PSYCHOLOGICAL STRESS: EFFECT ON HUMORAL IMMUNE FUNCTIONING AS MEASURED BY IMMUNOGLOBULIN LEVELS

DISSERTATION

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

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By

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The purpose of the present study was to determine if psychological stress, defined as academic examination stress, would systematically produce changes in immune parameters (immunoglobulin concentration) and psychological functioning. It was hypothesized that as examination stress occurred there would be an effect on immunological function consistent with heightened psychological activity/stress.

Subjects were 23 master's and doctoral students in psychology who volunteered for the research project. All subjects were administered a series of psychological tests to measure stress, personality factors, emotional states, and anxiety levels. All tests were administered and blood samples drawn over a period of 15 months across two low-stress and two high-stress periods. Immunological tests included white blood cell (WBC) differential count and radial immunodiffusion (RID) for the determination of concentration of different immunoglobulin classes (IgA, IgG, IgM) in serum.
Data were treated to a one-way analysis of variance (ANOVA) with repeated measures, $t$-test for correlated samples, correlational matrix between variables across assessments and discriminant function analysis.

Results showed (1) increased immunoglobulin levels during periods of stress; (2) immunoglobulin G most consistently related to stress and probably most indicative of the stressed condition and biological resistance to stress; (3) anxiety related to external events; (4) increase in anxiety under stress; and (5) anxiety inversely correlated with emotional stability and coping skills while positively related to tension, increased number of somatic complaints, and obsessive-compulsive trends.

Firm support was provided for the hypothesis that as stress occurred, there would be consistent changes in immunological functioning associated with heightened psychological activity/stress. It was concluded that a response pattern to stress was adaptive along both psychological and immunological dimensions and that the concept of bodymind interaction was the most realistic approach to understanding the total response patterns.
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Research in psychosomatic and behavioral medicine has revealed that interactions between psychological and physical events influence major organ systems and homeostatic defense mechanisms (Ader & Cohen, 1984). The concept of psychosomatic medicine dates back to the origin of medicine itself when primitive healers emphasized a holistic concept by renewing the patient's will to health as well as casting out demons believed responsible for disease. The Babylonian-Assyrian civilization (2500-500 B.C.) emphasized the interaction of mind and body as did the ancient Greeks and Romans (400 B.C.-A.D.400) (Kaplan, 1985). Homer, Plato and Aristotle speculated on the relationship between mind and body over 2,000 years ago (Weiss, 1983). During the Middle Ages (500-1450), mysticism and religion dominated medicine. However, both physical and mental illnesses were treated by ministering to the whole person through the soul (Lewis & Lewis, 1972).

Renewed interest in the natural sciences was in evidence during the Renaissance (1500-1700) when psychic influences on the soma were rejected as unscientific (Kaplan, 1985). The modern concept of separation of mind and body can be traced to Rene Descartes, the
seventeenth-century mathematician and philosopher who said that mind and body were more easily conceived of as being separate, each responsible for its own functions, and interacting in a purely machine-like fashion (Benson, 1979). This notion of mind-body dualism appears to persist today among some health care practitioners, although multidisciplinary approaches to understanding the etiology of disease and the complex response of the organism to disease are eliminating the distinction between psyche and soma (Schlindler, 1985).

Physicians have long been aware of the relationship between stress and various emotional states and the occurrence of disease and indeed, the roots of the idea that psychological factors can precipitate or cause disease date back to antiquity (Plaut & Friedman, 1981). More recently the work of Dunbar (1943) and Alexander (1950) related specific psychological factors and personality types to the onset and course of disease.

Franz Alexander (1950) interpreted illness as falling into two groups arising from two basic emotional responses to stress, aggression or regression. Using this interpretation in addition to the findings of stress researchers such as Hans Selye, Walter Cannon and others, Hutschnecker (1951) hypothesized that susceptibility to infectious diseases was the result of a fearful, regressive personality producing too much
adrenocorticotropic and allied hormones and stated that more research was needed on the endocrine system to explore this new and revolutionary approach to illness. Hutschnecker also described a new understanding in medicine when the physician will recognize that an emotional disturbance has contributed to the disposition of disease. Sir William Osler, Claude Bernard and Walter Cannon also continued the effort toward understanding health and illness through mind-body integration (Weiss, 1983). Engel (1954, 1977) proposed a biopsychosocial disease model which considered the etiology of disease to be multifactorial.

Psychosocial factors have not influenced disease or health in a mystical way. Rather, it has been shown that psychological factors influence a wide range of physiological, hormonal, and biochemical responses as well as the natural history of many disease states (Plaut & Friedman, 1981). Immunological functioning plays a primary role in both the onset and course of many illnesses (Stein, Schleifer, & Keller, 1985). Stress, distress, and psychiatric disorders, particularly the affective disorders are increasingly reported to be associated with immunosuppression (Tecoma & Huey, 1985). However, it appears that psychosocial processes in general, which include a range of life experiences as well as state and trait characteristics of the person, influence the central nervous system (CNS) resulting in suppression or
enhancement of immune responses. Therefore, changes in immune system functioning may increase or decrease the risk of onset and subsequent course of disease (Stein et al., 1985).

Much work in the area of stress and disease was stimulated by the animal studies of Hans Selye. Selye (1982) described his work in 1936 which linked environmental stress to adrenocortical hyperactivity, shrunken lymphoid structures and gastrointestinal ulcers. He described this same pattern of responses to stress regardless of its source. Subsequently, the syndrome became known as the general adaptation syndrome (GAS) or biologic stress syndrome. Selye believed stress effects were mediated through the nervous and endocrine systems enabling adaptation to environmental change or stimuli. Selye (1982) also pointed out that the adaptive response could break down because of innate defects, understress, overstress, or psychological mismanagement resulting in common stress diseases such as peptic ulcers, cardiovascular disorders, and nervous disturbances. This implicit linkage of stress to the sympatho-adrenal system can overlook the role of other biological processes such as those involving the immune system (Knapp, 1985).

The term stress is difficult to define operationally because of different conceptions of stress. Lazarus (cited in Zegans, 1982) decided to use the word as a generic term
for the entire field of stress which included the stimuli which produced the stress reactions, the variations themselves, and the various intervening processes, and also considered physiological, sociological, and psychological phenomena and related concepts. Stress was a collective term for a field of study. Frazier (1977) defined stress as a life experience that causes physical and mental changes in an individual leading to a state of imbalance.

Palmblad (1981) regarded stress as any physiological, psychological or behavioral responses within the organism elicited by evocative agents. The evocative stimuli were called stressors and could be psychological or physical in nature. Solomon and Amkraut (1983) assumed that stress represented an extraordinary demand on physiological or psychological defenses with concomitant responses of neuroendocrine systems to the external elicitor.

Cohen (1983) indicated stress may have three different meanings: (1) an aversive stimulus, (2) a specific psychological or physiological response, or (3) a transaction between the person and the environment. Stressors are the stress events and are distinguished from the psychological state of stress and from stress responses. Stressors may be further classified according to duration ranging from acute and time-limited to chronic. Additionally, the organism's response to stress may be social, psychological or physiological with physiological
responses including autonomic nervous system changes as well as alterations in hormonal, neuroregulatory or immunological functioning.

The Immune System

An organism exists in harmony, a delicate system of complex and precise interactions. This integrity, however, can be threatened by such agents as disease-causing parasites, organ and tissue damage or neoplasms. Intraorganismic defense reactions via the immune system defend against such threats (Klein, 1982).

The term "immune," derived from the Latin immunis, meaning free from burden, which in a classical sense referred to the resistance of a host to reinfection by a given microbe. However, immune responses are not solely associated with resistance to infection and may even render noxious, unpleasant and harmful effects on the host, e.g., allergy or hypersensitivity. The immune system in addition to serving the function of defense against infectious agents, also concerns itself with homeostasis and surveillance. Homeostasis is maintained by the removal of effete and damaged "self" components. The immunologic surveillance response perceives and destroys mutant cells (Bellanti, 1985).

