Stress and Immunity

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INTRODUCTION

The proposed relationships between emotional and disease states have a long and colorful history. As early as the second century A.D., Galen reported that melancholy women appeared more likely to develop cancer than sanguine women. Despite the lengthy history of such conjectures, it is only recently that the knowledge base and methodological skills have sufficiently developed to allow empirical testing of these ideas.

Psychoneuroimmunology (PNI), as the field has come to be known, has its roots in ancient ideas and practices (Lloyd, 1987). Scientific exploration...
of this topic has progressed slowly over several decades, only to explode in the 1980s following the publication of Ader and Cohen's landmark work (Ader and Cohen, 1975). The complexity of the fields subsumed by PNI (psychology, behavioral medicine, endocrinology, neuroscience, and immunology, to name a few) have provided a wealth of information. However, this very complexity poses problems for the researcher trying to integrate and study this area. In this chapter, we will attempt to overview the relevant human studies in this expanding field, in particular, highlighting major areas of human studies with respect to specific types of stressors, health implications, and effects.

DEPRESSION AND BEREAVEMENT

Among the earliest reported human work in this area was a study by Bartrop et al. (1977) that explored the effects of spousal death on mitogen-stimulated lymphocyte proliferation. These researchers examined immune function (T- and B-lymphocyte number and function) in 26 bereaved spouses 2 and 6 weeks after bereavement; 26 hospital staff members served as controls. Results indicated that average T-cell function as measured by mitogen-induced stimulation was reduced following bereavement.

In a later prospective study, Schleifer et al. (1983) examined 16 men whose wives were dying of breast cancer. Peripheral blood was collected before and after the wives' deaths. Blastogenic responses following the death of their spouse were significantly suppressed compared to both prebereavement values. Consistent with these results, Irwin et al. (1989) reported that women whose husbands had recently died of lung cancer evidenced greater depression in immune function than women whose husbands were undergoing treatment for metastatic lung cancer, or women with healthy husbands. In a related study, Linn et al. (1984) found that only bereaved subjects with high depressive symptom scores (measured by the Hopkins Symptom Check List) demonstrated reduced lymphocyte responsiveness.

One possible explanation for the change in the immune response seen in bereaved subjects involves the mediating role of depression. The Linn et al. (1984) study provides some support for this hypothesis since bereavement in the absence of moderate to severe depression was not sufficient to bring about immune change.

A number of studies have further examined the relationship between depression and immune function. Stein and colleagues have performed a series of studies looking at the depression-immune function relationship. In their initial study, they found that depressed subjects had lower total T- and B-lymphocyte numbers, as well as lower mitogen-induced lymphocyte stimulation (Schleifer et al., 1984). These results were not replicated in a follow-up study (Schleifer et al., 1985). However, in a more recent study (Schleifer et al., 1989), while they did not find differences between depressed patients and controls in lymphocyte stimulation, natural killer (NK) cell activity, or lymphocyte numbers, there were age- and severity-related differences (i.e., as age and severity increased, there appeared to be an increasing negative association between depression and immune function).

In contrast, some studies have failed to find a relationship between depression and the immune system. Albrecht and colleagues (1985) studied 27 depressed patients and did not find altered immune function relative to normal controls. Similarly, Sengers et al. (1982) reported normal T- and B-cell function and numbers in 25 manic-depressed patients. However, both research groups provide an interpretational caveat, i.e., their results may have been affected by the treatment (e.g., electroconvulsive therapy, lithium, and/or tricyclic antidepressants) that a majority of the patients were concurrently receiving.

Considering specific mechanisms, some researchers have conjectured that depression and immune function are linked through cortisol secretion. Several studies have found both suppressed immune function and increased cortisol secretion in depressed subjects (Schleifer et al., 1984, 1989; Kronfol and House, 1984; Denney et al., 1988). Stein and colleagues (1985) have further suggested that immune changes may be related to underlying biological processes associated with depression. However, it must be pointed out that in the Denney et al. (1988) study, cortisol levels were not related to any lymphocyte measure, nor was cortisol related to depression itself. Furthermore, it is apparent in the depression literature that only subsets of depressed patients exhibit the abnormal cortisol secretion patterns (Rubin et al., 1987). As these relationships are not unambiguous, such findings should be interpreted cautiously. Further work in this area should attempt to more clearly delineate the relationships among cortisol, depression, and immune function. Special emphasis might be given to those suppressed patients who do exhibit abnormal cortisol patterns. There is also a need to look carefully at cortisol measurement methods.

Other researchers have considered the depression-immune relationship from a different angle, positing a role for the effect of chronic stress associated with depression. The link between chronic and acute stressors in immune function will be explored in the following sections.

ACUTE OR COMMONPLACE STRESSORS

In contrast to chronic stress, there is a relatively large body of literature that has examined more commonplace, or "acute" stressors. Lazarus and Folkman (1984) have suggested that everyday hassles and stressors are better
predictors of health and psychological problems. The study of acute stressors provides methodological advantages as well, allowing for better experimental manipulation, as well as more careful delineation of mechanisms and direct health consequences.

