research investigating the relationship between anger and health.

Anger and Immune Functioning

Typically, anger is not studied in relation to the immune system. Rather, it is investigated more often as a correlate of cardiovascular functioning. Nevertheless, anger-out has been found to impact an individual's immune
system by reducing NK cell cytotoxicity, and the relationship was exacerbated by
stress (Scanlan, Laudenslager, Legg, Broussard & Boccia, 1991).

**Anger and Health**

Among the diseases with which anger has been implicated are
hypertension, coronary heart disease, cancer (Appel, Holroyd & Gorkin, 1983),
and arthritis (Friedman & Booth-Kewley, 1987). Subjects who reported
chronically experiencing (trait anger), suppressing (anger-in), or aggressively
expressing (anger-out) their anger have demonstrated both negative and
positive physiological reactions. Trait anger, anger-in, and anger-out were
associated with elevated blood pressure according to some (Gentry, Chesney,
Gary, Hall & Harburg, 1982; Spielberger, Krasner & Solomon, 1988; Spielberger,
Ritterband, Sydeman, Reheiser & Unger, 1995). Others have reported conflicting
results; those higher on anger-out had lower heart rates and norepinephrine
reactivity levels (Mills, Schneider, & Dimsdale, 1989) and those high on trait
anger demonstrated no differences on measures of heart rate, pulse, and blood
pressure (Deffenbacher, et al, 1996). Anger-in also has been associated with
lower HDL concentration (Waldstein, Manuck, Bachen, Muldoon & Bricker,
1980), cardiac output, and peripheral vascular resistance (Schwartz, Weinberger

The relationship between anger and health status remains unclear and
may be impacted by gender, age and culture as well as other variables. Women
are more prone to experience discomfort with their own experience or display of
anger (Sharkin, 1996), and this may, in large part, be due to significant gender role differences in the expression of anger (Kopper & Epperson, 1996). Men and women alike are at significant risk for cardiovascular disease, but men do not have the protective effects of estrogen to assist in heart health maintenance (Hatcher, et al, 1995) and have higher rates of hypertension than women (Gentry, Chesney, Gary, Hall, & Harburg, 1982). Likewise, in a sample of college students, although anger was moderately related to stress, no associations between anger and health status were observed (Thomas & Williams, 1991) suggesting that adverse health consequences of maladaptive modes of anger expression may not be evident until later life. Cultural differences in health effects of anger expression patterns have been identified (Sharkin, 1996). Anger-out was correlated with adverse health outcomes in a national sample of Black Americans (Johnson & Broman, 1987); whereas, in a sample of Israeli men, frequency of anger expression was positively correlated with ill health, but the intensity of anger expression was negatively correlated with ill health. Engebretson and Stoney (1995) suggest that neither anger-out or anger-in is inherently health damaging or a cardiovascular health risk, but that inflexibility in using these ways of coping can be damaging to one's heart. The health promoting connotations of anger-discuss (Haynes, Levine, Scotch, Feinleib & Kannel, 1978) may be related to such a flexible coping style.

In summary, findings suggest that negative affect may be related to poorer immune functioning and illness, but further clarification is needed.
Depression severity and the specific immune parameter being studied both appear to impact findings. Various types of anger have been related to cardiovascular functioning, cancer, and arthritis, but few studies investigating an association between anger and immune functioning directly have been reported. There is no clear evidence for differences in predictive strength of state or trait anger and depression. Examining negative affect in greater depth may give us some insight into these relationships.

Epstein-Barr Virus (EBV)

Epstein-Barr Virus (EBV) is a human oncogenic herpesvirus which has been shown to be the etiologic agent for infectious mononucleosis (Henle & Henle, 1982). Indications of EBV in serum are typically obtained by measuring the level of antibodies to the EBV viral capsid antigen (VCA; ie., A capsid is a protein covering around the central core of a virus particle. The capsid protects the nucleic acid from the destructive enzymes in biological fluids and promotes attachment of the virus to susceptible cells). EBV-VCA antibodies usually emerge during the incubation period, and IgG antibodies to VCA persist for life. Increased levels are indicative of either a primary infection or another illness and a former EBV infection. In a study of EBV epidemiology, Sumaya, Henle, Henle, Smith, and LeBlanc (1975) found that geometric mean titers of VCA antibody were highest in early childhood, lowest in adolescence and young adulthood, and high in the elderly. In addition, titers were higher for females in all age
groups relative to males. Ninety percent of adults are seropositive for EBV (Sumaya, Henle, Henle, Smith, & LeBlanc, 1975).

Herpes virus antibodies have been assessed in a number of PNI studies. The level of these antibodies is thought to reflect the competence of the T cells in keeping the virus sequestered and latent; as the virus escapes, antibodies against it are produced and released into the bloodstream. Higher levels of antibody to latent viruses are interpreted as poorer outcomes because they indicate higher levels of virus replication. In contrast, lower levels of antibody are thought to reflect some increase in the ability of the cellular immune response to control the latent virus.

Certain unique characteristics of the herpesviruses (e.g., HSV and EBV) suggest that they might be particularly sensitive as markers of stress-related changes in cellular immunocompetence. EBV can be activated indirectly by psychological stress (Glaser, Pearson, Jones, Hillhouse, Kennedy, Mayo, & Kiecolt-Glaser, 1991), anxiety (Esterling, Antoni, Kumar, & Schneiderman, 1993), repression (Esterling, Antoni, Kumar, & Schneiderman, 1990), and depression (Cooke, Warsh, Hasey, McLaughlin, & Jorna, 1991). Others suggest that EBV titers are not measurably affected by depression (Amsterdam, et al, 1986; Maes et al, 1991) or by moderate in vivo stressors (Lee, Meehan, Robinson, Mabry, & Smith, 1992). Further investigation is warranted.
EBV and Health

EBV is a prime human tumor virus candidate because of its strong association with African Burkitt lymphoma and nasopharyngeal carcinoma (Tuckwiller & Glaser, 1983). It is also responsible for primary infectious mononucleosis. Research investigating the relationship of EBV to other viruses which are significantly symptomatic when activated, including HSV and HIV-1 suggests an association. In one study of gay men receiving notification of their HIV-1 seropositive status, EBV levels were measured once per week during the waiting period and again after subjects had been notified, a total of 10 times. HIV sero-positive men had higher EBV-VCA antibody titers than those diagnosed as seronegative at every time during the study, suggesting that some of the same mechanisms affecting HIV progression may involve EBV as well (Esterling, Antoni, Schneiderman, Carver, LaPeriere, Ironson, Klimas, & Fletcher, 1992). At this point, it is difficult to say whether stressor-induced immune alterations have substantial implications for health, but preliminary research indicates a possible connection with both HSV and HIV.

Oral contraceptive use, estrogen, and progesterone are associated with alterations in immune functioning. They are also related to health risks, much more so than with health benefits. In addition, oral contraceptives and the hormones they contain interact with negative affect, arousal, and stress. Stress appears to be related to illness and immune functioning; however, mediating variables are thought to be very important in understanding the relationship fully.
Negative affect is also related to immune functioning and health. However, the relationships between negative affect and EBV appear to less consistent or not investigated yet. Several interrelationships involving these variables have been significant, supporting the hypothesis that interactions may be useful as an adjunct to examining direct relationships.

There are over 50 million women using oral contraceptives (Peterson, 1995), 25% of women suffer from major depression, and stress is so common, it is part of everyday language in American culture. More now than ever before, Americans are concerned with factors which may impact their physical well-being. The present study was designed to measure the individual impact of oral contraception (ie., self-reported use, estradiol, and progesterone levels), stress (ie., daily hassles and a 1-item self-report measure), and negative emotionality (ie., depression and anger) on immune functioning (ie., EBV VCA IgG levels). In addition, the interaction of these factors were examined, and synergistic effects on immune functioning were investigated. It was hoped that some of the factors affecting immune functioning in women will be clarified.