Cohn (1985) described two problems the immune system must solve. The first involves the discrimination between self and nonself, requiring specificity in recognition as
well as in the induction of the immune response. The second is the determination of the class of the response. After recognizing an antigen or pathogen as foreign, distinct classes of effector functions are required to eliminate them. The immune system recognizes and responds to two categories of the "nonself" universe: cell-associated or intracellular (e.g., viruses) and noncell-associated or extracellular (e.g., bacteria). There are two major classes of immune effector function, cell-mediated and humoral responses. Cell-mediated immunity deals with intracellular pathogens and humoral immunity with extracellular pathogens.

Lymphocytes are responsible for specific immunity, both cellular and humoral (Bach, 1979). B lymphocytes and T lymphocytes are the two main types of lymphocytes named for the sites where they mature into immunologically competent cells, in the bone marrow in mammals and in the thymus, respectively. Upon being stimulated by an antigen or immunogen, B lymphocytes involved in humoral immune responses, proliferate and differentiate into plasma cells which synthesize and secrete antibody molecules (Eisen, 1980). Antibody in the human is associated with five major classes of complex proteins (immunoglobulins) that can be differentiated from one another according to size, biologic function or biochemical properties. They are IgG, IgA, IgM, IgD, and IgE. Although these proteins share many
biologic, structural and antigenic similarities, significant differences in the primary amino acid sequence permit them to be easily differentiated.

The overall functions of antibody in the immune response of the host against pathogen are to precipitate, agglutinate, and lyse antigen. In precipitation reactions, soluble antigens become bound to specific antibody and are cleared from the host via the reticuloendothelial system. In agglutination reactions, particulate antigen (bacteria, viruses, etc.) are aggregated by antibody and then more efficiently cleared from the system by neutrophil and macrophage phagocytosis. In conjunction with complement, antibody has the ability to lyse foreign organisms by disrupting their cell membranes. The complement system is a circulating group of plasma proteins which amplifies the humoral immune response (Boggs & Winkelstein, 1983).

The present study is concerned with the effects of stress on the humoral component of the immune response and particularly the immunoglobulins IgM, IgG and IgA. Immunoglobulin G, the most abundant of the immunoglobulins with a half-life of 23 days is concentrated in both the vascular and extra-vascular spaces and is believed to contribute to immunity against many blood-borne infectious agents including bacteria, viruses, parasites and some fungi. It also provides antibody activity in tissues. It is passively transferred across the placenta from mother to child. It is able to activate complement.
Immunoglobulin A, the second most abundant serum immunoglobulin, is found in high concentrations in colostrum, contributing to the immunity of newborns. Its most important contribution to immunity is in the external secretory system (e.g., saliva and tears) and it is produced in high concentrations by the lymphoid tissues lining the gastrointestinal, respiratory, and genitourinary tracts. Immunoglobulin A is combined with a secretory component which protects it against digestion by proteolytic enzymes in addition to facilitating its transport into secretions.

Immunoglobulin M, the largest of the immunoglobulin molecules, is restricted almost entirely to intravascular space because of its large size. It efficiently agglutinates particulate antigens such as bacteria, efficiently fixes complement, and seems to be of greatest importance in the first few days of the primary immune response when a foreign antigen is introduced into the host for the first time. Its synthesis precedes that of IgG.

Immunoglobulin D appears to be a specific surface receptor on lymphocytes in the initiation of the immune response, particularly in neonates. Immunoglobulin E, the reaginic antibody, is present only in trace amounts in serum. It has the ability to initiate aspects of the "allergic reaction." It is part of the external secretory system of antibody (Bellanti, 1985).
Cell-mediated immunity involves T lymphocytes, which proliferate and differentiate into a variety of effector T cells. Cytotoxic T lymphocytes destroy specifically any target cell with the appropriate surface antigen, such as virus-infected cells. Delayed-type hypersensitivity cells produce substances that cause local inflammation (Eisen, 1980). Helper and suppressor T cells regulate cytotoxic T cells as well as B cells (Vander, Sherman, & Luciano, 1985).

There are other important components of the immune system. The phagocytic system which consists of neutrophils, monocytes, eosinophils and basophils is important in nonspecific immunity and in the inflammatory response (Boggs & Winkelstein, 1983). The natural killer (NK) cells, large granular lymphocytes are the single most important effector cells in immune surveillance against neoplasms (Vander et al., 1985). A second type of cytolytic effector cells, referred to as K or killer cells have the ability to kill IgG-coated target cells directly and may be important in eliminating tumors and virally infected cells (Boggs & Winkelstein, 1983).

Stress and Alterations in Immune System Functioning

Many recent studies with humans and animals have demonstrated that stressful conditions can alter the immune system and that the processes linking stress and the immune system are highly complex. Research has focused primarily
on demonstrating that there are associations between the central nervous system (CNS) and the immune system. Examples of frequently utilized measures to assess CNS and behavior effects on immunity include in vivo assays such as quantification of peripheral blood antibody titer and of antibody producing cells and quantification of lymphocytes and lymphocyte subsets. Immune functioning has also been assessed using in vitro tests which measure lymphocyte proliferation activated with nonspecific stimulants known as mitogens (Schleifer, Keller & Stein, 1984). Other measures of immunity not as widely used will also be included in this review demonstrating the various components of the immune system which may be affected by stress.

The effects of stress on immunity have been measured using both naturally occurring or experimentally induced stressors in humans and animals and have generally been found to impair immunity. The results of recent animal studies will be reviewed first.

Keller, Weiss, Schleifer, Miller and Stein (1981) used a graded series of stressors in rats which produced progressively greater suppression of lymphocyte function suggesting immunity is suppressed in proportion to the intensity of the stressor. The number of circulating lymphocytes and mitogen stimulation in whole blood and isolated cultures were used as measures of immune
functioning. Pavlidis and Chirigos (1980) and Teshima, Nagota, Imada and Ago (1981) investigated the effects of stress on macrophages. Pavlides and Chirigos demonstrated that macrophages from mice submitted to acute immobilization stress showed decreased responsiveness to interferon or bacterial polysaccharide suggesting impaired immunosurveillance against tumor development or antibacterial activity. Teshima and his co-workers administered a variety of stressors to mice and observed changes in phagocytic activity, both enhancement and depression, for different durations of stress demonstrating that the timing of the stressor is important in modulating immune effects. Edwards and Dean (1977) and Edwards, Rahe, Stephens, and Henry (1980) demonstrated decreased antibody formation in mice and increased susceptibility to an infectious agent due to psychosocial environmental stress. Hara, Ogawa, and Imada (1981) also reported antibody production in rats unaffected after three days of activity stress but decreased after five and seven days of stress. They emphasized that an immunological response can serve as an indicator of the biological response for stress.

Grylewski, Marcinkiewicz, and Ptak (1985) subjected mice to surgical trauma to determine its effects on immune responsiveness. Cell-mediated immunity (e.g., contact sensitivity reaction) was found to be severely impaired while antibody response was enhanced. However, both
effects were transient. Monjan and Collector (1977) daily subjected rats to an auditory stressor for varying lengths of time and found that the stressor could enhance immune system functioning as well as depress it. The effects of early separation stress on subsequent immune function in adult Macaque monkeys was assessed by Laudenslager, Capitanio and Reite (1985). Proliferative responses to B and T cell mitogens were found to be reduced when compared with nonseparated controls. Stein et al. (1985) summarized the results of recent animal studies of stress and humoral immunity which suggested the effects of stress are related to the nature and intensity of the stimulus, biological and social characteristics of the organisms, and the timing and frequency of behavioral manipulation.

Human research has also examined the effects of naturally occurring and experimentally induced stressors on various immune parameters and has seemed to support the belief that a combination of excessive stress and inadequate coping skills may increase host susceptibility to illness and affect recovery periods (Locke, 1982). However, response to stress is often variable and may be a function of the severity of the stressor, individual perception of the stress, and personality characteristics.

Roessler, Cate, Lester, and Couch (1979) conducted a study in which they examined the relationship of coping ability and life-change stress to immune response. They
found antibody response to influenza vaccination decreased among high life-change stress subjects with low ego strength indicating poor coping skills. Locke et al. (1984) found similar results in a study of natural killer cell activity. Those subjects with poor coping skills, inferred from the self-report of large numbers of psychiatric symptoms, had significantly diminished natural killer cell activity compared with those with better coping skills experiencing large amounts of life-change stress. Stress and need for power and their relationship to immune function and illness was assessed in male prisoners by McClelland, Alexander and Marks (1982). Those prisoners high in need for power and reported stress showed the highest level of reported illness and lowest concentrations of salivary secretory immunoglobulin A (sIgA) which was used as the measure of immune functioning, which differed significantly from those high in need for power and low in stress.