A favorite paradigm for examining immunological effects of acute stressors has involved the study of college or postgraduate students engaged in examinations. As early as 1950, several researchers had begun assessing the immunological effects of examination stress (Humphreys and Raab, 1950; Kerr, 1955). More recently, research in our own and several other laboratories has utilized this stress paradigm.

Dorian and colleagues (Dorian et al., 1981, 1982) explored the effects of oral examinations on psychiatry residents compared to age- and sex-matched physician controls. Results indicated higher levels of emotional distress, reduced mitogen-induced lymphocyte proliferation, and some evidence for higher T- and B-lymphocyte counts in the preexamination residents, when compared to either controls or their own postexamination values.

Halvorsen and Vassend (1987) measured the psychological and immunological status of 12 psychology undergraduates taking an examination and 11 control subjects. Preexamination students demonstrated higher anxiety, greater self-reported distress, increased numbers of circulating monocytes, reduced expression of interleukin-1 (IL-2) receptors, and a reduction in lymphocyte responsiveness to PHA.

We have conducted a series of studies in our laboratory examining the relationship between loneliness and decreased immune function (Henne and Henle, 1982). For example, it has been noted that immunosuppressed patients (i.e., those with immunosuppressive illnesses or receiving immunosuppressive therapy) characteristically have elevated herpesvirus antibody titers. Elevation in antibody titers is thought to reflect inability of the cellular immune response to control the reactivation of viral products and infectious virus. We have found increased antibody titers to three herpesviruses: EBV, the etiological agent for infectious mononucleosis (IM), HSV-1 responsible for cold sores, and CMV, which produces a mononucleosis syndrome.

Recent findings have indicated that the activity of a lymphokine-designated leukocyte migration inhibition factor (LIF) that is suppressed during recrudescence of HSV type 2 infections (Sheridan et al., 1982) was also suppressed during examination periods. Also associated with examination stress were alterations in plasma and intracellular levels of cyclic AMP. This last finding may point to a possible mechanism explaining the changes in PBLs in the cellular immune response. Lastly, more self-reported illnesses were associated with exam periods than with baseline (Glaser et al., 1987).

With regard to psychological variables, several studies from our laboratory have identified a relationship between loneliness and decreased immune function (Kicic, Glaser et al., 1984; Glaser et al., 1985a). Lonelier students had poorer immune function than their less lonely counterparts. This represents an interesting finding, as it implies a potential role for personal relationships and/or social relations in affecting or buffering immune system changes.

A number of studies have examined the influence of examination stress on endocrine function. Hellhammer et al. (1985) studied ten healthy males taking final examinations in medicine or psychology. These authors found a relationship between salivary cortisol levels and examination stress, in which inadequate coping attempts were positively correlated with cortisol elevations. However, as cortisol levels were abnormally high in control (non-exam) subjects, this suggests that students may in fact represent a chronically stressed sample. In a similar study, Hodgens et al. (1989) found elevated cortisol levels both before and after an examination in 18 third- and fourth-year medical students. Proactin levels, however, were elevated only during preexamination. Lateinzing hormone levels were negatively correlated with anxiety levels both before and after the examination. The finding of elevated cortisol levels at both time points is suggestive of the experience of a more chronic stressor.

Extended space flight is yet another long-term mental and physical stressor in which immunological measures have been studied. Kimsey (1975) reported that sky lab astronauts had a depressed lymphocyte proliferative response to PHA post-flight as compared to pre-flight. He also reported a reduction in circulating T-lymphocytes. Taylor and Dardano (1983) reported lower post-flight lymphocyte stimulation to PHA in the space shuttle astro-
nauts. They reported a relationship between crew member ranking in terms of in-flight difficulties and decreased blastogenic response. In contrast, Voss (1984) failed to find any postflight differences in serum IgG, IgA, and IgM levels in sky lab astronauts.

In examining the effects of stress on immune function, few studies have utilized laboratory stressors. In a series of experiments, Palmblad and colleagues (Palmblad et al., 1976, 1979) examined the effects of sleep deprivation on immunological responses. In the first study, 8 female subjects underwent a 77-h sleep deprivation stressor. Results indicated that interferon-producing capacity rose during and after the vigil. Decreases in phagocytic activity were also demonstrated during the sleep deprivation period. In the second study, 12 male students participated in a 48-h sleep deprivation paradigm. Phytohemagglutinin-induced lymphocyte stimulation was reduced following the stressor.

In an another example of an experimentally manipulated stressor, Landmann et al. (1984) subjected 15 normal individuals to a mental stress test (a variation of the Stroop's Color-Word Conflict Test). This brief psychological stressor was found to produce higher cortisol levels, slight increases in lymphocyte and leukocyte numbers, and a significant increase in the number of circulating monocytes.

The greater case of experimental manipulation in measurement of physiological response provided by laboratory-induced stressors makes them particularly attractive at this point in the field's development. Nevertheless, these manipulations must be carefully thought out, not only with regard to the psychological stressor itself, but in relation to the kinetics of the endocrine and immunological measures of interest as well. Such experimentally manipulated stressors could provide elegant methods with which to carefully map out the mechanisms and kinetics of these complex relationships.