Hypotheses

Hypothesis 1. Oral contraceptive use will be associated with higher antibody levels to EBV-VCA.

Hypothesis 2. Higher levels of stress will be associated with higher antibody levels to EBV-VCA.
**Hypothesis 3.** Higher levels of anger and depressed mood will be associated with higher antibody levels to EBV-VCA.

**Hypothesis 4.** Oral contraceptive use, stress, anger, depression, and doctor's visits will additively predict antibody levels to EBV-VCA.
CHAPTER II

METHOD

Subjects

Thirty seven women between the ages of 18 and 32 were recruited from the Psychology department at the University of North Texas. Members of minority groups were encouraged to participate. Recruits received extra credit in exchange for their participation. A brief explanation of the research was provided on a sign-up sheet which was posted for volunteers to sign up for the study.

Instruments

Background and Medical History Information. This form provides information regarding demographic, health, and medication information (see Appendix A).

Daily Hassles Scale. The Daily Hassles Scale (Kanner, Coyne, Schaeffer & Lazarus, 1981) is designed to measure perceived stress in response to ongoing aspects of life that are troublesome. This scale consists of 117 items which are initially "x"ed if they occurred at all during the previous 6 months and subsequently are rated for their perceived severity (e.g., 1 = was not at all bothersome; 2 = irritating; 3 = very bothersome) during the previous month. The 117 item scale was reduced to 84 items, deleting those items which assess
health status and negative affect (Dohrenwend & Dohrenwend, 1981). The scale provides three indexes: 1) hassle frequency (a simple count of number of items checked (0-84)); 2) hassle severity (sum of the three-point severity ratings, range 0-252); and hassle intensity (hassle severity divided by hassle frequency, range 0-3). Higher scores indicate increased stress experiences. The entire scale takes approximately 15 minutes to complete. The authors report a high degree of face and content validity. In addition, the relationship between hassles and life events scores are modestly correlated (r = .36) suggesting to the authors that a large proportion of daily hassles is probably independent of life events (Lazarus & Folkman, 1989).

Clinical Analysis Questionnaire. The Clinical Analysis Questionnaire (CAQ) (Part 2) (Cattell & Delhees, 1970) is purported to measure clinical factors of depression, paranoia, psychopathic deviation, schizophrenia, psychasthenia, and psychological inadequacy. It consists of 144 items. Each of the items has three choices from which the examinee may select an answer. Generally, the middle response is an “in-between” or “uncertain” category, and instructions urge examinees not to use this category very frequently. The present study was concerned with seven depression scales provided from the examinees protocol (e.g., hypochondriasis, suicidal depression, agitated depression, anxious depression, low energy, guilt and resentment, and boredom and withdrawal). Higher scores indicate higher levels of depressed coping. Part 2 takes approximately 30 minutes to complete. Krug (1980) reports high test-retest and
internal consistency (r = .80 and .71, respectively) for the clinical scales as well as high factor validity for the depression scales specifically (r = .59 to .86).

**State Trait Anger Expression Inventory.** The State-Trait Anger Expression Inventory (STAXI; Spielberger, 1988) consists of 44 items which assess the experience and expression of anger. Respondents rate each item on a 4-point scale from "not at all" to "very much so." Item responses are rated from 1 to 4 and then added for a total raw score for each scale. Higher scores indicate a higher level of state anger, trait anger, trait anger-angry temperament, trait anger-angry reaction, anger in, anger out, anger control, and anger expression. The entire scale takes approximately 10 minutes to complete. Convergent validity studies suggest that trait anger is correlated with other measures of anger (r = .27 to .73 for a female sample). Also, trait anger and state anger are correlated with neuroticism and psychoticism (r = .20 to .49 for females) as well as with trait and state anxiety (r = .25 to .63 for females) (Spielberger, 1991). Reliability and validation studies report ranges from r = .70 to .73 and from r = .22 to .52, respectively (Knight, Chisholm, Paulin, & Waal-Manning, 1988).

**Complete Blood Cell (CBC) count.** The CBC consists of the measurement of the hemoglobin, hematocrit, white blood cell (WBC) count and differential (the classification of WBC's and the examination of the red blood cells (RBC's) and platelets). The CBC was used to rule out current infection based on WBC results.

**Estradiol and Progesterone.** Estradiol and progesterone levels were determined via radioimmunoassay (RIA) following preparation of blood samples.
Hormone levels for estradiol and progesterone were obtained in ng and pg units, respectively.

*Epstein-Barr Virus Viral Capsid Antigen IgG*. EBV VCA IgG levels were determined via ELISA assay following preparation of blood samples. Results were obtained in raw optical density units. A standard curve was generated using the mean of the lots in manufacture at the time the kit was purchased. (This was possible because the variance over the lots was negligible; see Appendix B).

**Procedure**

Volunteers who signed up for the study were contacted by telephone and screened prior to their participation. Exclusion criteria included currently experiencing any symptoms of illness with the exception of minor reaction to allergies; taking any prescription or over-the-counter medication 24 hours prior to the blood draw; using alcohol or illicit drugs 24 hours prior to the blood draw; and using or stopping use of oral contraceptives for less than 3 months. Volunteers were informed that they must bring their oral contraceptive pill package in order to document name and dosage of pill used. They were also told to be prepared to provide the date of their last menstrual period.

All volunteers were introduced to the study and gave informed consent, acknowledging that they could withdraw from participation in the study at any time without penalty (see Appendix C). Subjects were assured that by participating in the blood draw they would be at no greater risk than if they were participating in a screening process for donating blood to the Red Cross or
routine blood tests at a doctor’s office. As a group, volunteers initially completed background and medical history forms. Subsequently, the group was provided instructions for completing the remaining psychological questionnaires. Individual volunteers were summoned at random for blood draw in an adjacent room. A licensed medical technologist drew 5 ml of blood between the hours 2:00 and 5:00 pm, and an assistant hosted volunteers during post-blood draw recovery with beverage and snack. Following a 5-minute recovery period, volunteers returned to the research room where they completed the remaining questionnaires. Volunteers notified the researcher when they had completed all forms.

Blood samples were transported and complete blood counts (CBCs) were performed within 4 hours of collection. Serum samples for estradiol, progesterone, and Epstein-Barr Virus (EBV) Viral Capsid Antigen (VCA) Immunoglobulin G (IgG) were centrifuged and stored at -80 degrees Celsius and were assayed at a later date. Radioimmunoassays and ELISAs were performed according to standardized procedures published by the manufacturer. Blood test results indicated all subjects were healthy and all had been exposed to EBV. Thus all subjects remained in the data pool for analysis.
CHAPTER III

RESULTS

Descriptive statistics of the sample are as follows. Mean age of subjects was 22.13 years, SD = 3.41, and mean level of education was 13.84 years, SD = 1.42. All demographic variables were tested for correlations with EBV to identify any relationships which might be relevant in subsequent analyses. No significant relationships were identified (see Table 1, Appendix D). Because previous findings have suggested that users and nonusers differ on demographic and health behavior information, they were analyzed separately. Frequency distributions of marital status and race were similar for users and non-users. In the user group, 94% of women were single and 6% were married. In the non-user group, 87% of women were single, 7% divorced, and 7% widowed. T-tests were performed to detect differences between oral contraceptive users and non-users on various demographic and health behavior variables. Members of the two groups did not significantly differ on age, education, or quantity of alcohol consumed. However, users report having an exercise routine more than non-users, $t(30) = -2.24$, $p < .05$ and also report exercising more times per week than non-users, $t(31) = -3.21$, $p < .01$. Two-tailed correlations between exercise
routine, exercise frequency and EBV, partialling out oral contraceptive use, again revealed no significant relationships.