Jemmott et al. (1983) measured sIgA secretion in dental students during periods of high and low academic stress coinciding with examination periods. Secretion concentration was significantly lower in high-stress than low-stress periods. Those students with a high inhibited need for power continued to decline through the final low-stress period rather than recovering as in all other students.
Dorian et al. (1982) compared trainees in psychiatry taking oral fellowship exams to a control group and found transiently elevated numbers of T and B lymphocytes but impaired plaque forming cell and mitogen responsiveness in the highly stressed group prior to their exam which normalized later. Didriksen, Goven, and Butler (1986) measured the effects of academic stress on phagocytic immune functioning of neutrophils and found diminished activity during high-stress examination periods. Additionally, neutrophil functioning was found to be more predictive of a stressed condition than personality factors. Glaser et al. (1985) measured the percentages of total T lymphocytes, helper T cells, and suppressor T cells in medical students and found they were significantly lower during examination periods compared to baseline values obtained six weeks earlier. T lymphocyte response to mitogen was also significantly lower during examinations.

Schliefer, Keller, Camerino, Thornton and Stein (1983) in a prospective study of spouses of women with advanced breast carcinoma observed significantly suppressed lymphocyte stimulation responses to mitogen during the first two months following the death of a spouse. An intermediate level of mitogen responsivity was observed four to fourteen months after bereavement. Depressed lymphoblast transformation in bereaved spouses was also found by Bartrop, Lazarus, Luckhurst, Kiloh and Penny (1977) and by Schleifer, Keller, McKeon and Stein (1980).
The effects of experimentally induced stress on immune functioning demonstrated the critical role of timing and duration of the stressor in determining the nature of immune alterations. Palmblad et al (1976) employed sleep deprivation and exposure to a loud noise during a 72 hour continuous attention task vigil as the experimental stressors and found that neutrophils exhibited decreased ability to phagocytize Staphylococcus aureus during sleep deprivation. However, after the stressor was removed, phagocytosis was increased compared to pre-exposure levels. Interferon production by lymphocytes in response to a virus rose during the stressor exposure and was even higher after stressor exposure. In a later study, Palmblad, Petrini, Wasserman and Akerstedt (1979), using sleep deprivation again as the stressor, observed depressed lymphoblast transformation following the stressor with no change in granulocyte adherence.

Emotions and Immunity

Amkraut and Solomon (1975) reviewed evidence which indicated that immune responsiveness and the course of disease was influenced by emotional factors. More recent evidence seems to indicate that negative emotional states generally have adverse effects on immunologic functioning. Linn, Linn and Jensen (1981) measured anxiety in males without cancer, infection, or autoimmune disease upon hospital admission and observed decreased lymphocyte response in vitro but positive reactions to skin tests of
delayed hypersensitivity. Kronfol et al. (1983) investigated the immune status of patients with primary depressive illness and found a generalized and marked decrease in lymphocyte mitogenic activity among the depressive group. The effects of both recent stress and dysphoric mood on lymphocyte responsiveness was studied by Linn, Linn, and Jensen (1984). Data indicated that persons with higher scores on depression in both the stressed and nonstressed groups showed less responsiveness to phytohemagglutinin and allogeneic cells. Additionally, those with high and low depressive features could be differentiated by their immune responses. Schliefer et al. (1984) found differences in lymphocyte function between a group of hospitalized depressed patients and matched controls. T and B lymphocyte response to mitogen stimulation was significantly lower in the depressed group as well as the absolute number of T and B cells. The percentage of these cell types did not differ between the groups.

Kiecolt-Glaser et al. (1984) examined the associations among loneliness, life stress, urinary cortisol levels and cell-mediated immunity in psychiatric inpatients. Patients who scored above the median on loneliness had significantly higher urinary cortisol levels, lower levels of natural killer cell activity as well as poor T lymphocyte response.
to mitogen stimulation. There were no consistent significant effects associated with stressful life events.

Schleifer, Keller, Siris, Davis, and Stein (1985) explored the relationship between depression and immunity in ambulatory depressed patients, hospitalized schizophrenic patients, patients hospitalized for herniorrhaphy and matched controls. Mitogen-induced lymphocyte stimulation responses did not differ between the ambulatory depressed patients and matched controls and suggested that altered immunity in depression may be related to severity of depressive symptoms. There were no differences in lymphocyte responsiveness between the schizophrenic or herniorrhaphy patients and controls. However, the number of peripheral-blood T lymphocytes was decreased among the depressed but not among the schizophrenic patients. Keicolt-Glaser, Stephens, Lipetz, Speicher and Glaser (1984) used a measure of depression to differentiate high- and low-distressed individuals. The high-distress group had significantly poorer DNA repair in lymphocytes exposed to x-irradiation than low-distress subjects providing evidence for a direct pathway through which distress could influence the incidence of cancer.

Rather than exploring the effects of negative emotions on immunity, Dillon, Minchoff, and Baker (1985) examined the effect of positive emotional states on salivary immunoglobulin A (sIgA) concentration. Subjects showed significantly higher concentration of sIgA after viewing a
humorous videotape and no significant change after viewing a didactic videotape. Results suggest that enhancement of the immune system may be a link between claims of positive emotional state and healing.

Holmes and Rahe (1967) demonstrated through their research that increased incidence of stressful life changes seemed to be related to the increased incidence of disease. They developed the Social Readjustment Rating Scale to measure stressful life changes and their relationship to disease susceptibility. Numerous studies have shown that generally, the more life stresses a person has experienced, the higher the probability that some physical or psychiatric symptoms will develop (Borysenko, 1984). However, results of studies exploring the effects of life change on immunity are inconsistent.

Green, Betts, Ochitill, Iker, and Douglas (1978) studied the relationship between self-reported life stress and immunologic functioning and found the more life-change stress the subjects reported, the lower their degree of lymphocyte cytotoxicity and also a trend toward diminished lymphocyte response to mitogens. They found no significant linear relationship between life change stress and antibody response (Locke & Heisel, 1977; Locke, Hurst, Heisel, Kraus & Williams, 1979). Jemmott and Locke (1984) provided possible explanations for the absence of negative effects of life stress on antibody titers. They included the possibilities that antibody production may be more affected
by recent acute stress rather than by more temporally
distant stress and that response may be dependent on the
dose of vaccination used to elicit antibody response.

**Biological Mediators of Immunity**

Various factors may be involved in mediating
associations among stress, emotional states and immunity.
The endocrine system which is highly responsive to the
impact of life experiences and psychological states has a
significant effect on immune process. The most widely
studied hormones and their relationship to immunity have
been those of the hypothalamic-pituitary-adrenal (HPA)
axis. Corticosteroids have extensive effects on immune
processes (Schleifer et al., 1985). Baker et al. (1984)
measured anxiety, serum cortisol concentrations and
percentage of helper T lymphocytes in first and second year
medical students. Results revealed greater anxiety scores,
serum cortisol concentrations and increased percentage of T
helper cells in first year students demonstrating that the
immune system is affected by emotional factors. Kronfol
and House (1984) examined the relation between
psychological stress and immune function in relation to
depressive illness in a group of patients with a diagnosis
of major depression compared with healthy controls.
Depressed patients had significantly higher total leukocyte
counts, significant reduction in lymphocyte stimulation and
significantly higher cortisol concentrations. Although
secretion of corticosteroids has long been considered to be
the mechanism of stress-induced modulation of immunity, the regulation of the immune system in response to stress may not be limited to corticosteroids (Stein, Keller, & Schleifer, 1985).

Keller, Weiss, Schleifer, Miller and Stein (1983) investigated the effect of stressors in adrenalectomized rats compared with sham adrenalectomized and nonoperated rats and demonstrated that stress-induced lymphopenia in the rat occurs in association with secretion of corticosteroids induced by stress and can be prevented by adrenalectomy. However, their findings also showed that stress-related secretion of corticosteroids and catecholamines is not required for the stress-induced suppression of T cell mitogen stimulation indicating that other hormonal and neurosecretory systems may be involved in the adrenal-independent stress-induced reduction of subpopulations of T cells.