As noted with chronic stress, the acute stress literature also demonstrates relatively robust and consistent findings of generally reduced immune function in response to stress. However, the mechanisms behind these effects remain unclear. To clarify these relationships, a careful examination of the interaction of psychological stress and endocrine and immunological systems is needed. Such a study is currently in progress in our laboratory.

Utilizing a paradigm of baseline nonstress and examination stress, we are currently assessing the subgroup of medical students with regard to psychological, endocrinological, and immunological factors in collaboration with Dr. William Malarkey. One hundred medical students (20 students per year over 5 years) will provide 24-h samplings of various “stress hormones” from blood taken at the following intervals: 1 month prior to, within 3 d of, and 2 weeks after a major examination. We will be assaying growth hormone, prolactin, adrenocorticotropic hormone (ACTH), cortisol, and catecholamines along with immunological measures. Subjects will also complete a battery of psychological and health assessments. In this study, it is hoped that we will be better able to delineate the interactions and mechanisms involved in stress-endocrine-immune relationships.

**CHRONIC STRESSORS**

There are a variety of studies examining the effects of chronic stressors on immune function in humans. Among the stressors studied are divorce/separation, caregiving for Alzheimer's disease (AD) patients, the effects of extended space flight, and living near the Three-Mile Island (TMI) nuclear power plant.

Epidemiological data indicate that separated and divorced individuals are at a greater risk for mental and physical illness on an actuarial basis than married, single, or widowed individuals (Bloom et al., 1978; Verbrugge, 1979). Divorce can be conceptualized as a chronic stressor for those experiencing it, since adjustment appears to occur over several years (Weiss, 1975). Furthermore, continued preoccupation with the (ex)spouse (attachment to the former spouse) has been hypothesized to lead to distress-related symptoms (Weiss, 1975).

We have examined the immunological effects of divorce as a chronic stressor in two studies (Kiecolt-Glaser et al., 1987a, 1988). In the first study, 38 separated/divorced women were compared to sociodemographically matched married controls. Immunological assays included mitogen-stimulated lymphocyte proliferation to Con A and PHA, antibody titers to a latent herpesvirus, Epstein-Barr virus (EBV), and T- and NK cell numbers. The separated/divorced group evidenced significantly higher EBV antibody titers, significantly lower percentages of NK cells, and significantly different blastogenic response to PHA. Furthermore, “attachment” to the former spouse was negatively associated with immune function in this group.

In a follow-up study examining the effects of marital discord in males, 32 separated/divorced men were compared with matched married controls. Separated/divorced men appeared more psychologically distressed, lonelier, and reported more recent illnesses than married men. These individuals also had significantly poorer immune function in terms of antibody titers to EBV and herpes simplex virus type 1 (HSV), and T-helper to suppressor ratios. Separated/divorced men who had both initiated the separation and were separated within the last year appeared less distressed and reported better health than the noninitiators.

Caring for a patient with AD also represents a chronic stressor. Research has indicated that AD caregivers are at high risk for depression (Crook and Miller, 1985). We have been studying the immunological effects of this long-term stressor in our laboratory (Kiecolt-Glaser et al., 1987b). Immunological
and psychological data were collected from 34 caregivers and 34 matched comparison subjects. Caregivers demonstrated significantly greater emotional distress (as measured by the Beck Depression Inventory and other self-report assessments) and generally poorer immune functioning (e.g., higher EBV antibody titers and lower percentage of T-lymphocytes, and helper T-lymphocytes).

Living near the site of the nuclear disaster at TMI has also been examined as another potential chronic stressor (McKinnon et al., in press). There were persistent behavioral and endocrinological differences in TMI residents compared to matched controls living 80 miles from the power plant. These differences include elevated levels of urinary epinephrine and norepinephrine, as well as elevated cortisol levels. Immunological data revealed that the TMI residents have fewer B-lymphocytes, NK cells, and suppressor T-lymphocytes than comparison subjects. Differences have also been reported with regard to neutrophil numbers and antibody titers to cytomegalovirus (CMV), another latent herpesvirus. Thus, across a variety of subjects, situations, and immunological measures, chronic stressors appear to have deleterious effects on the immune system. However, the effects have not typically been either strong or consistent. Unfortunately, up to this time, little attempt has been made to delineate the kinetics, nor have the health implications been carefully examined. It would seem that one of the major problems facing this area is the absence of a strong conceptual base underlying the categorization of the psychological stressors or their individual effects. There is growing evidence that specific stressors can exert specific physiological reactions, and therefore may have specific immunological effects.

**INFECTION DISEASE**

The influence of stress on the incidence and duration of infectious disease is one interesting area of study with particular relevance to health. In an early, often-cited study, Kasl et al. (1979) examined psychosocial risk factors in the development of IM in a class of 1400 West Point cadets. The cadets who became infected and developed clinical IM could be distinguished from the infected cadets not manifesting clinical symptoms of IM on the basis of three factors: (1) having fathers who were overachievers, (2) having higher levels of motivation for a military career, and (3) scoring poorly on indices of relative academic performance. These factors were also related to length of stay in the hospital and levels of EBV antibody titers.