**Hypothesis 1.** Oral contraceptive use will be associated with higher EBV-VCA IgG levels (EBV). One-tailed Pearson Product Moment correlation results suggested no significant relationship between self reported use of oral contraceptives and EBV. Because OC use was found to be related to exercise, a correlation between OC use and EBV was tested, partialling out exercise. There remained no significant relationship. Hypothesis 1 was not supported.

Furthermore, neither ovarian hormone (e.g., estradiol and progesterone) was associated with EBV levels. Estradiol and progesterone were tested for associations with all demographic variables to determine relevance of other factors in the relationship between ovarian hormones and EBV. Estradiol was significantly related to age, $r = .56$, $p < .01$ and with being single, $r = -.44$, $p < .01$. Estradiol and EBV remained unrelated when age was partialled out. The hypothesis that oral contraceptive use is associated with immune challenge was not supported. Furthermore, there was no evidence to support an association between ovarian hormones and immune system functioning as measured by EBV-VCA IgG levels.

**Hypothesis 2.** Higher levels of stress will be associated with higher EBV levels. Pearson Product Moment correlations revealed no association among hassle frequency, hassle severity, hassle intensity, nor a one-item measure of current stress with EBV levels (see Table 2, Appendix D). Results did not
support the hypothesis that higher levels of stress as measured by the Daily Hassles Scale would be associated with immune system challenge. Correlations between the stress measures are provided in Table 3 (see Appendix D). Hassle frequency was highly correlated with hassle severity, $r = .91$, $p < .01$, and with a one-item self-report measure of stress, $r = .35$, $p < .05$.

**Hypothesis 3.** Anger and depressed mood will be associated with higher EBV levels. One-tailed Pearson Product Moment correlations were performed among anger and depression scores and EBV. Of the eight anger scales, angry reaction only was significantly correlated with EBV, $r = .41$, $p < .01$ (see Table 2, Appendix D). Of the seven depression scales, suicidal depression ($r = .36$, $p < .05$), low energy depression ($r = .31$, $p < .05$) guilt and resentment ($r = .34$, $p < .05$), and boredom and withdrawal ($r = .38$, $p < .05$) were significantly related to EBV levels (see Table 2, Appendix D). Hypothesis 3 was supported in part, with five of the fifteen negative affect scales correlating significantly with EBV.

**Hypothesis 4.** The independent variables will predict a significant proportion of the variance in EBV scores using an additive model. A priori step-wise regression analysis was performed to determine the relative contribution of oral contraceptive use, hassle intensity, negative affect (ie., a composite score made up of number of elevated scales on the STAXI and CAQ), and number of doctor’s visits in the past year in order to determine the amount of variance each contributes to immune functioning as measured by EBV levels. Using default criteria for inclusion in the regression model, none of the above variables or
combinations thereof predicted a significant proportion of the variance in EBV levels. Hypothesis 4 was not supported. Estradiol and progesterone were included in the above model as a substitute for oral contraceptive use. Again, results were not significant. Because the statistical program does not provide statistical results for models which have no significant variables entering the equation, no table is provided for these results.

Additional Statistical Analyses

Two-tailed Pearson Product Moment correlations were performed to test the relationships among independent variables. Stress, hassle frequency, and hassle severity were correlated with measures of negative affect, but hassle intensity was not (see Tables 4 and 5, Appendix D). Also, measures of anger and depression were correlated with each other (see Table 6, Appendix D). Likewise, anger scales were intercorrelated as were depression scales (see Tables 7 and 8, Appendix D).

A reduction in arousal and negative affect as a result of oral contraceptive use has been suggested. Therefore, these relationships were tested using Pearson Product Moment correlations. None of the relationships among oral contraceptive use, stress, anger and depression were significant. Results were not supportive of either suggestion (see Table 9, Appendix D).

Because of the small sample size, and the need to limit the number of independent variables entering the post-hoc analyses in order to find results which have not capitalized on chance, stepwise regression analysis was
performed. The four depression scales were entered to determine which of them accounted for most of the variance in EBV. Boredom and withdrawal accounted for the greatest proportion of the variance ($R^2 = .15$), and all other depression scores were excluded by the program using default criteria (see Table 10, Appendix D). Identical procedures were followed for the anger variables. Angry reaction and trait anger together accounted for 32% of the variance in EBV scores (see Table 11, Appendix D). Because angry reaction accounted for a significant proportion of the variance by itself, it alone was used in subsequent additive and multiplicative models.

Based on the findings which resulted from hypothesis testing, post-hoc hierarchical regression analysis was performed to evaluate the impact of angry reaction, boredom and withdrawal, doctor's visits, and oral contraceptive use. Angry reaction alone accounted for a large proportion of the variance ($R^2 = .17$); angry reaction with boredom and withdrawal accounted for the next largest proportion ($R^2 = .22$); and angry reaction, boredom and withdrawal, and doctor's visits accounted for the largest at 30%. Oral contraceptive use did not account for any additional variance in EBV levels (see Table 12, Appendix D).

**Post-hoc Interaction Analyses.** Post-hoc hierarchical regression analysis was performed to test the interaction model as a predictor of EBV levels. Hassle intensity x boredom and withdrawal + angry reaction + doctor's visits + oral contraceptive use x progesterone was tested as the model predicting EBV, and it accounted for 30% of the variance in EBV scores (see Table 13, Appendix D).
One post-hoc three-way interaction was tested with hassle intensity x angry reaction x boredom and withdrawal. This interaction accounted for 16% of the variance in EBV (see Table 14, Appendix D). And finally, one-tailed correlations were performed between the independent variables involved in the interaction terms (see Table 15, Appendix D). Angry reaction and boredom and withdrawal were significantly correlated ($r = .43$, $p < .01$).

Of the four a priori hypotheses, two were partly supported by the statistical findings. Oral contraceptive use and stress were not significantly correlated with EBV antibody levels. In addition, the chosen independent variables did not additively predict EBV levels. As hypothesized, however, negative affect was significantly related to EBV. Post-hoc analyses revealed significant correlations among stress and negative affect variables and the utility of an additive model of angry reaction and boredom and withdrawal as predictors of EBV. Interaction models were not significantly more predictive than negative affect alone.
CHAPTER IV

DISCUSSION

Recently, there has been a call for integrative research in the study of biological, psychological, and social health factors. Individual variables such as oral contraceptive use, negative affect, and hassles have been directly associated with immunosuppression, but inconsistencies abound in the literature. In the present study, attempts were made to replicate previous findings as well as to offer an integrative model, consistent with the biopsychosocial theory, which would contribute to a better understanding of factors impacting illness.

In relation to the first hypothesis, oral contraceptive use was not related to EBV levels. The immunosuppressive effects of oral contraceptives have been well established in the literature, and the pill's constituent hormones (e.g., estradiol and progesterone) have known immunosuppressive effects as well (Johnson & Everitt, 1980). Therefore, similar findings would have replicated well-known relationships. Alternatively, that oral contraceptive use would result in immunoenhancement was also a viable hypothesis. If intervening variables of decreased arousal and reduction of negative affect were active as suggested by previous findings, we might have observed a lower level of EBV antibodies for OC users. However, results are not supportive in either direction.
In contrast to oral contraceptive users, nonusers have varying levels of ovarian hormones during their menstrual cycles; consequently, stress reactivity, negative affect, and their relationship to immune functioning may vary over the course of the month. The present study failed to control for phase of the menstrual cycle, consequently, no insight into this relationship was gleaned from this data. However, future studies which account for phase are recommended. Repeated measures design employing assigned groups of oral contraceptive users and nonusers is recommended as well.