A range of neuroendocrine processes may be involved in stress-induced altered immunity. Studies by Morley, Kay, Allen, Moon, and Billington (1985) suggest that circulating endogenous opioid peptides may regulate immune function and tumor growth. They found that endorphins enhanced natural killer (NK) cell activity and the enhancement is of the same magnitude as that produced by interferon. In a study with humans, naloxone, an opiate receptor blocker, failed to affect NK activity in vitro and suggested that the acute
effects of endorphins as lymphocyte stimulators may not be replicated during long-term administration.

Shavit et al. (1985) examined the relationship among stress, opioid peptides, the immune system and cancer. They assessed the effects of opioid and nonopioid stress on NK cell cytotoxicity and the development of mammary tumor in rats. Exposure to the opioid form of footshock stress resulted in a significant suppression of NK activity. Naltrexone administration prevented this suppression. However, because tolerance did not occur to the opioid stress, it was suggested that the immunosuppressive effects of opioid stress are mediated by different opioid receptor types from morphine. Shavit and his co-workers also found the tumor-enhancing effect of opioid stress was blocked by naltrexone.

Plasma catecholamines and changes in immunity have also been explored. Landmann et al. (1984) measured lymphocyte subpopulations before and after physical and psychological stress and correlated these measurements with plasma catecholamine and cortisol levels. During psychological stress, increases were observed in monocytes, NK cells, B cells, and heart rate while catecholamines remained unchanged. With physical stress, granulocytes, monocytes and all lymphocyte subsets increased significantly. Adrenaline and noradrenaline concentrations also increased while cortisol remained unchanged. Increases of circulating B, T suppressor and NK cells
during adrenergic activation as well as the relationship of T cell changes to plasma adrenaline suggest an immunoregulatory effect of the plasma catecholamines in stress. Boxer, Allen, and Baehner (1980) found diminished polymorphonuclear leukocyte (PMN) adherence after epinephrine administration. It appeared that decreased PMN adherence is mediated through endothelial cell Beta-receptor activity. Berk, Tan, Eby, Carmona, and Vorce (1984) examined the effects of physiologic concentrations of epinephrine, norepinephrine and dihydroxyphenylacetic acid on NK cytotoxicity and found it to be decreased as catecholamine doses were increased. As stress increases catecholamines, these findings may represent a potential interrelationship between stress, the nervous system and the immune system.

Solomon (1985) has begun to develop a model of the links between the central nervous system and immune system and has noted several analogies between the two. Both serve functions of adaptation and defense and both have the capacity for memory. Pathological syndromes may occur in each system as a result of inadequate defenses and prior experience of a stimulus or noxious agent could lead to tolerance or sensitivity in each system. He has listed 14 hypotheses which represent possible connections between the two systems. The following hypotheses have been considered of particular importance to the present research.
1. **Enduring coping style and personality factors** (trait characteristics) should influence the susceptibility of an individual's immune system to alteration by exogenous events, including reactions to events.

2. **Emotional upset and distress** (state characteristics) should alter the incidence, severity, and/or course of diseases that are immunologically resisted (infectious and neoplastic diseases) or are associated with aberrant immunologic function (allergies, autoimmune disease, AIDS).

3. **Experimental behavior manipulation**—in terms, for example of stress, conditioning and early experiences—should have immunologic consequences.

The purpose of the present study is to determine if psychological stress, defined as academic examination stress, can systematically produce changes in immune parameters (immunoglobulin concentration) and psychological functioning. It is hypothesized that as academic examination stress occurs there will be an effect on immunological functioning consistent with heightened psychological activity/stress.

**Method**

**Subjects**

Subjects were 23 master's and doctoral students in psychology at North Texas State University who volunteered for the research project. There were four men and 19 women aged 23 to 44 years with a mean age of 31 years. All
subjects signed an Informed Consent Form (Appendix A) allowing for blood samples to be drawn and psychological tests to be administered to them. Subjects were chosen by means of a Health Questionnaire (Appendix B) which screened for excessive alcohol intake, use of medications and/or other drugs, normal blood pressures (below 140/90) and health problems in general as well as provide information on exercise, diet and environmental conditions.

Test Instruments and Laboratory Techniques

State-Trait Anxiety Inventory (STAI). Separate self-report scales to measure state anxiety, STAI-I, (a transitory emotional state) and trait anxiety, STAI-II (a relatively stable individual difference in anxiety proneness) was developed by Spielberger, Gorsuch, and Lushene (1970). Retest reliabilities are reported in the high .70s for A-trait. A-State correlations range from .27 to .54 (Anastasi, 1982).

Clinical Analysis Questionnaire (CAQ). The CAQ (Cattell, 1973) was developed to measure both pathological and normal personality factors (Appendix C). The validity of this instrument was determined by eight major factor analytic studies, all of which reported significant results (Krug, 1980). The validity of the CAQ is reported to range from .45 to .86. Reliability ranges from .51 to .90.

Brief Stress Questionnaire. This questionnaire (Appendix D) was designed to obtain a self-report by
subjects regarding whether or not they were experiencing psychological stress and the nature of the stress.

**WBC Differential Count.** A differential white blood cell count was utilized using techniques described in Diggs (1976). Slides were stained with Wright's stain and 100 cells were counted to determine the percentage of each cell type.

**Radial Immunodiffusion (RID).** A quantitative technique designed for the determination of one particular antigen in a solution, and used mainly for the determination of the concentration of different immunoglobulin classes (IgA, IgG, IgM) in serum. This technique of single radial immunodiffusion was first developed for quantitative purposes by Mancini and co-workers in 1964. When antigen has diffused from a cyclindric well into an agar gel containing its homologous antibody, a circular area of precipitation proportional to the antigen concentration forms around the well (Van Oss & Bartholomew, 1980). The immunoprecipitin ring diameters are measured before equivalence. Antigen concentrations for equal volumes of experimental samples are determined by relating the log of the concentration to the precipitin ring diameter. This relationship is linear when plotted in semilogarithmic graph paper (Fahey & McKelvey, 1965).

**Procedure**

All psychological tests were administered to all subjects and scored according to standardization procedures.
over a period of 15 months during two final examination periods defined as high-stress periods and two nonexamination periods defined as low-stress periods.

For each of the four assessment periods, participants were asked to refrain from taking medications (with the exception of oral contraceptives) or consuming alcohol for 24 hours before blood samples were obtained. Blood was not drawn from women during menses. Blood samples (7 ml) were obtained by venous puncture using a vacutainer by trained phlebotomists under the supervision of a licensed physician. The time blood samples were drawn was held constant for each subject within one hour. After blood samples were obtained, psychological tests were administered. The Clinical Analysis Questionnaire, State-Trait Anxiety Inventory, and Brief Stress Questionnaire were administered at each assessment period. Immediately after blood samples were drawn, slides were prepared for WBC differential count. Staining and counting of cells were completed at a later date. Serum samples were frozen and concentrations of IgA, IgG, and IgM were quantified using the radial immunodiffusion technique at a later time.

Single radial immunodiffusion assays for the quantitative determination of immunoglobulin G, M, and A were performed using Kallestad Endoplate Test Kits (Kallestad Laboratories, Austin, TX). All test kits were of the same lot number. Endoplates, containing anti-Ig antibody in agarose, and reference sera were removed from
the refrigerator and equilibrated to room temperature. Reference serum immunoglobulins and patient serum samples were thoroughly mixed by inverting them several times. Using a volumetric pipette, 5 1 of each of three reference sera, control sera (Quanitrol Immunoassay Serum Control—Kallestad Laboratories, Austin, TX), and experimental subject samples were dispensed into the wells cut in the agarose.

Endoplates were sealed in plastic bags to prevent dessication and incubated at room temperature on a level surface for 18 hours. After incubation, the immunoprecipitin ring diameters were measured to the nearest 0.1 mm for the reference control and experimental samples using a dissecting microscope. Time of incubation and temperature were held constant throughout the experiment.