In a laboratory-controlled experiment, Broadbent et al. (1984) reported that virus shedding in subjects experimentally exposed to rhinoviruses and influenza viruses was related to their personality status as either introverts or extroverts. Individuals who reported greater distress on a self-report inventory had more evidence of nasal secretion after infection. Other researchers (Clover et al., 1989) have found that infection with influenza B virus was associated with familial cohesion and adaptability (measured by the Family Adaptability and Cohesion Scale), thus suggesting that family dysfunction may be related to altered immune response.

A series of studies have focused on the role of psychosocial factors in the recurrence of herpes labialis and the herpes viruses associated with cold sores (HSV-1 and HSV-2), or genital herpes. In their examination of the incidence of cold sore recurrence in a group of 61 nursing students, Katcher et al. (1973) found that psychosocial factors such as mood, social assets, and life change were able to account for 14% of their recurrence variance. In a follow-up study, Friedmann and colleagues (1977) found that mood was negatively associated with cold sore recurrence in 149 nurses.

Other studies have focused on the recurrence rates of genital herpes. Goldmeier and Johnson (1982) studied 58 patients with confirmed genital herpes. Patients evidencing higher distress demonstrated a much greater rate of recurrence than did less distressed patients. Schmidt et al. (1985) examined the role of stress in 35 genital herpes patients. The authors found that patients reported an increase in stressful life events, elevated anxiety, and increased daily hassles and frustrations prior to the appearance of a recurrent lesion, in contrast to the period after the lesion had disappeared. On a subgroup of 10 patients, these same authors collected immunological data 0 to 3 days after the appearance of a lesion, and found blunted T-lymphocyte blastogenesis at time of recurrence compared to nonrecurrence periods.

Silver et al. (1986) examined the relationship of psychological factors in recurrent HSV-induced lesions. HSV recurrences and pain were related to level of psychological distress. The most important variable in this study appeared to be coping strategies, as the greatest rates of recurrence were found in those subjects who took an emotional-focused, avoidant-coping approach. Vanderplut et al. (1988) examined the role of stress on HSV lesions as moderated by social support. Results indicated that both duration of disease and disease-specific social support were significant moderators of the relationship between HSV recurrence and stress in their 59 subjects. Specifically, when illness duration is short, stress and number of recurrences are positively associated. No relationship was noted with longer duration. At lower levels of social support, there was a positive relationship of stress to recurrence; however, with high support, no relationship was found.

Lastly, Kemeny and colleagues (1989) performed a prospective study that examined stress, life change, mood, HSV recurrence, and several immunological measures. While stress and mood scores were found to be uncorrelated with HSV recurrence, they were negatively associated with the proportion of helper and suppressor T-lymphocytes in the overall sample. Although helper T-lymphocyte proportions were not related to recurrence,
suppressor T-cells were negatively correlated with this variable. An association between depressive mood and recurrence was found in those patients not experiencing other infections.

The potential value of this line of research cannot be overstated, as the herpes virus literature provides a linkage between psychosocial factors and health behaviors that is crucial to this field. However, a majority of the reported studies have been retrospective in nature, and must be interpreted with caution, particularly with regard to inferences of causality. Furthermore, few of the studies have attempted to assess immunological function as well as disease status, with the exception of Kemeny et al. (1989). Based on the results of our medical student studies with regard to herpesvirus antibody titers, it is interesting to conjecture direct links among stress, immune function, and disease recurrence. However, the mechanism underlying this relationship awaits more accurate delineation. It would be of great interest to prospectively examine the relationships among stress, endocrine measures, carefully chosen immunological measures, and health status, such as HSV recurrence.

CANCER

Another area of interest is the relationship of psychosocial variables to cancer. Considerable literature has developed over the years, and will not be fully reviewed here. Temoshok et al. (1985) have suggested that this rather prodigious literature could be divided into seven main categories. Of these, the categories of major interest to PNI include (1) studies examining psychosocial characteristics of noncancer patients vs. cancer patients, (2) studies in which patients with suspicious lumps or lesions are assessed prior to biopsy, with results compared to actual diagnosis post-biopsy, (3) studies taking a prospective or retrospective approach to pre-morbid stress, psychosocial characteristics, or health habits, (4) studies examining the relationship of psychosocial variables to disease progress and/or survival times, and (5) studies focusing on the association of immunological variables presumed to be related to cancer initiation or exacerbation and psychosocial factors. The interested reader is referred to reviews of the first four of these areas (Bahonon, 1980, 1981; Cox and MacKay, 1982; Fox, 1978; Greer, 1983; LeShan, 1959) that also detail the contradictory results and methodological inadequacies found throughout this literature.

Of specific interest to this chapter are those studies that examine the relationship of psychological factors, specific immunological functioning, and cancer, although these are unfortunately rare within the literature. In one such study, Pettingale et al. (1977) examined the relationship of emotional expression and serum IgA in 160 breast cancer patients. Several studies have reported rises in serum IgA levels in patients with breast cancer (Roberts et al., 1975). Serum IgA levels were found to be higher in all patients who tended to suppress their anger preoperatively. At the postoperative follow-up, this pattern was demonstrated only by breast cancer patients.