The second hypothesis that higher levels of stress would be associated with higher EBV antibody levels was not supported. As recommended by others, stress was assessed with the revised Daily Hassles Scale which is devoid of items that overlap with negative affect and health concerns (Dohrenwend & Dohrenwend, 1981). Additionally, the one-item self-report measure of stress was included to determine whether merely asking someone if they were stressed would provide the same information as a more time consuming measure. Contrary to expectations, none of the stress measures was correlated with EBV, thus previous findings were not replicated in this study. Of the three hassles scores, hassles intensity has been most consistently related to immune functioning (Ruffin, 1993), but this finding also did not replicate. Explanations for these surprising results can be found in part by looking at correlations between hassles and negative affect. Hassles frequency and severity are both highly correlated with anger and depression; whereas, hassles intensity is not. Others
have been consistent in reporting a strong relationship between stress and negative affect, yet the one stress measure which so often correlates with immunosuppression did not correlate with negative affect for this sample. It may be that if the complete version of the Daily Hassles Scale had been employed that results would have been different. Also, proponents of the use of major life events as a more effective measure of stress have found that subjective measures such as the Daily Hassles Scale do not correlate consistently with immune measures unless the stressors are of high magnitude (Herbert & Cohen, 1993). The lack of significant associations found in the present study may be a reflection of inadequacies in the stress measure used. Because this measurement issue remains unresolved, it is likely that stress research will continue to make slow gains in this respect.

The relationship between the single item stress measure and the three hassles scores was assessed. Results suggest that a high severity but low frequency of hassles is more likely to implicate the person as feeling stressed on self report. This supports the finding that cognitive appraisal is vital to understanding the stress construct. In addition, a single item stress measure may be an effective assessment question for mental and physical health service providers when initially screening patients.

Hypothesis 3 was partially confirmed. Angry reaction to the exclusion of the other anger variables was significantly correlated with EBV. Spielberger (1991) describes individuals with high angry reaction scores as highly sensitive
to criticism, perceived affronts, and negative evaluation by others, and that these individuals experience intense feelings of anger under such circumstances. Angry reaction is conceptualized as a stable pattern of emotional management. Of the trait anger variables, angry reaction has not been found to be associated with health outcomes, but the primary factor of trait anger has been related consistently to cardiovascular parameters (Gentry, Chesney, Gary, Hall, & Harburg, 1982; Mills, Schneider, & Dimsdale, 1989) and less frequently to cell-mediated immunity for women (Franks, 1992). Surprisingly, in this study no relationship was observed between trait anger and EBV scores, although additively, both angry reaction and trait anger predicted EBV. The relatively small sample size may explain the lack of correlation for trait anger and EBV. This finding implicates anger more directly in immune-related illnesses and more research in this area is encouraged. In contrast, previous findings that anger-discuss has health promoting effects were not replicated (Haynes, Levine, Scotch, Feinleib & Kannel, 1978). Flexibility in anger management may be preferable to highly rigid management style or extremes in either direction (Engebretson & Stoney, 1995). No comparable scale to anger-discuss exists on the STAXI; however, possibly a combination of high anger-in and anger-out scores would be equivalent in meaning (Spielberger, 1991). High anger-in/anger-out scores were not tested for an association with EBV. More research in this area is warranted in order to better clarify which relationships exist between anger management styles and immune measures.
In addition, hypothesis 3 results revealed consistent relationships between various styles of depressed coping and EBV. These results are somewhat surprising because of the consistent findings that ambulatory or less severely depressed individuals may have undetectable changes in EBV and other immune parameters (Cooke, Warsh, Hasey, McLaughlin, & Jorna, 1991; Schleifer, Keller, Siris, Davis, & Stein, 1985). However, the pattern of results suggests that this finding is real and not due to error variance. Suicidal depression, low energy depression, guilt and resentment, and boredom and withdrawal all were modestly correlated with EBV. However, of these four depressed coping styles, boredom and withdrawal accounted for most of the variance in EBV levels.

Krug (1980) described high scorers on the boredom and withdrawal scale as feeling that life is too pointless and silly to care at all, a tendency to avoid people, feeling too depressed and useless to want to interact with other people, and feeling happier alone, away from people. According to Krug (1980), both schizophrenics and narcotic abusers tend to score high on this scale. The name of this scale suggests that it assesses more than depression. Individuals researching boredom have found an array of correlates and meanings for the construct including loneliness (Kristensen, 1995), lack of purpose in life (Weinstein, Xie, & Cleanthous, 1995), poor quality of life (Watten, Syversen, & Myhrer, 1995), role loss (Crist-Houran, 1996), disinhibition (Koopmans, Boomsma, Heath, & van Doornen, 1995), sleepiness (Mavjee & Horne, 1994),
dogmatism, unsociability, low persistence (Leong & Schneller, 1993), impulsivity (Hennig, Becker, & Netter, 1995), dissatisfaction, low need for cognition (Watt & Blanchard, 1994), and listlessness (Mehrabian, 1997). Boredom has been reported by obese women who crave sweets (Schlundt, Virts, Sbrocco, Pope-Cordle, et al, 1993), binge eaters (Lacey, Coker, & Birtchnell, 1986), repetitive strain injury employees (Tyrer, 1994), the elderly disabled (Wilhite, 1994), the mentally ill (Segal, & VanderVoort, 1996), smokers (Forgas & Meyer, 1996; Wang, Fitzhugh, Cowdery, & Trucks, 1995), marijuana users (Globetti, Lo, & Globetti, 1994), hair pullers (Stanley, Borden, Mouton, & Breckenridge, 1995) and those diagnosed with self-induced water intoxication (May, 1995). Boredom is low in athletes (Rossi & Cereatti, 1993), religious copers (Koenig, Cohen, Blazer, & Kudler, et al, 1995), volunteers (Weinstein, Xie, & Cleanthous, 1995), children who engage in more imaginative play (Harris & Beggan, 1994), and those individuals who are more inclined to provide their own cognitive stimulation (Miller & Niemi, 1995; Watt & Blanchard, 1994). These findings suggest that common themes among bored individuals are passivity, lack of initiation in making things happen, and an inability to set and achieve goals. In this sample of normal young adult women, it is possible that they are individuals who sit back and wait to be entertained, hired for jobs, and passed in class. They may spend little time acting on their environment, rather they expect their environment to act upon them and then are dissatisfied and withdraw when their needs are not met. Overlap of this construct with the other depression scales which also correlated
with EBV (e.g., suicidal depression, low energy, and guilt and resentment) provides some validity for this theory.

Hypothesis 4 that an additive model including oral contraceptive use, hassle intensity, negative affect, and number of doctor's visits would predict EBV antibody levels was not supported. Allowing the default criteria to select significantly predictive variables resulted in no viable model to account for variance in EBV scores. As discussed above, oral contraceptive use and hassles intensity simply were not players in the relationship. In consideration of the consistently found relationship between depression and EBV scores, it is likely that important predictive value was lost when the anger and depression scores were collapsed into one composite variable of negative affect. Because correlations were modest between the four depression scores and EBV and between angry reaction and EBV, they simply did not hold up when they were recoded using median split scores and combined.

Consistent with findings in the literature, the stress and negative affect variables were highly correlated. Consequently, the subsequent analyses were hierarchical with stress always entered as the first step. This procedure was followed under the assumption that if stress was forced to enter the model and negative affect was still a significant predictor, then we would be able to set forth two possible explanations. The first is that the measure of stress used in the analysis was inadequate and did not measure stress as conceptualized for this study. The second explanation is that despite the high correlations between the
two constructs, stress and negative affect scales are actually measuring two different experiences and negative affect may actually be the better predictor of EBV. No conclusions can be made regarding which of these two explanations is more accurate; however, further investigation is warranted.