A reference curve was constructed on semilogarithmic graph paper by plotting the precipitin ring diameters of the reference sera on the linear scale versus their corresponding concentrations on the logarithmic scale and connecting the adjacent points. The immunoglobulin concentrations of the experimental samples were determined by locating each sample’s ring diameter on the reference curve and reading the concentration on the logarithmic scale. Concentrations were reported as mg/dl of IgG, IgM and IgA. The minimum detectable level of IgG, IgM and IgA is approximately 4.6, 4.5, and 3.9 mg/dl, respectively.
Results

Data were treated to a one-way analysis of variance with repeated measures to determine differences during high- and low-stress periods on biological and psychological variables. Significant differences were found on IgG, STAI I, Brief Stress Questionnaire, CAQ-D1 and CAQ-AS (see Table 1).

Table 1

Analysis of Variance with Repeated Measures for Differences Psychological/Immunological Variables Between High- and Low-Stress Periods

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall $PR &gt; F$</th>
<th>Contrast</th>
<th>$F$ Value</th>
<th>$PR &gt; F$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>0.055***</td>
<td>1-4</td>
<td>12.29</td>
<td>0.0039***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-3</td>
<td>8.32</td>
<td>0.0128**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-4</td>
<td>5.88</td>
<td>0.0306**</td>
</tr>
<tr>
<td>IgA</td>
<td>0.0720*</td>
<td>2-4</td>
<td>4.96</td>
<td>0.0443**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-2</td>
<td>4.13</td>
<td>0.0631*</td>
</tr>
<tr>
<td>IgM</td>
<td>0.1641*</td>
<td>1-4</td>
<td>4.29</td>
<td>0.0626</td>
</tr>
<tr>
<td>STAI I</td>
<td>0.0001****</td>
<td>1-4</td>
<td>33.86</td>
<td>0.0001****</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-4</td>
<td>16.24</td>
<td>0.0006****</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-3</td>
<td>11.14</td>
<td>0.0031****</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-4</td>
<td>8.49</td>
<td>0.0083***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-2</td>
<td>5.67</td>
<td>0.0286</td>
</tr>
<tr>
<td>Stress</td>
<td>0.0001****</td>
<td>1-4</td>
<td>50.29</td>
<td>0.0001****</td>
</tr>
<tr>
<td>Questionnaire</td>
<td></td>
<td>2-4</td>
<td>24.00</td>
<td>0.0001****</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-3</td>
<td>16.92</td>
<td>0.0005****</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-3</td>
<td>7.76</td>
<td>0.0108**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-4</td>
<td>7.76</td>
<td>0.0108**</td>
</tr>
<tr>
<td>CAQ-D1</td>
<td>0.0100**</td>
<td>2-4</td>
<td>9.04</td>
<td>0.0067***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-4</td>
<td>6.73</td>
<td>0.0161**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-4</td>
<td>5.28</td>
<td>0.0320**</td>
</tr>
<tr>
<td>CAQ-As</td>
<td>0.0110**</td>
<td>3-4</td>
<td>7.56</td>
<td>0.0117**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-4</td>
<td>6.51</td>
<td>0.0182**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-4</td>
<td>5.08</td>
<td>0.0345**</td>
</tr>
</tbody>
</table>

***$p < .0001 - p < .0006$; **$p < .001 - p < .008$; 
$**p < .01 - p < .05$; *$p > .05$; $N = 23$. 
The data were also subjected to the $t$ test for correlated samples of subjects between reported stress, no-stress conditions for all variables. Significant differences were found on: IgG ($p < .0026$), IgM ($p < .0358$), and CAQ-D1 ($p < .0448$). There were strong differences in means on other psychological variables but because of wide variability, significance levels were not attained (see Table 2).

### Table 2

**Correlated Samples $t$ test for Antibody Levels Between Stress and No-Stress Conditions**

<table>
<thead>
<tr>
<th>Variable</th>
<th>$SE$</th>
<th>$t$</th>
<th>$PR &gt; t$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>63.221</td>
<td>3.60</td>
<td>0.0026**</td>
</tr>
<tr>
<td>IgM</td>
<td>39.224</td>
<td>2.31</td>
<td>0.0358*</td>
</tr>
<tr>
<td>IgA</td>
<td>32.195</td>
<td>1.72</td>
<td>0.1060</td>
</tr>
</tbody>
</table>

$N = 16$

**$** $p < .003$

*$p < .04$

Pearson product moment correlations were utilized to examine relationships between biological and psychological variables. Correlation coefficients were obtained on all variables and separately on each stress, no-stress assessment. Significant correlation coefficients were reported at or above .40. In assessment 1 (low-stress) 15 variables were found to be significantly correlated (see Table 3).
### Table 3
Significant Correlations Between Variables in Assessment 1 (Low-Stress)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable</th>
<th>Correlation Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>IgA</td>
<td>.75</td>
<td>&lt; .002</td>
</tr>
<tr>
<td></td>
<td>Stress</td>
<td>.58</td>
<td>&lt; .03</td>
</tr>
<tr>
<td>IgM</td>
<td>CAQ-D1</td>
<td>.63</td>
<td>&lt; .02</td>
</tr>
<tr>
<td>STAI I</td>
<td>Stress</td>
<td>.41</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>STAI II</td>
<td>CAQ-C</td>
<td>-.74</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-D1</td>
<td>.51</td>
<td>&lt; .02</td>
</tr>
<tr>
<td></td>
<td>CAQ-Q4</td>
<td>.64</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>.60</td>
<td>&lt; .003</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>.56</td>
<td>&lt; .006</td>
</tr>
<tr>
<td>CAQ-C</td>
<td>CAQ-Q4</td>
<td>-.58</td>
<td>&lt; .003</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>-.63</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>-.53</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>CAQ-Q2</td>
<td>Stress</td>
<td>.44</td>
<td>&lt; .03</td>
</tr>
<tr>
<td>CAQ-Ps</td>
<td>CAQ-D1</td>
<td>.60</td>
<td>&lt; .003</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>.54</td>
<td>&lt; .008</td>
</tr>
</tbody>
</table>

N = 23

In assessment 2 (low-stress) 16 variables were found to be significantly correlated (see Table 4). Highly correlated variables in assessment 2 were Stress with STAI I, CAQ-C with STAI II (negative), CAQ-D1 with CAQ-Ps, and STAI II with CAQ-AS (negative).
Table 4

Significant Correlations Between Variables in Assessment 2 (Low Stress)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable</th>
<th>Correlation Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>IgA</td>
<td>.43</td>
<td>&lt; .04</td>
</tr>
<tr>
<td>Stress</td>
<td>IgM</td>
<td>.45</td>
<td>&lt; .04</td>
</tr>
<tr>
<td></td>
<td>STAI I</td>
<td>.67</td>
<td>&lt; .0005</td>
</tr>
<tr>
<td>STAI II</td>
<td>CAQ-PS</td>
<td>.52</td>
<td>&lt; .01</td>
</tr>
<tr>
<td></td>
<td>CAQ-C</td>
<td>-.68</td>
<td>&lt; .0004</td>
</tr>
<tr>
<td></td>
<td>CAQ-Q4</td>
<td>.54</td>
<td>&lt; .008</td>
</tr>
<tr>
<td></td>
<td>CAQ-D1</td>
<td>-.43</td>
<td>&lt; .04</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>-.63</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>-.56</td>
<td>&lt; .006</td>
</tr>
<tr>
<td>CAQ-Q4</td>
<td>CAQ-D1</td>
<td>.49</td>
<td>&lt; .02</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>.58</td>
<td>&lt; .004</td>
</tr>
<tr>
<td>CAQ-D1</td>
<td>CAQ-As</td>
<td>.51</td>
<td>&lt; .01</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>.68</td>
<td>&lt; .0003</td>
</tr>
</tbody>
</table>