In a follow-up to this study, Pettingale and colleagues (1981) examined serum immunoglobulin (IgG, IgA, and IgM), several hormones (progesterone, testosterone, estradiol, cortisol, prolactin, growth hormone, and thyroxine), and lymphocyte proliferation in response to PHA in 69 women with breast cancer. Patients were classified according to their psychological response to cancer diagnosis (i.e., denial, fighting spirit, stoic acceptance, or helpless/hopeless). At preoperative assessment, no relationship was found between psychological response style and the biological measures. However, at 3-month follow-up, patients in the denial group demonstrated increased levels of serum IgM compared to the other groups. There were no associations between psychological response styles and PHA-induced lymphocyte proliferation.

Levy et al. (1987) examined the associations among stress, NK cell activity, and predicted prognosis in 75 women with breast cancer. Using multiple regression analyses, these authors report that, in general, patients reporting depressive, fatigue-like symptoms and complaining of a lack of family support at baseline had a decrease in NK activity at 3 months follow-up.

Levy et al. (1987) have suggested that emotional, cognitive, and behavioral responses are “biological response modifiers” that have relevance for cancer risk and progression. While the authors admit that the biology of the tumor is the most important determinant of cancer outcome, they point out that numerous epidemiological risk factors for breast (and possibly other) cancers have possible endocrine pathways (i.e., sex, age at menarche, etc.). The possibility arises that response styles mediated through endocrine changes may be associated with cancer outcome.

Unfortunately, there have been few well-controlled, prospective human studies that have examined cancer-immunology-psychosocial associations in sufficient detail. While the work by Levy and others is encouraging, it is clear that further delineation of the relationships among cancer onset, progression, and endocrine and immune system function is needed. One avenue of future study might involve the examination of specific and well-defined populations across many data points. The use of treatment interventions as experimental manipulations may also prove fruitful in clarifying these associations.

Some interesting data from our laboratory may shed some light on the psychoimmunology-cancer relationship. In both human (Kiecolt-Glaser et al., 1985b) and animal studies (Glaser et al., 1985c), we have demonstrated that stress can affect DNA repair mechanisms. In the human study, DNA repair
(recovery of nucleoid sedimentation following irradiation of PBLs with 100 rad of X-irradiation) was assessed in 28 newly admitted, nonmedicated, nonpsychotic, psychiatric inpatients. A significant difference in DNA repair was found between high- and low-distress subject groups (measured by scale 2 depression on the Minnesota Multiphasic Personality Inventory, MMPI), with the high-distress group evidencing poorer DNA repair. Such alterations in DNA repair might have a number of potentially important consequences, not the least of which could include increased risk for cancer. Most carcinogens appear to induce cancer by damaging the DNA in cells, resulting in abnormal cells. The body's ability to repair damaged cells is therefore critical, and there is evidence that faulty DNA repair is associated with an increased incidence of cancer (Takabe et al., 1983). In the next section, we will consider the application of psychological interventions to this field.

INTERVENTIONS

Few studies have examined the effects of psychosocial interventions on immune status and/or infectious disease status. This likely reflects the relative "youth" of the field and difficulties associated with the conduct of well-controlled treatment intervention research.

Among the earliest studies exploring the ability of an intervention to affect immunological reactivity were several experiments with hypnosis reported by Black and colleagues (Black, 1963a, 1963b; Black et al., 1963). These authors assessed the effects of hypnotic suggestion on the delayed hypersensitivity reaction to tuberculin, using four highly selected subjects. Skin biopsies revealed that these subjects exhibited normal cellular infiltration, but demonstrated a reduced amount of edema. As this work was not controlled, conclusions must remain very tentative.

In an attempt to follow-up this line of evidence, as well as the more recent conditioned immunosuppression animal work of Adler and Cohen (1975), Smith and McDaniels (1983) examined the effects of conditioning on the tuberculin reaction in 7 human subjects. Using the color of the skin test vial (red for saline, green for tuberculin) as the conditioned stimulus, subjects were assessed monthly over 6 months. When the vials were reversed (red for tuberculin, green for saline) at the sixth trial, results indicated that the tuberculin response at this trial was reduced in terms of erythema and induration.

Gould and Tissier (1984) reported on two case studies (32- and 26-year old females) that examined the effects of hypnotic suggestion on genital HSV recurrence. After three sessions of hypnosis, as well as audio tape-guided self-hypnosis, the older subject was able to go 3 months without a recurrence, while the 26 year old went 7 months without a recurrence. These results are particularly impressive in light of the fact that both women had been experiencing almost monthly recurrences prior to treatment. Unfortunately, this work lacked experimental controls.

Our laboratory has been involved in a number of studies examining the effects of psychosocial interventions on immunological parameters. In one study that examined the effects of relaxation training in a geriatric sample (Kiecolt-Glaser et al., 1985a), the relaxation group was able to significantly decrease distress at post-treatment (as measured by the Hopkins Symptom Checklist) relative to social contact or no contact controls. Immunologically, these subjects also demonstrated increased NK cell activity and decreased HSV-antibody titers, with the latter presumably reflecting some increase in the ability of the cellular immune response to control the latent virus.