In post-hoc analyses, both angry reaction and boredom and withdrawal consistently predicted EBV in an additive model. While angry reaction appears to be the more predictive of the two measures, together they characterize those women in the sample who have higher antibody levels to EBV-VCA. These emotional coping styles may be assessing the group of people in their early 20's who are called by the media the Generation X. Not only has this group's sense of entitlement and existentialist passivity been considered a serious social problem, but it may also be impacting this group's health.

Several interaction models were tested to evaluate the possibility of a synergistic effect of stress and negative affect on EBV-VCA IgG levels. Unfortunately, these interactions were equally or less effective in predicting EBV scores than the additive model of angry reaction, boredom and withdrawal, and doctor's visits. Again, this finding may suggest that our revised measure of stress was inadequate.

Additional findings of interest include the relationship of oral contraceptive use and exercise. Results suggest that oral contraceptive users tend to report exercising more regularly and with higher frequency than nonusers. There is no history of such a pattern in the literature. In fact, generally, oral contraceptive use
decreases arousal. If that is the case, then users may be attempting to increase their artificially low state of arousal by exercising more. Furthermore, as arousal is lowered by pill use, energy and resources are conserved, thus allowing for availability of energy to be expended through exercise. The present study did not investigate these possibilities, but the finding is provocative and warrants further investigation.

Also, analysis of relationships between demographic variables and EBV revealed that exercise was not correlated with EBV. Consistently, researchers have found a cardiovascular protective effect of exercise (Morris, Everitt, Pollard, Chave, & Semmence, 1980; Paffenbarger, Hale, Brand, & Hyde, 1977). However, the findings regarding effects of exercise on immune functioning are less consistent. Several reports and reviews suggest improved immune state with exercise (Green, Kaplan, Rabin, Stanitski, & Zdziarski, 1981; Simon, 1984; Nash, 1986) while others suggest there is an increased susceptibility or a decreased resistance to minor infections in athletes (Tomasi, Trudeau, Czerwinski, & Erredge, 1982; Jokl, 1974; Roberts, 1986). Increase in NK cell response, number, and cytotoxicity has been found, regardless of exercise duration (Hickson & Boone, 1991), whereas; exercise intensity has generally been found to have no effect on a variety of immunological parameters. Interestingly, exercise has been used as a stress reduction technique for gay men waiting to receive their HIV seropositive status. Exercise was found to act as a buffer, both psychologically and physiologically during HIV antibody status
notification (Esterling, Antoni, Schneiderman, Carver, La Perriere, Ironson, Klimas, & Fletcher, 1990). So, while one study has found that exercise buffers the effects of stress on EBV levels, there is a paucity of research employing both variables. Thus the present findings that exercise and EBV are not correlated will contribute to the small number of studies presently reported.

The present study set out to investigate the biopsychosocial model of illness using variables which have been identified as having possible direct or mediating roles in illness. Results were provocative in regards to the additive prediction made by angry reaction and boredom and withdrawal. For young people in Generation X as well as the unemployed and bereaved who may be experiencing similar loss of meaning, interventions designed toward goal setting, achievement motivation, and volunteer work may assist these individuals in obtaining or regaining their sense of identity and purpose in life. Such interventions may not only improve their psychological status but also improve their immune functioning and illness susceptibility.
APPENDIX A

BACKGROUND AND MEDICAL HISTORY FORM
BACKGROUND AND MEDICAL HISTORY INFORMATION

ID# __________  Sex: M/F  Age: __  Marital Status: _____ Race: White/Black/Hispanic/Asian

Last Grade Completed: _____  Last menstrual period: ________

Do you feel any pronounced stress at this time?  Y/N  If yes, name major stressors: __________

How many times per week do you use alcohol? ___  Per month? ___  None ___

Do you smoke cigarettes or a pipe?  Y/N  Average amount per day? ______

Do you follow a regular exercise routine?  Y/N  Times per week: _____  Describe: __________

Are you currently using hormones as a contraceptive device?  Y/N

If currently using oral contraceptives, please indicate name and dosage: ________________

Describe your overall physical health in the past year:

Excellent ___  Very Good ___  Good ___  Poor ___  Very Poor ___

Times you've seen a physician (for other than a "check-up") in the past year?

0 / 1 / 2 / 3 / 4 / 5 / 6 / 7 / 8 / 9 / 10 / more than 10

In your opinion, is there anything chronically or acutely wrong with you at the present time?  Y/N

If yes, please explain: __________

Do you consider yourself to be generally optimistic?  _______ pessimistic?  ______

What is the worst allergic reaction you have ever had?  ____  When did it occur?  ______

Check beside a chemical if you think you may have been exposed in toxic amounts.

____ Carbon Dioxide:  Do you work in a building which has no open windows?  Y/N  How many times per week do you work in this environment? _____

____ Carbon Monoxide:  Do you commute in rush hour traffic?  Y/N  How many times per week do you commute in rush hour traffic? _____

____ Formaldehyde:  Do you live or work in a place which has been newly carpeted?  Y/N  When was it carpeted?  __________

____ Pesticides:  Do you spray your living quarters for bugs?  Y/N  How many times per year?  _____
Place a check in the 1st column if you have had more problems in that area than is usual for you during the past year. Place a check in the 2nd column if you are taking medication for the problem. In the 3rd column, name the medication and dosage you are taking.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Medication</th>
<th>Name Medication/Dosage</th>
</tr>
</thead>
</table>
| aches, pain | ___ | ___ | ___________
| alcohol problems | ___ | ___ | ___________
| allergies | ___ | ___ | ___________
| arthritis | ___ | ___ | ___________
| asthma | ___ | ___ | ___________
| bowel disturbances | ___ | ___ | ___________
| coughing | ___ | ___ | ___________
| depression | ___ | ___ | ___________
| diabetes | ___ | ___ | ___________
| dizziness | ___ | ___ | ___________
| drug problems | ___ | ___ | ___________
| ear problems | ___ | ___ | ___________
| eye problems | ___ | ___ | ___________
| fainting spells | ___ | ___ | ___________
| fatigue | ___ | ___ | ___________

---

<table>
<thead>
<tr>
<th>Times per month</th>
<th>&gt;=average</th>
</tr>
</thead>
<tbody>
<tr>
<td>___ Copy Machine Dispersant</td>
<td>___</td>
</tr>
<tr>
<td>___ Finger nail polish</td>
<td>___</td>
</tr>
<tr>
<td>___ Gasoline</td>
<td>___</td>
</tr>
<tr>
<td>___ Hair Spray</td>
<td>___</td>
</tr>
<tr>
<td>___ Paint</td>
<td>___</td>
</tr>
<tr>
<td>Condition</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>---</td>
</tr>
<tr>
<td>headaches</td>
<td></td>
</tr>
<tr>
<td>heart palpitations</td>
<td></td>
</tr>
<tr>
<td>heart problem</td>
<td></td>
</tr>
<tr>
<td>high blood pressure</td>
<td></td>
</tr>
<tr>
<td>inflammation</td>
<td></td>
</tr>
<tr>
<td>no appetite</td>
<td></td>
</tr>
<tr>
<td>numb/tingling limbs</td>
<td></td>
</tr>
<tr>
<td>psych problems</td>
<td></td>
</tr>
<tr>
<td>rainy nose</td>
<td></td>
</tr>
<tr>
<td>sexual problems</td>
<td></td>
</tr>
<tr>
<td>sinus problems</td>
<td></td>
</tr>
<tr>
<td>skin problems</td>
<td></td>
</tr>
<tr>
<td>sleeping trouble</td>
<td></td>
</tr>
<tr>
<td>stomach trouble</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX B

REGRESSION LINE FOR EBV STANDARDS
Independent: XAXIS

<table>
<thead>
<tr>
<th>Dependent Mth</th>
<th>Rsq</th>
<th>d.f.</th>
<th>F</th>
<th>Sigf</th>
<th>b0</th>
<th>b1</th>
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</thead>
<tbody>
<tr>
<td>YAXIS LIN</td>
<td>.779</td>
<td>1</td>
<td>3.53</td>
<td>.311</td>
<td>.8444</td>
<td>.0014</td>
</tr>
</tbody>
</table>

means of standards for 12/5/94 assay

means of calibrators for lots in manufacture
RESEARCH CONSENT FORM

You, ________________, are agreeing to participate in a women's health study investigating the relationships between emotions, medication use, and immune system functioning. Because few studies have been done in this area, we would like more information to determine correlates of women's health.