N = 23

Table 5 illustrates that in assessment 3 (high stress), 19 variables were found to be significantly correlated. Highly correlated variables in assessment 3 were STAI I with CAQ-C (negative), STAI II with STAI I, STAI II with CAQ-C (negative), and IgG with IgA.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable</th>
<th>Correlation Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>IgA</td>
<td>.59</td>
<td>&lt; .003</td>
</tr>
<tr>
<td>STAI I</td>
<td>CAQ-Q4</td>
<td>.41</td>
<td>&lt; .05</td>
</tr>
<tr>
<td></td>
<td>CAQ-D1</td>
<td>.55</td>
<td>&lt; .006</td>
</tr>
<tr>
<td></td>
<td>CAQ-C</td>
<td>-.71</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CAQ-C</td>
<td>CAQ-Q4</td>
<td>-.42</td>
<td>&lt; .05</td>
</tr>
<tr>
<td></td>
<td>CAQ-D1</td>
<td>-.45</td>
<td>&lt; .03</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>-.57</td>
<td>&lt; .004</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>-.43</td>
<td>&lt; .04</td>
</tr>
<tr>
<td>CAQ-Q4</td>
<td>CAQ-D1</td>
<td>.51</td>
<td>&lt; .01</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>.43</td>
<td>&lt; .04</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>.43</td>
<td>&lt; .04</td>
</tr>
<tr>
<td>STAI II</td>
<td>STAI I</td>
<td>.74</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-Q4</td>
<td>.67</td>
<td>&lt; .004</td>
</tr>
<tr>
<td></td>
<td>CAQ-C</td>
<td>-.66</td>
<td>&lt; .0006</td>
</tr>
<tr>
<td></td>
<td>CAQ-D1</td>
<td>.58</td>
<td>&lt; .004</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>.53</td>
<td>&lt; .009</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>.56</td>
<td>&lt; .005</td>
</tr>
<tr>
<td>CAQ-As</td>
<td>CAQ-D1</td>
<td>.44</td>
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</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>.51</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

N = 23
In assessment 4 (high stress) 17 variables were found to be significant. The most significant were STAI II with CAQ-D1, and CAQ-C negatively with CAQ-Q4, CAQ-D1, CAQ-As, and CAQ-Ps, and CAQ-D1 with CAQ-Q4 (see Table 6).

### Table 6

Significant Correlations Between Variables in Assessment 4 (High-Stress)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable</th>
<th>Correlation Coefficient</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>CAQ-I</td>
<td>.43</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>STAI II</td>
<td>STAI I</td>
<td>.46</td>
<td>&lt; .03</td>
</tr>
<tr>
<td></td>
<td>CAQ-Q4</td>
<td>.61</td>
<td>&lt; .0005</td>
</tr>
<tr>
<td></td>
<td>CAQ-D1</td>
<td>.64</td>
<td>&lt; .0011</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>.53</td>
<td>&lt; .01</td>
</tr>
<tr>
<td></td>
<td>CAQ-C</td>
<td>-.63</td>
<td>&lt; .002</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>.48</td>
<td>&lt; .03</td>
</tr>
<tr>
<td>CAQ-C</td>
<td>CAQ-Q4</td>
<td>-.71</td>
<td>&lt; .0003</td>
</tr>
<tr>
<td></td>
<td>CAQ-D1</td>
<td>-.66</td>
<td>&lt; .0008</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>-.71</td>
<td>&lt; .0002</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>-.68</td>
<td>&lt; .0008</td>
</tr>
<tr>
<td>CAQ-D1</td>
<td>CAQ-Q4</td>
<td>.81</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>.46</td>
<td>&lt; .03</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>.75</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CAQ-As</td>
<td>CAQ-Ps</td>
<td>.49</td>
<td>&lt; .02</td>
</tr>
<tr>
<td></td>
<td>CAQ-Q4</td>
<td>.48</td>
<td>&lt; .02</td>
</tr>
<tr>
<td>CAQ-Q4</td>
<td>CAQ-Ps</td>
<td>.56</td>
<td>&lt; .008</td>
</tr>
</tbody>
</table>

\( N = 23 \)
Correlation coefficients were obtained on all variables across all assessments. There were 18 variables significant at or beyond the .0001 level of significance (see Table 7).

**Table 7**

Significant Correlations Between All Variables on All Assessments

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable</th>
<th>Correlation Coefficient</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>IgA</td>
<td>.40</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>STAI I</td>
<td>Stress</td>
<td>.47</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>STAI II</td>
<td>STAI II</td>
<td>.46</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>STAI II</td>
<td>CAQ-C</td>
<td>-.66</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-Q4</td>
<td>.62</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-D1</td>
<td>.53</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>.50</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>.53</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CAQ-C</td>
<td>CAQ-Q4</td>
<td>-.53</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-D1</td>
<td>-.47</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>-.62</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>-.56</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CAQ-Q4</td>
<td>CAQ-D1</td>
<td>.53</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-As</td>
<td>.49</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>.44</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CAQ-D1</td>
<td>CAQ-As</td>
<td>.48</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>CAQ-Ps</td>
<td>.61</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CAQ-As</td>
<td>CAQ-Ps</td>
<td>.48</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

N = 92
Additionally, all the immunological and psychological variables were subjected to discriminant function analysis for prediction of group classification by stress. Low stress groups were correctly classified with 87 percent accuracy. High stress groups were correctly classified with 72 percent accuracy (see Table 8).

Table 8

Discriminant Analysis of Immunological/Psychological Data for Prediction of Group Classification by Stress Condition

<table>
<thead>
<tr>
<th>Groups</th>
<th>Percent Classifications</th>
<th>Percent Classifications</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low stress</td>
<td>87.18</td>
<td>12.82</td>
<td>100.00</td>
</tr>
<tr>
<td>High stress</td>
<td>28.21</td>
<td>71.79</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Group classification by stress using only psychological variables yielded a correct classification in the low stress groups of 84 percent. High stress groups were correctly classified with 68 percent accuracy (see Table 9).

Table 9

Discriminant Analysis of Psychological Data for Prediction of Group Classification by Stress Condition

<table>
<thead>
<tr>
<th>Groups</th>
<th>Percent Classifications</th>
<th>Percent Classifications</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low stress</td>
<td>84.44</td>
<td>15.56</td>
<td>100.00</td>
</tr>
<tr>
<td>High stress</td>
<td>31.82</td>
<td>68.18</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Group classification by stress using only immunological variables yielded a correct classification in the low stress group of 58 percent. High stress groups were correctly classified with 61 percent accuracy (see Table 10).

Table 10

<table>
<thead>
<tr>
<th>Groups</th>
<th>Percent Classifications</th>
<th>Percent Classifications</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low stress</td>
<td>57.50</td>
<td>42.50</td>
<td>100.00</td>
</tr>
<tr>
<td>High stress</td>
<td>39.02</td>
<td>60.98</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Results for WBC differential count showed that numbers of neutrophils, lymphocytes, monocytes, eosinophils, and basophils were within normal ranges, indicating that none of the subjects had developed an illness. For this reason, differences in antibody levels are probably not due to an immune response against infection.

Antibody levels for each subject between stress, no-stress conditions may be seen in figures 1-3. Scores on state anxiety, trait anxiety, and hypochondriasis between stress, no-stress conditions for each subject may be seen in figures 4 and 5 (see Appendix E).
Discussion

The results provide firm support for the hypothesis that as psychological stress occurs, there is a corresponding change or effect on immunological functioning as measured by levels of immunoglobulins IgG, IgM, and IgA. The immunological changes are consistent with heightened psychological activity/stress, verified by changes in immunological and psychological parameters over the four assessment periods (two high-stress final examination periods, 3 and 4; and two low-stress periods beginning and mid-semester, 1 and 2).

Adaptation levels appear to reflect consistent changes indicative of psychobiological interaction in accordance with bodymind resistance functions in response to stressful stimuli. The heightened psychological activity-anxiety/stress and increased antibody production appeared representative of the first and second stages of the adaptation process in Selye's general adaption syndrome with the probability that anxiety-alarm stage is the precursor to the antibody production of the second stage, resistance. While the pattern of responses are general, the variability found within this pattern may be accounted for by the conceptualizations within Randolph's specific adaptation syndrome which encompasses individuality of susceptibility and response patterns (Randolph, 1962).
All immunoglobulin levels increased during high-stress conditions—final examinations. The greatest difference occurs in IgG is are seen between the first low-stress period and the second final examination period. Although IgG is the only antibody to show overall significant changes, IgA also shows a significant increase between one high- and low-stress period.

Psychological measures indicate that anxiety increases during the high stress periods with greatest anxiety during the last final examination period as measured by STAI I (state anxiety) and CAQ-AS (Psychasthenia). Additionally, students perceive themselves as being significantly more stressed during final examinations as indicated by their own report on the Brief Stress Questionnaire. Concomitantly students also report an increase in bodily dysfunctions during final examination periods.