In a second study examining the effects of relaxation, we studied 34 first-year medical students randomly divided into relaxation and control groups (Kiecolt-Glaser et al., 1986). Students were bled at the beginning of their school quarter and again during final examinations. The relaxation group received relaxation training preceding the second blood draw. At examination time, the relaxation group reported decreased anxiety and distress compared to controls. For both groups, there was a decrease in the percentage of T-helper cells, T-helper/T-suppressor ratio, and NK cell lysis at examination time, but no interaction was found. Interestingly, the frequency of relaxation practice was a significant predictor of the T-helper cell percentage during examinations.

In a collaborative study with Dr. James Pennebaker, we examined whether actively confronting upsetting experiences might have positive effects on immune function (Pennebaker et al., 1988). Twenty-five of 50 undergraduate subjects spent 4 d writing about personal traumatic experiences which they had not revealed to others. The remaining 25 students spent the same amount of time writing about trivial experiences. Following this writing experience, the "trauma subjects" were found to have a higher blastogenetic response to PHA and a decreased number of health center visits for illnesses. These subjects also reported feeling happier than did controls at 3-month follow-up. When the trauma group was split into high- and low-disclosure groups, the high disclosures had an improved mitogen-induced lymphocyte response compared to low disclosures and controls.

Lastly, there is one recent study that failed to demonstrate positive immunological effects as a result of a psychosocial intervention. Coates and colleagues (1989) reported that stress reduction training (relaxation, stress management) did not change immunological measures of lymphocyte subsets, NK cell function, mitogen-induced lymphocyte response, or serum IgA levels in 64 men who were positive for HIV. The authors conjectured that the immune response may be difficult to modulate in a person who is debilitated due to HIV infection.

The body of work which has examined the effects of intervention on the
immune system is exciting in several respects. Most obvious are its possible implications regarding the treatment and prevention of immunologically relevant disorders. However, there are several difficulties in this area which must be overcome before we will be able to demonstrate a significant effect. At this point, it should be pointed out that most of the effects found in the above studies are relatively small and are of unknown physiological significance. One of the problems which remains for this area is our lack of understanding of the relationship of immunological variables and health status. Further research is clearly needed.

In the future, theoretically grounded, basic research that explores the mechanisms of the immune response and the long-term kinetics of its various components is strongly encouraged. Another major difficulty concerns our lack of well-defined assessments of immune-related health. Most studies have relied on retrospective accounts or number of health center visits, which is clearly not adequate to delineate this complex relationship. The work with herpessivirus is exciting in this respect, as these studies provide a clearly defined health outcome, namely, lesion recurrence or release of infectious virus. The inclusion of relevant immunological measures is particularly important as well.

In our laboratory, a research project is currently underway that will attempt to address at least some of these issues. We will be examining the effects of a stress-management-based intervention on the immunological status of hospital nurses. Both immune parameters and health information will be assessed. It is hoped that nurses will represent a population that is able to provide accurate and relevant health data. Assessments will include daily diary generated data as well as blood drawn on consecutive days to obtain a clearer picture of the kinetics of the immune response to such intervention.

Intervention-based studies are also noteworthy as an experimental manipulation of stress. While this paradigm has largely been overlooked to date, it has a potential to yield important and relevant data. The basic concept is as follows: if stress has the effect of modulating the immune system in some fashion, then the reduction of stress should serve to return the immune system to its prior state. Viewing stress intervention as an experimental manipulation allows us to provide more causal inferential information, as well as to map out the kinetics of the response. With interventions we can carefully time and quantify our manipulations with an eye toward enhanced understanding of the relationships.

**OVERVIEW OF THE STRESS-IMMUNO RELATIONSHIP**

In the past decade, researchers have begun to map out the cognitive, emotional, physiological, and behavioral aspects of stress. Of particular interest to PNI is how stress-related physiological changes impinge upon immune function. For the purposes of this chapter, we have focused primarily on the immunological effects of psychological stress. Psychological stress can be differentiated from physical stress in that it is subject to cognitive appraisal (Paterson and Neufeld, 1989).

Psychological stressors have been conceptualized as interactions among external threats, internal evaluations of threats, personal resources available to deal with the threat, and potential physical and psychological outcomes (Lazarus and Folkman, 1984). These interactions are thought to result in the cognitive, emotional, physiological, and behavioral manifestations of stress mentioned above.

The physiological effects of stress can generally be categorized under the rubric of arousal. Arousal would include such physical alterations as elevated heart rate, blood pressure, and respiration, as well as the endocrine changes associated with stress. Emotional presentations are typically interrelated with physiological arousal, and are often grouped under the heading of anxiety. Anxiety has more simply been described as a disagreeable emotion associated with fear, and involving short-term physiological responses (Lewis, 1970). Alternatively, others have characterized anxiety as a state of general arousal related to diverse emotions such as anger, fear, excitement, or depression (Paterson and Neufeld, 1989). This last definition would seem to have the greatest relevance for the present discussion.