As a participant, your involvement in this study may involve completion of forms, questionnaires, and checklists relating to your feelings, attitudes, and medical history. In addition, you will be asked to give no more than two blood samples during the course of the study. This will help us to evaluate your current level of immune system functioning and will be used in relation to your responses on the subjective tasks to gather information. You will be at no more risk during this blood drawing procedure than would be involved in the same procedure done at a physician's lab for health screening or during the screening typically done prior to your giving blood. There will be minimal risk involved and by signing this form you are agreeing to participate in this aspect of the study.

Any information obtained in this study will be recorded with a code which you will select and which will allow the researchers to determine your identity. At the conclusion of this study, the key that relates your name with your assigned coded number will be destroyed. Under this condition, you are agreeing that any information obtained from this research may be used in any way thought best for publication or education.

There is minimal personal risk or discomfort directly involved with this research, and you are free to withdraw your consent and discontinue participation in this study at any time.

If you have any questions or problems that arise in connection with your participation in this study, you should contact Dr. Joseph Doster, the project director, at (817) 565-2671 (Work) or (817) 566-2538 (Home).

We appreciate your participation in this study. Thank you.

(Date) __________________________________________ (Signature of Participant)

(Date) __________________________________________ (Researcher)

(Date) __________________________________________ (Witness)*

*Witness signatures are required whenever the capacity of the subject to understand the description of the project and its associated risks is in question or when required by the IRB.
Table 1

Correlations Among Demographic Variables and EBV Levels (N = 33)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Correlation with EBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>22.13</td>
<td>3.41</td>
<td>21.50</td>
<td>-.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Education</td>
<td>13.84</td>
<td>1.42</td>
<td>14.00</td>
<td>-.13&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Single</td>
<td>.91</td>
<td>.29</td>
<td>1.00</td>
<td>.10</td>
</tr>
<tr>
<td>White</td>
<td>.71</td>
<td>.46</td>
<td>1.00</td>
<td>.05&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Drinks per week</td>
<td>.94</td>
<td>1.34</td>
<td>.00</td>
<td>-.32</td>
</tr>
<tr>
<td>Drinks per month</td>
<td>4.79</td>
<td>6.48</td>
<td>2.00</td>
<td>-.28</td>
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<tr>
<td>Regular exercise</td>
<td>.50</td>
<td>.51</td>
<td>.50</td>
<td>-.28</td>
</tr>
<tr>
<td>Exercise frequency</td>
<td>1.94</td>
<td>2.09</td>
<td>2.00</td>
<td>-.27</td>
</tr>
<tr>
<td>Doctor's visits</td>
<td>2.21</td>
<td>1.60</td>
<td>2.00</td>
<td>.31</td>
</tr>
<tr>
<td>Current problems</td>
<td>.27</td>
<td>.45</td>
<td>.00</td>
<td>.20</td>
</tr>
<tr>
<td>Health past year</td>
<td>2.30</td>
<td>.73</td>
<td>2.00</td>
<td>.23</td>
</tr>
</tbody>
</table>

<sup>a</sup> n = 32
<sup>b</sup> n = 31; (two-tailed)
Table 2

Mean, Standard Deviation, Median, and Pearson Product Moment Correlations for Independent and Dependent Variables (N = 33)

<table>
<thead>
<tr>
<th>Variable</th>
<th>M</th>
<th>SD</th>
<th>Median</th>
<th>Correlation with EBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV</td>
<td>1.46</td>
<td>.57</td>
<td>1.40</td>
<td>1.00</td>
</tr>
<tr>
<td>OC use</td>
<td>.45</td>
<td>.51</td>
<td>0.00</td>
<td>-.07</td>
</tr>
<tr>
<td>Estradiol</td>
<td>230.62</td>
<td>356.57</td>
<td>120.39</td>
<td>.09</td>
</tr>
<tr>
<td>Progesterone</td>
<td>5.39</td>
<td>10.44</td>
<td>.76</td>
<td>.10</td>
</tr>
<tr>
<td>Hassle frequency</td>
<td>27.03</td>
<td>19.21</td>
<td>20.00</td>
<td>-.03</td>
</tr>
<tr>
<td>Hassle severity</td>
<td>47.49</td>
<td>29.94</td>
<td>34.20</td>
<td>-.01</td>
</tr>
<tr>
<td>Hassle intensity</td>
<td>1.82</td>
<td>.40</td>
<td>1.80</td>
<td>.06</td>
</tr>
<tr>
<td>Stress item</td>
<td>.55</td>
<td>.51</td>
<td>1.00</td>
<td>.17</td>
</tr>
<tr>
<td>State anger</td>
<td>12.45</td>
<td>3.58</td>
<td>11.00</td>
<td>.23</td>
</tr>
<tr>
<td>Trait anger</td>
<td>20.06</td>
<td>5.26</td>
<td>19.00</td>
<td>.12</td>
</tr>
<tr>
<td>Angry temperament</td>
<td>6.76</td>
<td>2.54</td>
<td>6.00</td>
<td>-.10</td>
</tr>
<tr>
<td>Angry reaction</td>
<td>9.70</td>
<td>2.38</td>
<td>10.00</td>
<td>.41**</td>
</tr>
<tr>
<td>Anger in</td>
<td>17.03</td>
<td>4.58</td>
<td>16.00</td>
<td>.16</td>
</tr>
<tr>
<td>Anger out</td>
<td>17.48</td>
<td>4.58</td>
<td>17.00</td>
<td>-.05</td>
</tr>
<tr>
<td>Anger control</td>
<td>22.52</td>
<td>5.38</td>
<td>22.00</td>
<td>-.20</td>
</tr>
<tr>
<td>Anger expression</td>
<td>29.45</td>
<td>12.18</td>
<td>29.00</td>
<td>-.08</td>
</tr>
<tr>
<td>Hypochondriasis</td>
<td>3.15</td>
<td>3.87</td>
<td>2.00</td>
<td>.25</td>
</tr>
<tr>
<td>Suicidal depression</td>
<td>1.45</td>
<td>3.05</td>
<td>0.00</td>
<td>.36*</td>
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<tr>
<td>Agitated depression</td>
<td>8.79</td>
<td>5.63</td>
<td>8.00</td>
<td>.27</td>
</tr>
<tr>
<td>Anxious depression</td>
<td>5.09</td>
<td>3.21</td>
<td>4.00</td>
<td>.10</td>
</tr>
<tr>
<td>Low energy depression</td>
<td>6.55</td>
<td>6.77</td>
<td>4.00</td>
<td>.31*</td>
</tr>
<tr>
<td>Guilt and resentment</td>
<td>6.24</td>
<td>6.16</td>
<td>4.00</td>
<td>.34*</td>
</tr>
<tr>
<td>Boredom and withdrawal</td>
<td>3.03</td>
<td>3.32</td>
<td>2.00</td>
<td>.38*</td>
</tr>
</tbody>
</table>