It appears that the most accurate measure of whether or not a student is stressed is their self-report. When these data are examined on an individual basis, not every student reported stress during final examination periods and some students reported stress during nonexamination periods due to other factors, such as interpersonal conflict, finances, family illness, lack of exercise, etc. Therefore data grouped according to self report of stress, and immunological and psychological variables irrespective of the defined high- and low-stress periods show significant differences on correlated samples t test.
between levels of IgG and IgM, with antibody levels increasing during perceived stressful periods. Significant psychological variables influencing the stress state are increased somatic complaints and expressions of concern about bodily dysfunctioning. Wide variability among subjects on other psychological variables preclude the attainment of statistically significant differences among means (see Appendix E).

The review of the literature of stress and its effects on immunity as well as our prior work (Didriksen, Goven, & Butler, 1986) clearly indicate associations between the immune system and central nervous system (CNS). However, these relationships appear to be quite complex when behavior, attitudes, coping skills, social support systems, general state of emotional and physical health, genetic and neuroendocrine factors are considered and their interactions with the immunological status of individuals. Of primary importance is the individual's perception of an event as being stressful or not. Since not every student in this study perceived each final examiantion period as a stressful occasion, results of stress effects on immunity may be somewhat inaccurate because of the individual differences in perception.

The majority of research on stress effects on immunity have shown stress to have immunosuppressive effects both in vivo and in vitro and perhaps increasing the organism's vulnerability to infection, neoplasms or autoimmune
diseases. However, other studies have indicated that stress may enhance some aspects of immune functioning as shown in the present study. Multiple mediating mechanisms are considered as possible explanations for increases in antibody titers in individuals reporting a stressed condition.

Studies on human immunoglobulins show that levels vary relatively widely among individuals but probably by no more than approximately 20% within a given individual during the course of a year (Rogers, Dubey, & Reich, 1979). The individuals who participated in the present study also demonstrate wide variability among themselves but many show more than a 20 percent increase in antibody levels during periods of high stress compared with periods of low stress. Thus it is unlikely that the changes found in this study are due to normal variation over the course of time such as seasonal rhythmicity.

Circadian rhythms in humoral immunity (secretory IgA, and plasma cell and immunoglobulin level response to antigen) as well as quantitative levels of circulating lymphocytes and their response to mitogen stimulation have been reported (Rogers et al., 1979). Since the time blood was drawn was held constant for each individual within one hour, observed changes did not appear to be due to circadian variations in the course of a day.

There are several medications known to increase immunoglobulin levels in humans. These include
anticonvulsants, antihypertensives, oral contraceptives, and nonsteroid antiinflammatory agents (Rogers, 1979). None of the participants in the study reported taking these drugs, with the exception of two using oral contraceptives, taken over the duration of the study.

The nature of a stressor and the timing of its application relative to the induction of an immune response by antigen, as well as duration of the stressor may determine whether the stressor suppresses or enhances the immune response. Soloman (1969) effectively reduced primary and secondary response to antigen with overcrowding stress but not apprehension-electric shock stress prior to and subsequent to immunization. Riley (1981) in two separate experiments demonstrated that immunocompetence could be enhanced if corticoids (the stressor) were administered before the implantation of a tumor rather than after implantation. Antibody synthesis in rats to administered antigen, was enhanced two hours after a surgical procedure but not at 24 hours when compared with controls, demonstrating the differential effects of time after the stressor on the degree of immune response (Konnaert, Mahieu, & Van Geertruyden, 1978).

The intervals between the stress and the immune measurements are extremely important as there may be a rebound overshoot of immune functions at some time after the occurrence of the stressor (Borysenko & Borysenko,
1982). Other, mechanisms underlying immunoenhancement subsequent to stress may be due in part to elevations in somatotropin (growth hormone) and thyrosin, known to increase in the plasma during long-term exposure to stress.

It is possible that any or all of these factors may have contributed to the observed increase in antibody titers. Some students who may regard attending graduate school as chronically stressful may have adapted with enhanced antibody production. Others may have experienced an acute stressor, such as a particularly difficult final examination in close temporal proximity to blood drawing, evidencing elevated levels of immunoglobulins. Further, it is likely that many students during the stress of final examinations did not obtain enough rest, maintain an adequately nutritious diet, or achieve a generally healthy balance in life style. These factors may contribute to the maladaptive process and enhanced antibody production.

The interaction of immune processes with neuroendocrine functions provides an explanation of how stress may influence immunologic processes. One classic neuroendocrine pathway has already been described in this paper, Selye’s general adaptation syndrome (GAS). Another is Cannon’s fight-or-flight response where the perception of stress produces excitation in the brain stem resulting in increased activity of the sympathetic branch of the autonomic nervous system and release of norepinephrine and epinephrine. During acute psychological stress there is
evidence of high plasma cortisol secretion rates as well as increases in levels of epinephrine and norepinephrine (Rose, 1980). Increases in cortisol have been associated with decreases in the ability of lymphocytes to respond to mitogens and destroy foreign cells (Jemmott & Locke, 1984). Receptors for catecholamines and other stress-related hormones have been discovered on lymphocytes suggesting an immunoregulatory function (Borysenko & Borysenko, 1982). Stimulation of beta-adrenergic receptors results in a decrease of responsiveness of T lymphocytes B lymphocytes and macrophages mediated by 3' - 5' adenosine monophosphate (cyclic AMP or cAMP) which depresses the metabolic, proliferative, cytotoxic and secretory activity including antibody production in mature cells (Grieco, Siegel, & Goel, 1976). Conversely alpha-adrenergic and cholinergic stimulation causes an increase in cyclic 3' - 5' guanosine monophosphate (cGMP) and augments both T and B lymphocyte responses (Jemmott & Locke, 1984).

These factors may have influenced the immunoglobulin levels found in our subjects. However, to verify this interaction, measurement of corticosteroids and catecholamines would be necessary. Corticosteroids exert regulatory influences positively or negatively on almost every stage of the inflammatory and immune response in animals and man. Fauci, Pratt and Whalen (1977) demonstrated the relative resistance of human B cell function to the suppressive effects of pharmacologic
concentrations of corticosteroids and that in vitro corticosteroids in physiologic and pharmacologically attainable concentrations caused a marked enhancement of human B lymphocytes to mitogen stimulation, most likely by potentiation of the normal triggering signal presented to the B cell or by the inhibition of the normal negative regulatory signal. Cooper, Duchett, Petts and Penny (1979) also found corticosteroid enhancement of immunoglobulin in vitro synthesis in response to mitogen stimulation postulating that corticosteroids may enhance immunoglobulin production in vivo by affecting peripheral lymphoid tissues which contribute to immunoglobulin production in response to antigenic challenge. It is possible that the enhanced antibody production observed during stress is possible due to this corticosteroid enhancement of B lymphocytes in peripheral lymphoid tissues.

Frankenhaeuser and her colleagues (1978) studied the effects of examination stress and found significantly greater increases in urinary excretion of cortisol, adrenaline, noradrenaline and its metabolite 3 methoxy-4-hydroxy-phenylethylene glycol (MHPG) in males than females. The majority or the participants in this study are females. They may not respond as greatly as males in secretion of potentially immunosuppressive catecholamines or corticosteroids.

The psychological variables in this study also fit the pattern of both the general adaptation syndrome and
specific adaptation syndrome in terms of the perception of stress in both low- and high-stress conditions. There is also a process of psychological responsivity which appears biphasic with first an anxiety or stimulatory reaction and then an adaptation or maladaptation reaction which can be labeled by the behaviors which are coping or perseverative-compulsive-depressive in nature. In general, the results of this study are highly indicative of a group of individuals whose competencies enable them to initiate and carry out task-oriented, problem-solving behaviors even under stress. The activity level is heightened under stress thereby enhancing the goal-directed behavior even though some individuals utilize some maladaptive behaviors in the process. While variations occur, anxiety, which in this instance does not appear to be a nameless dread or sense of foreboding, but instead the individual’s perception of external events, is representative of a challenge which must be met and thus is more likely to reflect the individual's belief in his or her ability to meet the challenge. The variability of response patterns may be seen in anxiety being inversely correlated with the ability to set and reach mature goals, remain calm in the face of adversity, and meet the challenges or opportunities of the day, to "roll with the punches," and to remain emotionally stable under conditions of stress. Further, these adaptive responses to stress are also inversely correlated with those features of behavior more
specifically related to anxiety which include increased tension, frustration, possible conflict, impatience, irritability, excitability, and diminished ability to rest or restore oneself when necessary. Other maladaptive responses involve increased concern about the state of one's health, bodily dysfunctioning, and general somatic complaints, sometimes to the point of preoccupation or even obsessive-compulsive behaviors.