Most researchers would agree that anxiety and/or stress has a necessary cognitive component. Stress can act to affect both the content and capacity of cognitive functioning (Paterson and Neufeld, 1989). With respect to content, stress tends to create worry or rumination. Stress also affects performance (capacity) in a well-defined manner. This effect is known as the Yerkes-Dodson law, which states that as arousal increases, performance improves, and with further increases, decays.

Lastly, stress may affect behavior generally by boosting activity level. In addition, it leads the individual to attempt to engage in coping behaviors. Of particular interest in this regard is the interaction and influence of this behavioral component of stress upon other domains, and the modifications which result. Thus, the stress response is not a static response. Rather, it fluctuates and changes as the person interacts with and responds to the stressor. It is this type of change and flux that should be kept in mind when attempting to understand or describe the endocrine and immune consequences of stress.

**ENDOCRINE RESPONSE TO STRESS**

The endocrine reaction to stress is very complex and only partially understood. The hypothalamus (HT) appears to play a central role in coordinating
the endocrine, autonomic, and behavioral responses to stress. Select cell populations within the HT exert neural control over the two main axes (pituitary-adrenocortical and sympathetic-adrenomedullary). These axes are responsible for the glucocorticoid- and proopiomelanocortin (POMC)-derived peptides and the release of epinephrine and norepinephrine into circulation.

The HT neural regulation of these systems involves several neuropeptides, including corticotropin-releasing factor (CRF), vasopressin (VP), and oxytocin (OT) (Silverman et al., 1989). Specifically, CRF stimulation leads to co-secretion of ACTH and POMC-derived peptides (in particular β-endorphin) from the pituitary. The release of catecholamines (norepinephrine and epinephrine) constitutes an initial response to stressors, and is controlled via regional activation of sympathetic nerves and discharged from the adrenal medulla (Kopin et al. 1988). It appears that POMC-derived peptides act as a "brake" on the sympathetic and adrenomedullary systems whenever they are activated (Grossman, 1989). In this way, they probably serve to counterbalance stress-hormone release, possibly diminishing harmful consequences of frequent overstimulation by chronic stress. However, central opioids are also capable of eliciting catecholamine release.

Epinephrine, in yet another potential feedback loop, has been shown to be a potent releaser of ACTH and related POMC-derived peptides (Smelik et al., 1989). Lastly, glucocorticoids have been found to inhibit the release of ACTH from the pituitary through the action of a negative feedback loop (Dallman and Yates, 1969). Munch et al. (1984) propose that the physiological function of stress-induced increases in glucocorticoid levels is to protect, not against the stress itself, but against the normal defense reactions that are activated by stress. Glucocorticoids probably produce this effect by inhibiting defense reactions such as the release of insulin, lymphokines, and prostaglandins, thus preventing undesirable hypoglycemia, excessive lymphocyte activation, and uncontrolled inflammatory responses.

**EFFECTS OF STRESS AND/OR COPING ON THE ENDOCRINE RESPONSE**

Of special interest to PNI is the impact of chronic stress and/or coping responses on endocrine function, and the interaction of hormones with immune system function. The processes that control the blend and amount of neural hormone release (CRF, VP, and OT) depend on both the current physiological state of the organism and its prior exposure (Silverman et al., 1989). Silverman and colleagues found that in rats, exposure to complex, chronic stressors leads to physiological modifications of CRF cells in the paraventricular nucleus (the section of the HT containing the most numerous population of CRF-producing cells). The stress of prolonged immobilization leads to a reduction of CRF receptor number in the pituitary (Hauga et al., 1989).

While cortisol secretion is frequently elevated in response to a variety of stressors, it is the initial response that is most vigorous, with prolonged exposure leading to adaptation (Usnis et al., 1978). However, even in cortisol-adapted animals that are chronically stressed, exposure to novel stimuli results in an even more rapid endocrine response (Sakellaris and Vernikos-Danelis, 1975). It has also been reported that the adrenocortical response is dependent on the individual’s perception of the stressor’s impact (Bourne et al., 1968). Chronic stress may also reduce the sensitivity of the brain’s pituitary unit to glucocorticoid negative feedback (Keller-Wood and Dallman, 1984).

Considering catecholamines, it is of interest that at least one study has demonstrated that relaxation practice was associated with higher norepinephrine concentration in response to a physical stressor (Hoffman et al., 1982). The authors interpreted these results as reflecting reduced norepinephrine endorgan responsivity (i.e., more norepinephrine was required to produce compensatory increases in heart rate and blood pressure). It appears that the quality and magnitude of both the ACTH and catecholamine response depends upon the stressor attributes, individual personality, and previous exposure and experience with the stressor.

Thus, the endocrine response to stress is a complex one and involves numerous feedback loops. This response is individualized with respect to stressors and may be modified by behavior, prior exposure, and coping responses. Because of its complexity and tendency to fluctuate, it is crucial that the endocrine-stress response not be conceptualized as a linear function. It is difficult to predict the kinetics of this response based on one or even several data points or hormonal measures. Thus, there is a critical need for further exploration of the kinetics of the endocrine response to stress in relation to psychological processes. Wiener (1989) has suggested that one of the most important issues in stress research is to “develop classification schema of stressors based on broad biological principles.”