* p < .05
** p < .01; (one-tailed)
Table 3

Correlations Among Stress Measures (N = 33)

<table>
<thead>
<tr>
<th></th>
<th>Hassle frequency</th>
<th>Hassle severity</th>
<th>Hassle intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hassle severity</td>
<td>.91**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hassle intensity</td>
<td>-.24</td>
<td>.11</td>
<td></td>
</tr>
<tr>
<td>Under stress now</td>
<td>-.35*</td>
<td>.33</td>
<td>-.03</td>
</tr>
</tbody>
</table>

* p < .05
** p < .01 (two-tailed)
Table 4

Correlations Among Stress and Anger Variables (N = 33)

<table>
<thead>
<tr>
<th></th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
<th>A4</th>
<th>A5</th>
<th>A6</th>
<th>A7</th>
<th>A8</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRESS</td>
<td>.33*</td>
<td>.42**</td>
<td>.23</td>
<td>.51**</td>
<td>.20</td>
<td>.26</td>
<td>-.23</td>
<td>.13</td>
</tr>
<tr>
<td>HF</td>
<td>.45**</td>
<td>.54**</td>
<td>.48**</td>
<td>.48**</td>
<td>.06</td>
<td>.39*</td>
<td>-.38*</td>
<td>.44**</td>
</tr>
<tr>
<td>HS</td>
<td>.45**</td>
<td>.49**</td>
<td>.42**</td>
<td>.44**</td>
<td>.14</td>
<td>.45**</td>
<td>-.39*</td>
<td>.50**</td>
</tr>
<tr>
<td>HI</td>
<td>.03</td>
<td>-.07</td>
<td>-.17</td>
<td>-.02</td>
<td>.34*</td>
<td>.19</td>
<td>-.03</td>
<td>.18</td>
</tr>
</tbody>
</table>

Note: HF = hassle frequency; HS = hassle severity; HI = hassle intensity; A1 = state anger; A2 = trait anger; A3 = angry temperament; A4 = angry reaction; A5 = anger in; A6 = anger out; A7 = anger control; A8 = anger expression

* p < .05
** p < .01
Table 5

**Correlations Among Stress and Depression Variables (N = 33)**

<table>
<thead>
<tr>
<th></th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRESS</td>
<td>.21</td>
<td>.32*</td>
<td>-.09</td>
<td>.16</td>
<td>.31*</td>
<td>.40*</td>
<td>.25</td>
</tr>
<tr>
<td>HF</td>
<td>.63**</td>
<td>.57**</td>
<td>.19</td>
<td>.26</td>
<td>.42**</td>
<td>.63**</td>
<td>.44**</td>
</tr>
<tr>
<td>HS</td>
<td>.67**</td>
<td>.54**</td>
<td>.24</td>
<td>.44**</td>
<td>.55**</td>
<td>.70**</td>
<td>.48**</td>
</tr>
<tr>
<td>HI</td>
<td>-.03</td>
<td>-.12</td>
<td>-.16</td>
<td>.31*</td>
<td>.26</td>
<td>.07</td>
<td>.09</td>
</tr>
</tbody>
</table>

Note: HF = hassle frequency; HS = hassle severity; HI = hassle intensity; D1 = hypochondriasis; D2 = suicidal depression; D3 = agitated depression; D4 = anxious depression; D5 = low energy depression; D6 = guilt and resentment; D7 = boredom and withdrawal

* p < .05
** p < .01 (two-tailed)
Table 6

Correlations Among Anger and Depression Variables (N = 33)

<table>
<thead>
<tr>
<th></th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
<th>A4</th>
<th>A5</th>
<th>A6</th>
<th>A7</th>
<th>A8</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>.55**</td>
<td>.40*</td>
<td>.23</td>
<td>.41**</td>
<td>.30*</td>
<td>.36*</td>
<td>-.43**</td>
<td>.39*</td>
</tr>
<tr>
<td>D2</td>
<td>.72**</td>
<td>.37*</td>
<td>.18</td>
<td>.47**</td>
<td>.27</td>
<td>.27</td>
<td>-.29</td>
<td>.26</td>
</tr>
<tr>
<td>D3</td>
<td>.30*</td>
<td>-.07</td>
<td>-.07</td>
<td>.06</td>
<td>-.09</td>
<td>-.10</td>
<td>-.00</td>
<td>-.03</td>
</tr>
<tr>
<td>D4</td>
<td>.14</td>
<td>.36*</td>
<td>.17</td>
<td>.43**</td>
<td>.35*</td>
<td>.27</td>
<td>-.44**</td>
<td>.41**</td>
</tr>
<tr>
<td>D5</td>
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<tr>
<td>D6</td>
<td>.70**</td>
<td>.52**</td>
<td>.35*</td>
<td>.58**</td>
<td>.44**</td>
<td>.46**</td>
<td>-.48**</td>
<td>.53**</td>
</tr>
<tr>
<td>D7</td>
<td>.57**</td>
<td>.35*</td>
<td>.21</td>
<td>.43**</td>
<td>.57**</td>
<td>.25</td>
<td>-.44**</td>
<td>.46**</td>
</tr>
</tbody>
</table>

Note: A1 = state anger; A2 = trait anger; A3 = angry temperament; A4 = angry reaction; A5 = anger in; A6 = anger out; A7 = anger control; A8 = anger expression; D1 = hypochondriasis; D2 = suicidal depression; D3 = agitated depression; D4 = anxious depression; D5 = low energy depression; D6 = guilt and resentment; D7 = boredom and withdrawal

* p < .05
** p < .01 (two-tailed)
Table 7

**Correlations Among Anger Variables (N = 33)**

<table>
<thead>
<tr>
<th></th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
<th>A4</th>
<th>A5</th>
<th>A6</th>
<th>A7</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>.38*</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>.20</td>
<td>.84**</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>A4</td>
<td>.51**</td>
<td>.81**</td>
<td>.44**</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>A5</td>
<td>.38*</td>
<td>.04</td>
<td>-.10</td>
<td>.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A6</td>
<td>.20</td>
<td>.56**</td>
<td>.32*</td>
<td>.48**</td>
<td>.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A7</td>
<td>-.15</td>
<td>-.65**</td>
<td>-.50**</td>
<td>-.51**</td>
<td>-.34**</td>
<td>-.59**</td>
<td></td>
</tr>
<tr>
<td>A8</td>
<td>.34*</td>
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<td>.44**</td>
<td>.48**</td>
<td>.56**</td>
<td>.57**</td>
<td>-.70**</td>
</tr>
</tbody>
</table>

Note: A1 = state anger; A2 = trait anger; A3 = angry temperament; A4 = angry reaction; A5 = anger in; A6 = anger out; A7 = anger control; A8 = anger expression

* p < .05  
** p < .01 (two-tailed)
Table 8

Correlations Among Depression Variables (N = 33)

<table>
<thead>
<tr>
<th></th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2</td>
<td></td>
<td>.88**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D3</td>
<td>.31*</td>
<td></td>
<td>.32*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D4</td>
<td>.41**</td>
<td>.24</td>
<td>.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D5</td>
<td>.79**</td>
<td>.66**</td>
<td>.21</td>
<td>.56**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D6</td>
<td>.81**</td>
<td>.79**</td>
<td>.30*</td>
<td>.44**</td>
<td>.82**</td>
<td></td>
</tr>
<tr>
<td>D7</td>
<td>.70**</td>
<td>.69**</td>
<td>.06</td>
<td>.21</td>
<td>.79**</td>
<td>.78**</td>
</tr>
</tbody>
</table>