The ability of psychophysiological variables to predict membership in low-stress, high-stress groups is highly accurate. The combination of psychological and immunological variables is more useful than either the psychological or immunological variables alone, attesting to the greater accuracy and utility of bodymind interaction effects. The psychological factors while more predictive, in this instance, of a stressed condition than the biological factors, are more broadly based and are inclusive of normal and abnormal personality factors, emotional states and anxiety levels. The immunoglobulin levels, on the other hand, are but one component of immune system functioning and biological variables. Even in this rather restricted field of biological measures, antibody production not only correctly identifies a high- or low-stress condition in the majority of cases, but is a reasonable fit into the process of adaptation.

In summary, results of this study show (1) increased antibody levels during periods of stress; (2) IgG most
consistently related to stress and probably most indicative of the stressed condition and probably reflecting a biological resistance to stress; (3) anxiety related to external events; (4) increase in anxiety under stress and (5) anxiety inversely correlated with emotional stability and coping skills while positively related to tension, increased number of somatic complaints and obsessive-compulsive trends.
Appendix A

Informed Consent

I, ___________ wish to participate in a research project being conducted by Nancy A. Didriksen. I understand that the primary purpose of this research is to demonstrate the existence or nonexistence of a relationship between perceived psychosocial stress, various immune system parameters and personality factors. I understand that this research is being conducted in cooperation with the biology department and that I will be required to give from 4 to 6 blood samples during the course of this project. I understand that all blood will be drawn by a trained phlebotomist and that J. R. Toledo, M. D., will provide medical supervision. I understand that I will be required to take paper and pencil psychological tests each time a blood sample is taken.

I understand that all test results both psychological and biological, will be coded to ensure confidentiality and that feedback will be provided upon completion of the study. I understand that my participation in this study is completely voluntary and that I may withdraw at any time without jeopardy. I understand that the investigator may drop me from the study as long as this action is not detrimental to me.

This research project has been fully explained to me and I have read and fully understand this agreement. Therefore, I voluntarily agree to participate in this research project.

Signed ___________________________
Participant

Signed ___________________________
Witness

Date ______________________________
Appendix B

Name ____________________________  Today's date ____________________

Address __________________________________________________________

Residence Phone no. (____) __________

Business/other phone (____) __________

Date of birth ________________________  Sex _______  Race _______

Marital status __________  Other employment _______________________

Where employed __________________________________________________

Program at NTSU __________  Do you feel any pronounced stress at
this time? ________  If yes, describe the nature of the stress

Do you consider yourself generally optimistic __________

pessimistic __________

What are your primary foods and drink (please list) __________

Do you consider you diet nutritionally sound?  Explain __________

Do you take nutritional supplements?  List them.  How often?  How
much? __________________________________________


Describe the exercise _____________________________________________

Average number of drinks daily _____  Weekly _____  Do not drink_____  
alcohol at all_____ (no alcohol is permitted 24 hours before
blood samples are taken).  What is your height? __________________

Weight? _______  Last taken blood pressure__/_____

Have you ever had:  Anaphylaxis _____  Arthritis _____

Emphysema _____  Paralysis _____  Peptic ulcer _____  Stroke _____
Appendix B—continued

Tuberculosis  Convulsions  Diabetes
Heart attack  Severe dizzy spells  High blood pressure
Laryngeal edema  Loss of consciousness  Psychiatric care
Pneumonia  Severe reactions to allergy tests or allergy injections

What is the worst allergic reaction you have ever had?

Have you ever had a severe exposure to chemicals, for example, to pesticides?  If so, describe. When, where, etc.

Are you chronically being exposed to an chemicals now?  If so, describe

**DRUG HISTORY**

Check drugs taken on a regular basis:

- Cortisone
- Penicillin
- Marijuana
- Insulin
- Nose Drops
- Hormones
- Adrenalin
- Cough Medicine
- Antibiotics
- Metaprel
- Brondecon
- Theokin
- Phenobarbital
- Demerol
- Sleeping Pills
- Street Drugs
- Mycin Drugs
- Aspirin
- Tylenol
- Codeine
- Susphrine
- Decadron
- Aminodur
- Tranquilizers
- Digitalis
- Sulfa Drugs
- Paregoric
- A.C.T.H.
- Antihistimines
- Dilantin
- Laxatives
- Birth Control Pills
- Alupent
- Potassium Iodine
- Bronkephrine
Deconamine  Theophylline  Aminophyllin
Bronkodyl  Elixophyllin  Vanceril
Verequad  Bronkometer  Ephedrine
Aerosols  Prednisone
Others

Do you require: normal  low  high  doses of drugs as a rule? Explain

Do you require frequent use of antibiotics? Yes  No
Which

Do you get colds or other upper respiratory ailments frequently? Explain

Indicate your choice of day and time when you would be able to take part in this study for each of the 4 scheduled intervals:
First choice  2nd  3rd
Appendix C

Clinical Analysis Questionnaire (CAQ)  
Explanation of Factors

Factor C: Emotional Stability  
Low Score: easily upset, emotional  
High Score: emotionally stable, calm

Factor I: Sensitivity  
Low Score: tough-minded, insensitive  
High Score: sensitive, tender-minded unrealistic

Factor Q2: Self-Sufficiency  
Low Score: group-adherent, sociable  
High Score: self-sufficient, resourceful

Factor Q4: Tension  
Low Score: relaxed  
High Score: tense, frustrated, drivin

Factor D1: Hypochondriasis  
Low Score: few somatic complaints  
High Score: obsessed by ill health

Factor AS: Psychasthenia  
Low Score: noncompulsive  
High Score: obsessive, compulsive

Factor Ps: Psychological Inadequacy  
Low Score: feels competent, has sense of self-worth  
High Score: feels inferior and unworthy

Low Scores: 1-4  
Average: 5-6  
High Scores: 7-10
Appendix D

Stress-Immune Study

Code Number________________ Date __________________

Are you experiencing any significant psychological stress at this time? YES____ NO ____ If you answered yes, describe the stress ____________________________________________________________________________

Are you taking any medications at this time? YES____ NO ____ If you answered yes, list the medications. ________________________________

Have you changed your health habits in any way since the last assessment period? Explain: ________________________________

PLEASE COMPLETE BOTH SIDES OF THE STATE-TRAIT ANXIETY INVENTORY AND BOTH PARTS 1 AND 2 OF THE CAQ. PLEASE RETURN THIS QUESTIONNAIRE AND ALL TEST MATERIALS TO DR. BUTLER'S MAILBOX IN TERRILL HALL. THANKS.
Appendix E

Figures
Fig. 1. Immunoglobulin G concentrations in subjects during stress and no-stress periods defined by self-report.
Fig. 2. Immunoglobulin M concentrations in subjects during stress and no-stress periods defined by self-report.
Fig. 3. Immunoglobulin A concentrations in subjects during stress and no-stress periods defined by self-report.
Fig. 4. State anxiety and trait anxiety scores of subjects during stress and no-stress periods defined by self-report.
CAQ-D1: Hypochondriasis

Fig. 5. Hypochondriasis scores of subjects during stress and no-stress periods defined by self-report.
CAQ-C: Emotional Stability

Fig. 6. Emotional stability scores of subjects during stress and no-stress periods defined by self-report.
Fig. 7. Sensitivity scores of subjects during stress and no-stress periods defined by self-report.
Fig. 8. Self-sufficiency scores of subjects during stress and no-stress periods defined by self-report.
Fig. 9. Tension scores of subjects during stress and no-stress periods defined by self-report.
Fig. 10. Psychasthenia scores of subjects during stress and no-stress periods defined by self-report.
CAQ-Ps: Psychological Inadequacy

Fig. 11. Psychological inadequacy scores of subjects during stress and no-stress periods defined by self-report.
References