Goldstein and Halbreich (1987) offer another opinion, arguing that “stress should not be defined by hormonal response.” These authors correctly point out that a situation can be quite stressful without concomitant increases in “stress hormones.” Conversely, an increase in “stress hormones” does not always indicate the impact of the stressor. It would seem that much could be gained by assessing psychological responses and interpretations to ultimately define and quantify stress, while still utilizing hormone response profiles to assist in the categorization and specificity of stressors. It is clear that we must move away from unitary concepts of stress and begin to explore individual responses and patterns.
EFFECT OF ENDOCRINE RESPONSE AND IMMUNE FUNCTIONING

In general, stress appears to down-regulate the immune response in humans. More specifically, individual hormones have been shown to have distinctive effects on varying elements of the immune system. However, one should keep in mind that the majority of these studies involve in vitro assessments and/or administration of pharmacological doses of specific hormones.

Cortisol has been shown to inhibit (1) the proliferative response of T-cells to mitogens, (2) lymphokine production (IL-1, IL-2, T-cell growth factor), (3) monocyte function, (4) suppressor cells, (5) cytotoxic response, and (6) serum immunoglobulin production (Tsokos and Balow, 1986). It can also affect lymphocyte trafficking.

ACTH has been demonstrated to affect lymphocyte activation by enhancing intracellular Ca²⁺ increases in response to mitogens (Kavelaar et al., 1988) as well as in vitro antibody responses to T-cell-dependent and -independent antigens and the production of γ-interferon (Smith and Blalock, 1986).

POMC-derived peptides (i.e., β-endorphin) can (1) suppress NK cell activity, (2) modulate tumor growth, (3) inhibit T-lymphocyte chemotactic factor production, (4) augment interferon production, and (5) act as a potent inhibitor of PHA-induced lymphocyte proliferation (McCain et al., 1986).

Felten and Felten (1989) have presented evidence for noradrenergic innervation of lymphoid organs, thereby providing for the possibility of direct contact between these two systems. Epinephrine has been shown to increase the activity of NK cells (Kristofer et al., 1985). Norepinephrine completely blocked the capacity of interferon to activate murine peritoneal macrophages to a tumoricidal state (Koff and Dunegan, 1985). Norepinephrine can also enhance (1) the primary antibody response, and (2) the ability of cytotoxic T-lymphocytes to lyse target cells.

Thus, "stress hormones" can have a variety of effects on immune function. It should be noted that many of these studies were performed in vitro, often using pharmacological doses and testing the hormone in isolation. In vivo, there exists an endocrine "milieu" of many hormones in varying amounts. In a study examining the in vivo effects of a "physiological" hormone mixture, little immunological effect was found (Delich and Bridges, 1987). These authors conjectured that the hormones act to "cancel out" their individual effects on immune function. It is not possible to interpret from this in vitro study how such a hormone balance may be affected by infection, chronic stress, or behavioral coping.

In addition, recent work by Blalock's laboratory suggests that the role of hormones may be more complicated than classic endocrinologists had conceded. They have shown that lymphocytes can produce ACTH and β-endorphin (Blalock and Smith, 1985). This lymphocyte-derived ACTH can be stimulated by CRF (Meyer et al., 1987) and the ACTH released may be responsible for stimulating adrenal corticosterone production in hypophysectomized mice (Smith et al., 1982).

PSYCHOLOGICAL STRESS: ENDOCRINE AND IMMUNE INTERACTIONS

The kinetics and interaction of psychological stress, endocrine response, and immune function are complex. In an attempt to clarify this complexity, we offer a greatly simplified example. We can imagine an individual experiencing a major life stressor, such as marital difficulties. As the problems mount, the individual's perceived stress level would be assumed to rise and eventually peak.

Based on the literature reviewed here, it would be expected that this individual's hormone response might also change concomitantly with this rise in stress. "Stress hormones" might rise as the stress worsens, and then eventually there would be an adaptation in this response.

The immune system would probably be affected by these endocrine changes, with a down-regulation of the immune response, at least initially. However, by Jerne's network hypothesis (1974), the immune system has its own counterbalancing self-regulatory system. This could cause the immune system to "overshoot" and lead to transitory immune enhancement before eventually modulating "back and forth" until it reaches equilibrium (much like the physical action of a spring).

Therefore, depending on at what time one attempts to assess these systems, different results could be obtained. At one time, we may see the typically reported high stress, high "stress hormones," and suppressed immune response. At another time, it may be high stress and high "stress hormone," but enhanced immune function (a result that has also been reported in the literature). At still another time, there could even be high stress, low "stress hormones," and enhanced or suppressed immune function.

The point is that no single point measure provides the "true" picture of this complex interrelationship. Instead, longitudinal studies with many data points across the different systems are needed to understand these processes. It will not be possible to understand these systems until the time and effort is extended to carefully map out these interactions. As this model may vary across different categories of stressors, coping responses, and their interactions, such clarification will require a considerable expenditure of resources.

Returning again to the model, it should be noted that despite its complexity, this model does not consider (1) the effects of the introduction of infectious agents or (2) the possible health implications of these changes. The
first question could be explored utilizing creative experimental models, while the latter question awaits more accurate immunological markers of health status.

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