Note: D1 = hypochondriasis; D2 = suicidal depression; D3 = agitated depression; D4 = anxious depression; D5 = low energy depression; D6 = guilt and resentment; D7 = boredom and withdrawal

* p < .05
** p < .01 (two-tailed)
Table 9

**Correlations Among Oral Contraceptive Use, Stress, and Negative Affect**

**Variables (N = 33)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation with Oral Contraceptive Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hassle frequency</td>
<td>.04</td>
</tr>
<tr>
<td>Hassle severity</td>
<td>-.00</td>
</tr>
<tr>
<td>Hassle intensity</td>
<td>.10</td>
</tr>
<tr>
<td>State anger</td>
<td>-.20</td>
</tr>
<tr>
<td>Trait anger</td>
<td>.04</td>
</tr>
<tr>
<td>Angry temperament</td>
<td>.09</td>
</tr>
<tr>
<td>Angry reaction</td>
<td>-.12</td>
</tr>
<tr>
<td>Anger in</td>
<td>-.21</td>
</tr>
<tr>
<td>Anger out</td>
<td>.23</td>
</tr>
<tr>
<td>Anger control</td>
<td>-.14</td>
</tr>
<tr>
<td>Anger expression</td>
<td>-.06</td>
</tr>
<tr>
<td>Hypochondriasis</td>
<td>-.08</td>
</tr>
<tr>
<td>Suicidal depression</td>
<td>-.08</td>
</tr>
<tr>
<td>Agitated depression</td>
<td>-.20</td>
</tr>
<tr>
<td>Anxious depression</td>
<td>-.12</td>
</tr>
<tr>
<td>Low energy depression</td>
<td>-.08</td>
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<tr>
<td>Guilt and resentment</td>
<td>-.06</td>
</tr>
<tr>
<td>Boredom and withdrawal</td>
<td>-.06</td>
</tr>
</tbody>
</table>

(one-tailed)
Table 10

Summary of Post-hoc Stepwise Regression Analysis for Depression Variables

Predicting EBV levels (N = 33)

<table>
<thead>
<tr>
<th>Variable</th>
<th>$B$</th>
<th>SE $B$</th>
<th>Beta</th>
<th>$t$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boredom and withdrawal</td>
<td>.07</td>
<td>.03</td>
<td>.38</td>
<td>2.3*</td>
</tr>
</tbody>
</table>

*p < .05
**p < .01
Table 11

Summary of Post-hoc Stepwise Regression Analysis for Anger Variables

Predicting EBV Levels (N = 33)

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE B</th>
<th>Beta</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angry Reaction</td>
<td>.10</td>
<td>.04</td>
<td>.41</td>
<td>2.5*</td>
</tr>
<tr>
<td>Trait Anger</td>
<td>-.07</td>
<td>.03</td>
<td>-.65</td>
<td>-2.51*</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angry Reaction</td>
<td>.23</td>
<td>.06</td>
<td>.95</td>
<td>3.63**</td>
</tr>
<tr>
<td>Trait Anger</td>
<td>-.07</td>
<td>.03</td>
<td>-.65</td>
<td>-2.51*</td>
</tr>
</tbody>
</table>

*p < .05

**p < .01
### Table 12

**Summary of Post-hoc Hierarchical Regression Analysis for Variables Predicting EBV Levels (N = 33)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE B</th>
<th>Beta</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Angry Reaction</td>
<td>.10</td>
<td>.04</td>
<td>.41</td>
<td>2.50*</td>
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</tr>
<tr>
<td>Angry Reaction</td>
<td>.07</td>
<td>.04</td>
<td>.31</td>
<td>1.72</td>
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<tr>
<td>Boredom and Withdrawal</td>
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<td>.03</td>
<td>.25</td>
<td>1.42</td>
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</tr>
<tr>
<td>Angry Reaction</td>
<td>.08</td>
<td>.04</td>
<td>.34</td>
<td>1.98</td>
</tr>
<tr>
<td>Boredom and Withdrawal</td>
<td>.03</td>
<td>.03</td>
<td>.17</td>
<td>.97</td>
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<td>Doctor’s Visits</td>
<td>.10</td>
<td>.06</td>
<td>.28</td>
<td>1.71</td>
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<td><strong>Model 4</strong></td>
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<tr>
<td>Angry Reaction</td>
<td>.08</td>
<td>.04</td>
<td>.34</td>
<td>1.92</td>
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<tr>
<td>Boredom and Withdrawal</td>
<td>.03</td>
<td>.03</td>
<td>.17</td>
<td>.95</td>
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<tr>
<td>Doctor’s Visits</td>
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<td>.06</td>
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<td>Oral Contraceptive Use</td>
<td>-.02</td>
<td>.18</td>
<td>-.02</td>
<td>-.12</td>
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</table>

*p < .05*
### Summary of Post-hoc Hierarchical Regression Analysis for Interactions Predicting EBV Levels (N = 33)

<table>
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<tr>
<th>Variable</th>
<th>B</th>
<th>SE B</th>
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<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hassle intensity x</td>
<td>.03</td>
<td>.02</td>
<td>.33</td>
<td>1.93</td>
</tr>
<tr>
<td>Boredom and Withdrawal</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Model 2</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Hassle intensity x</td>
<td>.02</td>
<td>.02</td>
<td>.20</td>
<td>1.14</td>
</tr>
<tr>
<td>Boredom and Withdrawal</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Angry Reaction</td>
<td>.08</td>
<td>.04</td>
<td>.34</td>
<td>1.93</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
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<tr>
<td>Hassle intensity x</td>
<td>.01</td>
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<td></td>
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<td></td>
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<td>Angry Reaction</td>
<td>.09</td>
<td>.04</td>
<td>.38</td>
<td>2.21*</td>
</tr>
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<td>Doctor's Visits</td>
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<td>.06</td>
<td>.29</td>
<td>1.74</td>
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<td><strong>Model 4</strong></td>
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<tr>
<td>Hassle intensity x</td>
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<td>.02</td>
<td>.14</td>
<td>.75</td>
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<tr>
<td>Boredom and Withdrawal</td>
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<td></td>
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<td></td>
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<tr>
<td>Angry Reaction</td>
<td>.09</td>
<td>.04</td>
<td>.36</td>
<td>2.06*</td>
</tr>
<tr>
<td>Doctor's Visits</td>
<td>.10</td>
<td>.06</td>
<td>.27</td>
<td>1.64</td>
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<tr>
<td>OC Use x Progesterone</td>
<td>-.25</td>
<td>.34</td>
<td>-.12</td>
<td>-.75</td>
</tr>
</tbody>
</table>

* p < .05
** p < .01
Table 14

**Post-hoc 3-way Interaction Regression Model Predicting EBV Levels (N = 33)**

<table>
<thead>
<tr>
<th>B</th>
<th>SE B</th>
<th>Beta</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>.00</td>
<td>.00</td>
<td>.40</td>
<td>2.43*</td>
</tr>
</tbody>
</table>

Hassle Intensity x Angry Reaction x Boredom and Withdrawal

* p < .05
Table 15

**Correlations Among Hassle Intensity, Angry Reaction, Boredom and Withdrawal, and Doctor’s Visits (N = 33)**

<table>
<thead>
<tr>
<th></th>
<th>Hassle Intensity</th>
<th>Angry Reaction</th>
<th>Boredom &amp; Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angry Reaction</td>
<td>-.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boredom/Withdrawal</td>
<td>.09</td>
<td>.43**</td>
<td></td>
</tr>
<tr>
<td>Doctor’s Visits</td>
<td>.12</td>
<td>-.02</td>
<td>.23</td>
</tr>
</tbody>
</table>

** p < .01 (one-tailed)
REFERENCES


